EUROPEAN COLLABORATIVE ACTION

URBAN AIR, INDOOR ENVIRONMENT AND HUMAN EXPOSURE

Environment and Quality of Life

Report No 29

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JOINT RESEARCH CENTRE
Institute for Health and Consumer Protection
Chemical Assessment and Testing Unit

2013 **EUR 26168 EN**

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Co-ordinated by:

Stylianos KEPHALOPOULOS and **Otmar GEISS**, European Commission, Joint Research Centre, Institute for Health and Consumer Protection, Italy

Prepared with the contribution of the EU-LCI Working Group of European experts:

Erwin ANNYS, The European Chemical Industry Council (CEFIC), Belgium
Paolo CARRER, University of Milan, Dept. of Biomedical and Clinical Sciences "L. Sacco", Italy
Reto COUTALIDES, Bau-und Umweltchemie AG, Switzerland
Derrick CRUMP, Cranfield University, Institute of Environment and Health, United Kingdom
Christine DÄUMLING, Federal Environment Agency (UBA), Germany
Katleen DE BROUWERE, VITO, Belgium
Dieter DE LATHAUWER, Belgian Federal Public Services, Belgium
Nicole DOMMASCHK, Deutsches Institut für Bautechnik, Germany
Martin GLÖCKNER, Deutsche Bauchemie e.V., Germany
Paul HARRISON, PTCH Consultancy, United Kingdom (*Chairman*)
Birger HEINZOW, Landesamt für soziale Dienste (LAsD), Germany
Rudolf JÄCKH, BASF, Germany
Gunnar JOHANSON, Karolinska Institutet, Institute of Environmental Medicine, Sweden
Sandrine LE GUERN, French Agency for Food, Environmental and Occupational Health and Safety (ANSES), France
Christophe ROUSSELLE, French Agency for Food, Environmental and Occupational Health and Safety (ANSES), France
Jorma SÄTERI, FiSIAQ, Finland
Armin SCHUSTER, Universitätsklinikum Freiburg, Department of Environmental Health Sciences, Germany
Ana Maria SCUTARU, Federal Environment Agency (UBA), Germany
Peter TAPPLER, Federal Ministry of Agriculture, Forestry, Environment and Water Management, Austria
Maria UHL, Environment Agency, Austria
Thomas WITTERSEH, Danish Technological Institute, Denmark
Peder WOLKOFF, National Research Centre for the Working Environment, Denmark

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European Commission
Joint Research Centre
Institute for Health and Consumer Protection

Contact information
Stylianos Kephalopoulos
Address: Joint Research Centre, Via Enrico Fermi 2749, TP 281, 21027 Ispra (VA), Italy
E-mail: stylianos.kephalopoulos@ ec.europa.eu, JRC-IHCP-CAT@ec.europa.eu
Tel.: +39 0332 78 9871
Fax: +39 0332 78 5867

http://ihcp.jrc.ec.europa.eu/
http://www.jrc.ec.europa.eu/

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MANDATE: European Collaborative Action "**Urban Air, Indoor Environment and Human Exposure**" (formerly "Indoor Air Quality & it's Impact on Man")

For 25 years now the European Collaborative Action ECA "Indoor Air Quality & it's Impact on Man" has been implementing a multidisciplinary collaboration of European scientists the ultimate goal of which was the provision of healthy and environmentally sustainable buildings. To accomplish this task ECA is dealing with all aspects of the indoor environment including thermal comfort, pollution sources, the quality and quantity of chemical and biological indoor pollutants, energy use, and the ventilation processes which all may interact with indoor air quality. The work of ECA has been directed by a Steering Committee, which is hosted and managed by the European Commission's Joint Research Centre.

In order to provide a broader view on air pollution exposure in urban areas, both indoors and outdoors, the ECA Steering Committee decided to put more emphasis on the links between indoor and outdoor air quality and to focus its further work under a new title "*Urban Air, Indoor Environment and Human Exposure*". The focus of the renewed activity is urban & indoor air pollution exposure assessment, seen as part of environmental health risk assessment and also considering the needs of urban and indoor air quality management. The new approach is supported by those activities of the Joint Research Centre's Institute for Health and Consumer Protection dealing with exposure to physical and chemical agents, chemical assessment and testing and associated health effects.

This focussed activity proceeds within the broader framework of (i) health and comfort of the citizens, (ii) building technologies and source controls, and (iii) requirements of sustainability, energy efficiency and conservation of natural resources.

Specific examples of the working areas of ECA are:

- the relative importance of outdoor and indoor sources of pollution,
- the building-related interaction between outdoor urban air and indoor air,
- exposure to pollutants from the different urban outdoor and indoor sources and its relation to health and comfort.

By addressing such topics ECA will lay the ground for air quality management to minimise exposures to air pollutants. It will thus continue to contribute to pre-normative research needed by EC services and national authorities responsible for preventing pollution and promoting health, comfort and quality of life.

In this series the following reports have already been published:

Report No. 1: Radon in indoor air. EUR 11917 EN, 1988. *
Report No. 2: Formaldehyde emission from wood-based materials: guideline for the determination of steady state concentrations in test chambers. EUR 12196 EN, 1989. *
Report No. 3: Indoor pollution by NO_2 in European countries. EUR 12219, EN1989.
Report No. 4: Sick building syndrome - a practical guide. EUR 12294 EN, 1989.
Report No. 6: Strategy for sampling chemical substances in indoor air. EUR 12617 EN, 1989.
Report No. 7: Indoor air pollution by formaldehyde in European countries. EUR 13216 EN, 1990. *
Report No. 8: Guideline for the characterization of volatile organic compounds emitted from indoor materials and products using small test chambers. EUR 13593 EN, 1991.
Report No. 9: Project inventory – 2nd updated edition. EUR 13838 EN, 1991.
Report No. 10: Effects of indoor air pollution on human health. EUR 14086 EN, 1991.
Report No. 11: Guidelines for ventilation requirements in buildings. EUR 14449 EN, 1992.
Report No. 12: Biological particles in indoor environments. EUR 14988 EN, 1993.
Report No. 13: Determination of VOCs emitted from indoor materials and products. Interlaboratory comparison of small chamber measurements. EUR 15054 EN, 1993.
Report No. 14: Sampling strategies for volatile organic compounds (VOCs) in indoor air. EUR 16051 EN, 1994.
Report No. 15: Radon in indoor air. EUR 16123 EN, 1995.
Report No. 16: Determination of VOCs emitted from indoor materials and products: Second interlaboratory comparison of small chamber measurements. EUR 16284 EN, 1995.
Report No. 17: Indoor air quality and the use of energy in buildings. EUR 16367 EN, 1996.
Report No. 18: Evaluation of VOC emissions from building products – solid flooring materials. EUR 17334 EN, 1997.
Report No. 19: Total Volatile Organic Compounds (TVOC) in indoor air quality investigations. EUR 17675 EN, 1997.
Report No. 20: Sensory evaluation of indoor air quality, EUR 18676 EN, 1999.
Report No. 21: European Interlaboratory Comparison on VOCs emitted from building materials and products, EUR 18698 EN, 1999.
Report No. 22: Risk assessment in relation to indoor air quality, EUR 19529 EN, 2000.
Report No. 23: Ventilation, Good Indoor Air Quality and Rational Use of Energy, EUR 20741 EN, 2003.
Report No. 24 Harmonisation of indoor material emissions labelling systems in the EU, Inventory of existing schemes, EUR 21891 EN, 2005.
Report No. 25: Strategies to determine and control the contributions of indoor air pollution to total inhalation exposure (STRATEX), EUR 22503 EN, 2006.
Report No. 26: Impact of Ozone-initiated Terpene Chemistry on Indoor Air Quality and Human Health, EUR 23052 EN, 2007.
Report No. 27: Harmonisation Framework for Indoor Products Labelling Systems in EU, EUR 25276 EN, 2012.
Report No. 28: Health Risks from Indoor Particulate (INDEX-PM), EUR 25588 EN, 2012.
* out of print

Abstract

ECA-IAQ (European Collaborative Action, Urban Air, Indoor Environment and Human Exposure), 2013. Harmonisation framework for health based evaluation of indoor emissions from construction products in the European Union using the EU-LCI concept, Report No 29. EUR 26168 EN. Luxembourg: Office for Official Publications of the European Communities

This report describes a harmonised procedure for establishing a list of compounds and their associated LCI (Lowest Concentration of Interest) values for the evaluation of emissions from construction products (EU-LCI) taking into account existing procedures used in some Member States (i.e. ANSES in France and AgBB in Germany). It provides an appropriate health-protective, science-based and transparent yet pragmatic approach with a flexible framework that enables review of the EU-LCI procedure to take into account new knowledge (e.g. data resulting from the REACH implementation process) for future revision of the EU-LCI master list in terms of both the compounds listed and their EU-LCI values.

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EXECUTIVE SUMMARY

The health based evaluation of chemical emissions from construction products is an integral part of the harmonisation framework for indoor products labelling schemes in the EU. The harmonisation process for the health based evaluation of gas-phase chemical emissions from construction products in Europe is based on the LCI ('Lowest Concentration of Interest') approach[1], described fully in this report.

The work was co-ordinated by the European Commission's Directorate General Joint Research Centre (DG JRC) and performed in the context of the PILOT INDOOR AIR MONIT administrative arrangement with the Directorate General for Health and Consumers (SANCO) in liaison with experts from some EU Member States, the construction industry, the European Chemicals Industry (CEFIC), and also in consultation with the Directorate General for Enterprise and Industry (DG ENTR).

The EU-LCI development work outlined in the present report builds on firm foundations of the existing national evaluation systems established by AgBB (German Committee for Health-related Evaluation of Building Products) in Germany and ANSES (French Agency for Food, Environmental and Occupational Health and Safety) in France that currently apply the LCI concept, the Danish Indoor Climate Labelling (DICL), the Finnish (M1) and Belgium labelling schemes, and from chemical emission test laboratories in the UK, France, Finland and Denmark. Ultimately, the harmonisation process and procedures described here will allow voluntary and mandatory labelling schemes to evaluate product emissions in the same way by using a robust health-based procedure. This work also supports the establishment of future emission classes for CE marking (Conformité Européenne) under the European Construction Products Regulation (CPR, 2011) with a harmonised list of LCI values (EU-LCIs).

In the EU-LCI work performed to date, only volatile organic compounds (VOCs) have been considered. Very volatile organic compounds (VVOCs), semi-volatile organic compounds (SVOCs) and carcinogens were not considered at this stage of the process.

This phase of the EU-LCI harmonisation process has established:

1. A robust protocol for establishing a harmonised list of compounds and their associated EU-LCI values which takes into account the existing procedures used in some EU Member States. This procedure, based on sound toxicological and risk assessment principles, represents an appropriate health-protective, science-based and transparent yet pragmatic approach for the evaluation of chemical emissions from construction products.
2. A list of interim EU-LCI values for 82 compounds, which includes some of the compounds most relevant to DG ENTR's ad hoc group on emission classes (i.e., acetaldehyde, toluene, xylene, 1,2,4-trimethylbenzene, 1,4-dichlorobenzene, ethylbenzene, 2-butoxyethanol and styrene) and two compounds of recent concern in Germany (ε-Caprolactam) and Belgium (α-pinene).
3. A flexible framework that enables future revision of the content of the EU-LCI list in terms of both the type and number of compounds included and their

[1] LCI = Lowest Concentration of Interest (of individual VOCs). The LCI concept was first developed by the European Collaborative Action on 'Indoor Air Quality and its Impact on Man' when considering the best way to evaluate emissions from solid flooring materials. It was defined (see ECA Report No.18, 1997) as "the lowest concentration above which, according to best professional judgement, the pollutant may have some effect on people in the indoor environment".

associated EU-LCI values. The framework provides the possibility of taking into account new knowledge (e.g. data resulting from the REACH implementation process or compounds identified and suggested by EU national authorities).

The detailed protocol developed for the *de novo* derivation of EU-LCI values includes the following parts:

a) *Definition of EU-LCI*

EU-LCI values are health-based reference concentrations for inhalation exposure used to assess emissions after 28 days from a single product during a laboratory test chamber procedure as defined in the Technical Specification TS 16516 of the horizontal testing method developed by CEN TC 351/WG 2. EU-LCI values are applied in product safety assessment with the ultimate goal to avoid health risks from long-term exposure of the general population and they are usually expressed as $\mu g/m^3$.

b) *Data Compilation Sheet*

All relevant toxicological data from different sources in the literature (indoor air quality guidelines, toxicological reference values or occupational exposure limits from established international and national committees and information available through the REACH process) for each compound are assimilated into one table. This simplifies the identification of commonalities and differences and also guarantees the fundamental principle of transparency in deriving the EU-LCI values.

c) *Fact Sheet*

To ensure that the derivation of EU-LCI values is transparent, a summary fact-sheet with standardised format is generated for each compound. This comprises four main sections: a) general information; b) toxicological database (values derived from the data compilation process described above); c) assessment factors; and d) the derivation of the EU-LCI value. At the end of the factsheet the rationale for the derivation of the EU-LCI is given. This succinctly explains/justifies the selection and use of key data in the derivation of the EU-LCI value, in particular the selection of the key study used to determine the point-of-departure value. It also, where necessary, explains/justifies the use of particular assessment factors, especially non-default factors.

The protocol also provides guidance on applying a harmonised application of read-across and assessment factors in EU-LCI derivation.

Through application of the principles and rationale developed by the EU-LCI Working Group (EU-LCI WG) for the establishment of EU-LCI values, EU-LCI values have been established for a number of priority compounds. The EU-LCI WG compiled an EU-LCI master list containing a total of 177 compounds subdivided into two groups, the first containing 82 compounds with agreed interim EU-LCI values and the second containing 95 compounds for which EU-LCI values are still to be derived.

The practical application of the EU-LCI values and the necessary consideration of multiple sources that are normally present in real building scenarios are discussed and potential harmonisation issues related to the overall evaluation of emissions from construction products (for example, common criteria and threshold values for total volatile organic compounds (TVOC), R-value, SVOC, sensory evaluation and the sum of "not-yet-assessable" compounds) are identified.

Finally, developments concerning policies at both EU and national levels that have explicitly or implicitly considered and/or referred to the work of the EU-LCI WG are reported.

In summary, this report presents the outcome of the preparatory work performed by the EU-LCI WG and represents a first consensus among the experts and representatives of the European Commission, some EU member states and the chemical and construction products industry who participated in the EU-LCI WG. The developed EU-LCI harmonisation framework is now open for a wider and formal consultation process at policy level which, however, is not yet in place.

The EU-LCI work is considered an integral part of the harmonisation framework for indoor product labelling schemes in the EU which has potential for wide application across Europe, ensuring stronger protection of the health of European citizens from chemicals emitted from indoor products.

1. INTRODUCTION

1.1 Background

Since 2007, European experts in health related evaluation of construction materials and emissions testing have been working to establish a harmonised set of criteria for European construction material labelling schemes. The framework for harmonised criteria is set out in the report "Harmonised framework for indoor material labelling schemes" (ECA Report No. 27, 2012). Concerning the health based evaluation of emissions from construction materials the experts concluded that the **"Lowest concentrations of interest" (LCI)** approach is the most feasible strategy for assessing the health effects of compounds emitted from construction materials.

The LCI strategy is used to assess the potential risks to health arising from inhalation exposure to individual VOCs. The ECA Report no. 18 on "Evaluation of VOC Emissions from Building Products – Solid Flooring Material" (1997) presented the key elements of this strategy. During the development of the national labelling approaches in Germany, France and Belgium, emphasis was put especially on the evaluation of individual compounds by consideration of LCI-values. Procedures have been developed in Germany and France that provide transparent systems for setting these values. The procedures and the main differences between these two approaches are outlined in ECA report no. 27.

The need to harmonise the health based evaluation of emissions from construction products in Europe based on the LCI concept was discussed and consensus on the way forward achieved during the Workshop "Harmonisation of the health based evaluation of emissions from building products in the EU using the LCI concept" which was organised and hosted by the European Commission's Joint Research Centre on 13-14 September 2010 in Ispra (JRC Workshop report, 2010).

Subsequently, in 2011 an EU-LCI working group comprising toxicologists and experts in chemical emission testing and product labelling was established and co-ordinated by JRC (as part of the PILOT INDOOR AIR MONIT administrative arrangement no. SI2.582843 with DG SANCO) with the objective to develop a harmonised framework for the health based evaluation of emissions from construction products in the EU using the LCI concept (the EU-LCI common list of compounds and values). Since December 2010, the EU-LCI work has been integrated into the activities on indoor air quality led by DG SANCO.

This work is also linked to DG ENTR's EGDS *ad hoc* group on emission classes for dangerous compounds under the remit of the Construction Products Directive (89/106/CE) (CPD, 1989). This group was set up by DG ENTR in November 2010 to develop a harmonised procedure for the classification of emission performance of construction products to be used in technical specifications and also included in the information provided with the CPD CE marking.

Ultimately, the EU-LCI harmonisation framework will allow voluntary and mandatory labelling schemes to evaluate product emissions in the same way using a robust health-based procedure and will support the establishment of future emission classes for CE marking under the European Construction Products Regulation (CPR, 2011) with a harmonised list of LCI values.

At this stage of the EU-LCI harmonisation work only volatile organic compounds (VOCs) have been considered. Other very volatile (VVOCs) and semi-volatile organic compounds (SVOCs) are to be addressed in the future.

Nonetheless, in the context of the EU-LCI framework the starting list contains around 177 VOCs commonly detected in emission tests of construction materials. The work builds on firm foundations laid by the labelling scheme and the protocol for qualifying emissions from construction products and decorating materials established by AgBB (German Committee for Health-related Evaluation of Building Products) and ANSES (French Agency for Environmental and Occupational Health and Safety) that currently apply the concept of LCI values, as well as schemes in Finland, Denmark and Belgium.

The focus of the EU-LCI working group was the establishment of a harmonised and robust protocol for the derivation of EU-LCIs which is decribed in this report. It is based on sound toxicological and risk assessment principles and in accordance with REACH guidance on information requirements and chemical safety assessment (Chapter R.8: Characterisation of dose [concentration]-response for human health).

1.2 The AgBB and ANSES lists of compounds as the starting point for EU-LCI harmonisation

As mentioned in section 1.1 of the present report, the notified regulations of France and Germany constitute the basis for the harmonisation of LCIs. The first AgBB LCI-list was adopted from ECA Report No. 18 (1997), which included 163 compounds. The respective LCI values were also adopted. The establishment of an expert group inside AgBB in 2001 with toxicologists from the Federal States regulators, and later also from industry along with representatives of manufacturing associations, provided a process to revise the German LCI-list taking into account current toxicological knowledge and the assumed or proven occurrence of particular compounds in construction products. Also new compounds were included, which was partly the result of new knowledge resulting from emission tests and partly due to the request from industry to develop LCI values for specific compounds (Däumling, 2012).

In 2002, some compounds which were included in the ECA 18 list and usually considered as 'pollutants', were removed from the AgBB-list because they were not relevant for assessing emissions from construction products (e.g. dichloromethane, carbon tetrachloride, 1,4 dichlorobenzene). LCI-values for VVOC were also removed (e.g. formaldehyde, acetaldehyde, acetone, propanal) because the evaluation of VVOC emissions was postponed. In addition, the group of phthalates was removed for analytical reasons. Further reductions in the number of LCI-values resulted from the grouping and rearranging of compounds, especially in the group(s) of saturated aliphatic hydrocarbons and terpenes. A major increase in the number of compounds occurred between 2002 and 2004, when a large number of applications for establishing LCI values for additional compounds were submitted by different stakeholders: by the Federal Institute for Materials Research and Testing (BAM), the chemical industry (VCI – Verband der Chemischen Industrie), GUT (label for carpets) and also Umweltbundesamt – the German Federal Environment Agency (UBA). In 2003 alone, 16 compounds were added to the list (some glycols, some esters and others).

In 2005, when the AgBB-Scheme became part of the approval requirements in Germany issued by Deutsches Institut für Bautechnik - German Institute for Building Technology

(DIBt), awareness of the possibility to apply for new or altered LCI values spread rapidly and the German LCI expert group also started receiving applications from foreign manufacturers for the determination of LCI-values (10 applications in 2008/2009 from 'Global Players' affiliations in France and the Netherlands). After 2010 a large number of applications were submitted by the paint industry. One explanation for this increase in applications is the now completed revision of the evaluation criteria for the award of the Blue Angel UZ 12a.

The development of the German LCI lists, from the former ECA report no. 18 LCI list in 1997 to the most recent update of AgBB in 2012, is outlined in Table 1.

Table 1. *Development of the AgBB-list of assessable compounds*

Assessable compounds in LCI lists from ECA 18 (1997) to AgBB (2012)	
ECA 18 (1997)	163
AgBB 2001	163
AgBB 2002	122
AgBB 2003	138
AgBB 2004	167
AgBB 2005	167
AgBB 2008	164
AgBB 2010	170
AgBB 2012	176

2002: removal of "general"pollutants (i.e. not found to be emitting from building materials) and VVOC

2004: Addition of glycols

In the framework of the 2004-2008 French National Environment and Health Action Plan (NEHAP), the French Agency for Environmental and Occupational Health Safety (AFSSET) established a health-related protocol for the evaluation of VOC and formaldehyde emissions from construction products. For the health based evaluation of the emissions of individual VOCs, AFSSET established a list of 165 LCIs in 2009.
Subsequently, in the context of the mandatory labelling of volatile emission from construction products, floorings, wall coverings, paints and varnishes (which has been established in France by Decree n° 2011-321 (March 23, 2011) and Order of April 19, 2011) focus was placed on emissions of 10 individual compounds and TVOC according to four emission classes (from very low emissions to high emissions). The 10 individual compounds[2] were selected because of their occurrence indoors in French dwellings and their classification as dangerous compounds through inhalation according to EU classification.

The definition of the LCI values and the corresponding decision trees for the LCI setting in the French and German schemes are reported and compared in the ECA report no. 27 (2012).

[2] Formaldehyde, acetaldehyde, toluene, tetrachlorethylene, xylene, 1,2,4-trimethylbenzene, 1,4-dichlorobenzene, ethylbenzene, 2-butoxyethanol, styrene, TVOC

1.3 References

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REACH guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. (http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment)

2. HARMONISATION FRAMEWORK FOR HEALTH BASED EVALUATION OF INDOOR EMISSIONS FROM CONSTRUCTION PRODUCTS IN THE EUROPEAN UNION BY USING THE EU-LCI CONCEPT

2.1 Objectives of the EU-LCI harmonisation process

The objectives of the EU-LCI harmonisation process, as proposed during the JRC Workshop on "Harmonisation of the health based evaluation of emissions from building products in the EU using the LCI concept" (September 2010, Ispra) and confirmed by the EU-LCI WG, are as follows:

Objectives of the EU–LCI harmonisation process

1. To devise a harmonised procedure for establishing a list of compounds and their associated EU-LCI values (including consideration of carcinogens) for the evaluation of emissions from construction products taking into account existing procedures used in some Member States (e.g. ANSES in France and AgBB in Germany) and to recommend an appropriate health-protective, science based, transparent and yet pragmatic approach.

2. To propose a flexible framework that enables future review of the procedure to take into account new knowledge (e.g. data resulting from the REACH implementation process) and revise the content of the EU-LCI list both in terms of number of compounds and EU-LCI values.

3. To establish EU-LCI values for compounds on the EU-LCI list and new compounds.

2.2 EU-LCI definition

EU-LCI values serve a different purpose from classic IAQ guideline values. They are intended only for evaluating emissions from single products and not for evaluating indoor air quality.

The EU-LCI refers to a 28-day test period, conforming to one of the testing times referred to in the Technical Specification TS 16516 of the horizontal testing method developed by CEN TC 351/WG 2. Since primary emissions decline with time, this time scale is considered to constitute a 'worst case' assumption for the long-term indoor air VOC emission scenario in the absence of oxidants.

It is acknowledged that the test procedure (using chambers and correction factors relating to a 'standard' room) provides only an approximation to the situation in a real indoor environment; concentrations in actual rooms will depend on emission rates of products used in the specific indoor environment, the number of sources for a given chemical, variability of environmental conditions (i.e. temperature, humidity, air exchange rate), chemical transformation, sink effects (adsorption and desorption), etc.

In determining appropriate maximum emissions from products through the application of EU-LCI values, and/or in product selection, account has to be taken of the emission

rates of individual compounds from multiple sources in a given indoor environment (see also chapter 5 of the present report).

Definition of EU-LCI

1. EU-LCIs are health-based values used to evaluate emissions after 28 days from a single product during a laboratory test chamber procedure (as defined in the Technical Specification, TS 16516 of the horizontal testing method developed by CEN TC 351/WG 2).

2. EU-LCIs are applied in product safety assessment with the ultimate goal to avoid health risks from long-term exposure for the general population.

3. EU-LCI values are usually expressed as µg/m^3.

4. Only values derived by application of the process established by the EU-LCI WG and described herein and ratified by the EU-LCI WG shall be called EU-LCIs.

2.3 Principles and Rationale for the Establishment of EU-LCI values

1. LCI values for a number of compounds have been produced independently by AgBB (Germany) and ANSES (France).
2. Some of these values are the same (sometimes because they have a common source/origin), but many are different because of different methods of derivation, even when based on the same source/origin.
3. The starting list for the EU-LCI setting process comprises those compounds that have been given LCI values by AgBB and ANSES (177 VOCs commonly detected in emission tests of construction materials).
4. In case where a compound has, for whatever reason, identical or very similar (differing by 20% or less) ANSES and AgBB LCI values, the shared value or the lowest value for that compound in the two lists is termed the 'ascribed interim' EU-LCI. In due course, this compound will be re-evaluated using the EU-LCI agreed protocol to produce *de novo* 'derived interim' EU-LCI value.
5. Compounds with different values in AgBB and ANSES will be assessed according to the EU-LCI WG's agreed protocol to derive *de novo* EU-LCI values. These will be designated 'derived interim' EU-LCI values. Compounds awaiting assessment are termed EU-LCI 'derivation pending'.
6. When a formal process is set in place at EU level the 'ascribed interim' and 'derived interim' EU-LCI values shall undergo a final evaluation and be assigned as 'confirmed' EU-LCI values.
7. At any time, additional compounds (EU-LCI 'candidate' compounds, e.g. compounds identified by EU national authorities) may be added to the EU-LCI master list and subsequently evaluated.
8. The EU-LCI master list comprises compounds with 'confirmed' EU-LCI values, 'interim' ('ascribed' and 'derived') EU-LCI values, EU-LCI values 'with derivation pending', and 'candidate compounds'.
9. The EU-LCI 'interim' values ('ascribed' and 'derived') in the EU-LCI master list in the ECA report no. 29 will be the harmonised values that can be used by the EU

Member States and voluntary indoor air labelling schemes in the absence of any formal process underway at EU level to transform them into 'confirmed' EU-LCI values.

10. There should be a periodic review of all EU-LCI values. This review may be accelerated in the event of significant new information (e.g. toxicity data) becoming available for any compound(s) on the EU-LCI master list.
11. In due course, procedures shall be established for carcinogens (Category 1A and 1B as defined in the CLP Regulation (EC) no. 1272/2008) and ultimately for 'not yet assessable' compounds.
12. SVOC and VVOCs will not be considered at this stage of the process by the EU-LCI WG, with the exception of acetaldehyde and formaldehyde.
13. To support the on-going activities of DG ENTR's Expert Group on Dangerous Substances (EGDS), the EU-LCI WG will focus first on compounds under consideration by the EGDS ad hoc group on classes (AGC).

2.4 Protocol for the *de novo* derivation of EU-LCI values

With the clear and determined objective at the outset of establishing a robust scientific methodology, various alternative approaches for the EU-LCI setting process were discussed by the EU-LCI WG. The methodology was then developed through initial application to some compounds that have very different LCI values in the German AgBB and the French ANSES lists and which are also included in the "Individual substances list" in the DG ENTR's EGDS ad hoc group's proposal – namely *toluene, xylene, ethylbenzene and styrene.*

Although these compounds are not very typical or prominent in product emissions, they served as examples for the establishment of a well documented toxicology-based assessment method. For these five compounds, values for Occupational Exposure Limits (OEL) and also Indoor Air Quality Guideline Values (IAQGV) were screened for their suitability for the evaluation of product emissions. The LCI derivations in the French and the German lists were then compared, but also a new evaluation conducted by going back to the critical effects, the key studies, the LOAELs (Lowest Observed Adverse Effect Levels) or NOAELs (No Observed Adverse Effect Levels) of suitable endpoints and applying appropriate assessment factors. In addition, compounds that appear in emission tests and for which such a broad background of toxicological evaluations does not exist had also to be considered. For all compounds a standard protocol for the *de novo*, transparent and harmonised derivation of EU-LCI values was developed by the EU-LCI WG via an iterative process.

The procedure for the *de novo* derivation of EU-LCI values consists of three main steps:

- *data compilation*
- *data evaluation* and
- *derivation of the EU-LCI value on the basis of a standardised factsheet generated for each compound.*

These steps are described in the remaining sections of chapter 2 of this report.

2.4.1 Data compilation

Data compilation is an important prerequisite and the first step in deriving an EU-LCI value. Regarding the data sources to use, detailed consideration of available summarised information on indoor air quality guidelines, other toxicological reference values or occupational exposure limits from established international and national committees were considered. The EU-LCI WG agreed that evaluations for indoor air quality guidelines (e.g. by WHO) are a reliable information source, since they undergo an intense peer-review process. Also, documented derivations of occupational exposure limits by -authoritative committees and documentation for toxicological reference values are considered as good references for data mining.

Furthermore, information available through the REACH process is also considered. A vast amount of registration data is published on the ECHA website in the form of IUCLID (International Uniform Chemical Information Database) datasets, where DNELs (Derived No Effect Levels) are also included. The EU-LCI WG agreed that only information from published reports (e.g. for compounds of very high concern/SVHC) could be used, or that access to registration dossiers should be arranged (via the respective EU competent bodies) so that the derivation of specific DNELs could be fully comprehended.

Several aspects are considered when assessing and comparing data to be used as the basis for EU-LCI derivation, such as date of publication and type of key study, critical health endpoints assessed, the point of departure (such as NOAEL or LOAEL, benchmark dose), the assessment factors used, the species considered, and the duration and route of exposure.

All relevant toxicological data retrieved for each compound shall then be assimilated into one table (the data compilation sheet). The data compilation simplifies the identification of common points and differences and guarantees the fundamental principle of transparency in deriving the EU-LCI value.

Critical dose effects, key studies and critical dose values (NOAEL, LOAEL, benchmark dose (BMD)) shall be identified for each EU-LCI candidate compound by reviewing toxicological reference values (TRVs) from authoritative sources (where available) such as EU risk assessment reports (EU RARs), RIVM, Health Canada, US-EPA, ATSDR, OEHHA, ANSES and also indoor air quality guideline (e.g. by WHO) and/or occupational exposure limit documents (e.g. by SCOEL).

It should be underlined that all relevant studies, including but not limited to the key study(ies)[3] selected, along with the data compilation sheet and the standardised summary factsheet (see chapter 2.4.3.1 of the present report) are used for deriving the EU-LCI value for each compound of interest.

[3] The key study(ies) is (are) the one (s) selected as the starting point for the derivation of the EU-LCI value. Various criteria apply to the selection of the key study including endpoint(s), type of study, route of exposure, experimental design, and quality assurance aspects.

2.4.2 Data evaluation

All relevant risk assessment reports shall be considered (including REACH Chemical Safety Reports), irrespective of publication date. With regard to individual studies, study design and quality is more important than the date of the study.

Relevant key studies are to be listed in the data compilation sheet, unless the derivation of the EU-LCI is making use of published risk assessments, which already include and discuss the key-study(ies).

The key study is chosen after thorough evaluation by the experts of the EU-LCI WG. Selection of the lowest reasonable point of departure (POD) of the key study (ies) will similarly be based on expert judgment.

If the database reveals inconsistencies or lack of data, assessment of the original studies shall be undertaken.

2.4.2.1 Studies and endpoints

"Chronic"[4] studies are generally preferred, except where a "short term" study provides valuable information about an important end point.

Human studies are preferred to animal studies, provided the study design is robust.

Inhalation studies are preferred to oral studies, although the latter can be used with an appropriate route-to-route extrapolation factor applied to the derived critical dose value.

All specific endpoints relevant to EU-LCI setting will be documented, together with additional supporting information if needed.

For all compounds, the associated REACH Chemical Safety Report(s) should be consulted and shall be taken into account provided that robust study summaries and/or raw data are available.

2.4.2.2 Point of departure values

NOAELs are normally preferred over LOAELs. If only a LOAEL is available then in line with REACH guidance a correction factor of 3 is generally applied. This factor will be addressed on a case by case basis and may vary from 1 to 10 depending on the type of effect and the shape of the dose-response curve.

Benchmark dose (BMD) and physiologically based pharmacokinetic (PBPK) modelling data arealso considered if the quality of the data is sufficient.

Assessment factors are applied to the point of departure (POD) to derive an EU-LCI value considered to be safe for humans (including children) following life-time exposure to VOCs emitted from a product. The use of assessment factors shall be in accordance with ECHA guidance[5]. Guidance on the application of read across for establishing EU-LCI values from data-poor compounds is given in chapter 2.5 of the present report.

[4] For the definition of "chronic" studies please refer to section 2.5 of the current report.

[5] "Typically, the overall assessment factor is the product of the individual assessment factors, by assuming independency of the factors. It is to be realised that this multiplication is in general very conservative: when each individual assessment factor by itself is regarded as conservative, multiplication will lead to a

2.4.2.3 Other effects

All other relevant information shall be recorded under 'Other effects'. This will include, but not necessarily be limited to, information relating to odour, endocrine disrupting properties, known mixture effects, etc.

2.4.3 EU-LCI derivation

A key aspect of the EU-LCI setting process is the transparency of the process at all stages. This is achieved by the quality system applied by the EU-LCI WG which consists of:

- Generating for each compound a summary factsheet with a standardised format (see section 2.4.3.1 of the present report) based on draft versions of the factsheets developed independently by at least two members of the EU-LCI WG (assessors). At the end of the draft summary factsheets a rationale is added explaining which study was used to derive the point-of-departure and how the assessment factors were applied. This allows potentially different approaches to be taken on board and maximises the possibility of obtaining an unbiased result when deriving the EU-LCI values. A final summary factsheet is produced after review of the draft factsheets by the entire EU-LCI WG.
- Ensuring the harmonised application of assessment factors and read-across elaborated by the EU-LCI WG and described in sections 2.5 and 2.6 of the present report. This is facilitated by the 'memorandum of decision' which tabulates the assessment factors agreed upon for the compounds assessed (see table 7). The use of this table ensures the harmonised application of assessment factors and facilitates identification of potential outliers for further review.
- Creating for each compound an EU-LCI "dossier" containing the final summary factsheet along with its associated data-collection sheet and a copy of the key-study (ies) used for the derivation of the EU-LCI value.

2.4.3.1 Standardised Summary Fact Sheet

To ensure that the derivation of EU-LCIs is transparent, a summary fact-sheet with a standardised format is generated for each compound. This comprises four main sections:

1. General information,
2. Toxicological database (values derived from the data compilation process described in chapter 2.4.1),
3. Assessment factors and
4. The derivation of the EU-LCI value.

Parameters in the factsheet are accompanied when necessary by an explanatory note.

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piling up of conservatism. Hence, the more extrapolation steps are taken into account, the higher the level of conservatism". (Source: Chapter R.8, page 67, ECHA Guidance on information requirements and chemical safety assessments, Version 2, December 2010).

A written 'rationale' explaining/justifying the selection of the key study(ies) and other key elements of the derivation of the EU-LCI value will always be provided and integrated into the standardised summary fact sheet.

The standardised summary fact sheet template developed by the EU-LCI preparatory WG is shown in Table 2.

Table 2. *Standardised Summary Fact Sheet Template*

Compound	**NAME OF COMPOUND**		***Factsheet***
Parameter	**Note[6]**	**Comments**	**Value / descriptor** *Please use the period (.) as decimal mark*
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	
EU-LCI status	2	interim / confirmed	
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS - NLP	
CAS-Nr.	6	Chemical Abstracts Service number	
Harmonised CLP classification	7	Human health risk related classification	
Molar mass	8	[g/mol]	
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	
Species	11	Rat,… human	
Route/type of study	12	Inhalation, oral feed, …	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	
POD Value	17	[mg/m^3] or [ppm]	
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	
AF Study length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF	22a	Reliability of dose-response,	

[6] Explanation of notes are found at the end of section 2.4.3.1

Dose-response		LOAEL → NOAEL	
	22b	Severity of effect *(R 8-6d)*	
Interspecies differences	23a	Allometric Metabolic rate *(R8-3)*	
	23b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	
AF Sensitive population	25	Children or other sensitive groups	
Other assessment factors: quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	..... µg/m³ ..... ppb
Molar adjustment factor	29	Used in read-across	
Rounded value (EU-LCI)	30	[µg/m³]	
Additional Comments	31		
RATIONALE Section	32		

Explanation of notes:

1) **EU-LCI value**: numerical value of the LCI in µg/m³ (mass/volume) – transcript of line 30.

2) **EU-LCI status**: interim or confirmed.

   Interim: approved by the EU-LCI WG
   Confirmed: approved by a formal body (potential future option)

3) **EU-LCI year of issue:** year when the EU-LCI value has been issued by the EU-LCI WG (or the formal body).

4) **CLP Number:** according to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Implementing the globally harmonized system of chemical classification or GHS.
   http://guidance.echa.europa.eu/docs/guidance_document/clp_introductory_en.pdf

5) **EC Number:** under European Inventory of Existing Commercial chemical Substances (EINECS), ELINCS (European List of Notified Chemical Substances) in support of Directive 92/32/EEC, the 7th amendment to Directive 67/548/EEC, NLP (No-Longer Polymers)
   See: ESIS: European chemical Substances Information System: http://esis.jrc.ec.europa.eu/index.php?PGM=dat

6) **CAS Number:** collection of disclosed chemical compound information by Chemical Abstracts Service. Almost all molecule databases can be searched by CAS Registry Number.

7) **Harmonised CLP classification:** CLP classification including CMR and other health relevant effects. In the case that classification is not harmonised, this should be stated. For self-classifications by industry the ECHA- CLP inventory can be searched at: http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database

8) **Molar mass:** symbol *M*, is a physical property characteristic of a given substance (chemical element or chemical compound), namely its mass per amount of substance [g/mol].

9) **Key study, Authors, Year:** bibliography (citation) including authors and year of publication of selected study demonstrating the toxic effect of concern and considered to be the most relevant and appropriate study selected for derivation of the EU-LCI.

10) **Read-across compound**: compound on which read-across is based (reference compound).

11) **Species:** animal species (rat, etc.), or human study.

12) **Type of study:** type and circumstances of the study, indicating the route of exposure (e.g. occupational, inhalation study, oral study). Inhalation studies to be preferred if available.

13) **Study length:** duration of the study in days

    a. Acute: Exposure by the oral, dermal, or inhalation route for 24 hours or less.
    b. Short-term: Repeated exposure(a) by the oral, dermal, or inhalation route for more than 24 hours and, up to 30 days.
    c. Subchronic: Repeated exposure by the oral, dermal, or inhalation route for more than 30 days, up to approximately 10 percent of the life span in humans (b) (more than 30 days and up to 90 days in typically used laboratory animal species(c)).
    d. Chronic: Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10 percent of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species)

14) **Exposure duration:** exposure conditions in hours per day and days per week.

15) **Critical endpoint:** critical toxicological effect observed in the study and used for derivation of the limit value. A critical effect is described as "either the adverse effect that first appears in the dose response curve, or as a known precursor to the first adverse effect."

16) **Point of departure (POD):** the dose corresponding to a given effect. Lowest concentration or dose at which the critical effect occurred or did not occur. The POD value is used for further derivation. POD will be mainly NOAEC*L, or LOAEC*L, BMD*L. It represents the lower confidence bound on the lowest experimental dose that showed an effect. Data from oral studies have to be converted to the corresponding inhalation dose data first (see note 21).

17) **POD value:** numerical value of the POD in [mg/m^3] or [ppm]. → Use the unit given in study.

18) **Assessment Factors (AF):** the numerical adjustment used to extrapolate from experimentally determined dose- response relationships to estimate the compound exposure at and above which adverse effects may occur in the population exposed. Assessment factors account for differences between species and variability within populations, as well as differences in study protocols and

exposure conditions (i.e. of the general population) and other uncertainties.

Table 3. *Default assessment factors*[7]

Assessment factor – accounting for differences in:		**Default value systemic effects**	**Default value local effects**
Interspecies	- correction for differences in metabolic rate per body weight - remaining differences	AS[a,b] 2.5	- 1[f] 2.5[g]
Intraspecies	- worker	5	5
	- general population	10[c]	10[c]
Exposure duration	- subacute to subchronic	3	3[h]
	- subchronic to chronic	2	2[h]
	- subacute to chronic	6	6[h]
Dose-response	- issues related to reliability of the dose-response incl. LOAEL-NOAEL extrapolation and severity of effect	1[d]	1[d]
Quality of whole database	- issues related to completeness and consistency of the available data - issues related to reliability of the alternative data	1[d] 1[e]	1[d] 1[e]

[a] AS = factor for allometric scaling (see Table 4)
[b] Caution should be taken when the starting point is an inhalation or diet study
[c] Not always covering for very young children; see text for deviations from default
[d] See text for deviation from default
[e] Special consideration needed on a case-by-case basis
[f] For effects on skin, eye and GI track via simple destruction of membranes
[g] For effects on skin, eye and GI track via local metabolism; for effects on respiratory tract
[h] For effects on respiratory tract

[7] Source: Table R.8-6 from REACH guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Table 4. *Allometric scaling factors for different species as compared to humans*[a][8]

Species	**Body weight (kg)**	**AS factor[b]**
Rat	0.250	4
Mouse	0.03	7
Hamster	0.11	5
Guinea pig	0.8	3
Rabbit	2	2.4
Monkey	4	2
Dog	18	1.4

[a] Assuming the human body weight is 70 kg
[b] Not applicable when setting an inhalation DNEL based on an inhalation animal study (see APPENDIX R. 8-2 of the following source: http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf)

19) **Adjustment for exposure duration:** adjustment for the exposure duration setting in the critical study; a repeated exposure may be continuous, periodic, or intermittent.

   a. A continuous exposure is a daily exposure for the total duration of interest.
   b. A periodic exposure is one occurring at regular intervals (e.g. inhalation exposure 6 hours/day, 5 days/week; or oral exposure 5 days/week).

   Note: After length and duration adjustment, the POD can be converted into a human equivalent concentration (HEC) from the experimental animal dose. The HEC is a human equivalent for 24hrs, 7 days (assumed 70-year) of continuous exposure.

20) **AF Study length:** adjustment for the study length, from short exposure periods to chronic exposure, i.e from s.a., s.c. to c (subacute, subchronic, chronic).

   Acute: Exposure by the oral, dermal, or inhalation route for 24 hours or less.

   Subacute: Repeated exposure (a) by the oral, dermal, or inhalation route for more than 24 hours, up to 30 days.

   Subchronic: Repeated exposure by the oral, dermal, or inhalation route for more than 30 days, up to approximately 10 percent of the life span in humans (b) (more than 30 days up to 90 days in typically used laboratory animal species(c)).

[8] Source: Table R.8-3 from REACH guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Chronic: Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10 percent of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species)

Table 5. *Assessment factors for duration extrapolation*[9]

Duration	Default assessment factor
Subchronic to chronic	2
Subacute to chronic	6
Subacute to subchronic	3

Note: - 'subchronic' usually refers to a 90 day study
- 'subacute' usually refers to a 28 day study
- 'chronic' usually refers to a 1.5 – 2 years study (for rodents)

21) **Route-to-route extrapolation factor:** approaches for deriving LCI using route-to-route extrapolation from non-inhalation studies. See for procedures: ECHA and IEH-IGHRC. See Guidelines on Route-to-Route Extrapolation of Toxicity Data when Assessing Health Risks of Chemicals (cr12) http://ieh.cranfield.ac.uk/ighrc/igpublications.html

22) **AF Dose response:**

22a) relates to the reliability of the dose-response relationship and LOAEL to NOAEL extrapolation.

22b) relates to the severity of effect[10]

The concept of severity of effect commonly used in toxicology is related to adversity and describes the severity of a particular outcome of exposure and the continuum of effects from physiological changes of uncertain significance to pathophysiological changes, morbidity, and finally, mortality. The reversibility of an outcome is often related to severity; generally, an outcome is considered more severe if it is irreversible.

Severity descriptors (ratings) commonly applied are:

- No-effects
- Mild effects that are reversible and do not interfere with normal function
- Moderate effects that alter organ function or interfere with normal activity but are reversible or effects that are irreversible but do not alter organ function or interfere with normal activity.
- Severe effects that are irreversible and alter organ function or interfere with normal activities

The term "adverse" in LOAEL distinguishes between outcomes that are detrimental to an organism and outcomes that are temporary physiological responses with no detrimental impact.

[9] Source: Table R.8-5 from REACH guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

[10] Source: Assessment of Exposure-Response Functions for Rocket-Emission Toxicants. Subcommittee on Rocket-Emission Toxicants, Committee on Toxicology, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council, NATIONAL ACADEMY PRESS, Washington, D.C., 1998

23) **Interspecies differences:**

23a) interspecies extrapolation factor i.e. dosimetric adjustment, uncertainty factor for allometric differences;
23b) kinetic and dynamic differences between the studied species and humans.

24) **Intraspecies differences:** intraspecies extrapolation factor, variation within the human population, an uncertainty factor for kinetic and dynamic differences.

25) **AF (sensitive population):** assessment factor for sensitive subgroups, which are not covered by the database and key study. Sensitive populations such as neonates and genetically sensitive subgroups, and also fetuses and children which may be particularly vulnerable during development and maturation.

26) **Other adjustment factors (quality of the whole database):** used to compensate for lack of knowledge and quality of whole database. Relates to completeness and consistency of the available data and reliability of alternative data on a case-by-case basis.

27) **Summary of assessment factors:** Total Assessment Factor (TAF) → product of all single factors used in the process (usually between 100 and 3000).

28) **POD/TAF:** numerical value in µg/m³ and ppbV (Conversion at 23 °C and 101.3 KPa)

1 mol ≈ 24.295084 liter
Conc.[µg/m³] = (Conc[ppbV] * M[g/mol]) / 24.295084 liter

29) **Molar adjustment factor:** only necessary if read-across is used. Factor used to adjust difference in molecular weight between the compound for which the LCI is derived and the compound on which read-across is based.

30) **Rounded value:** value of the EU-LCI rounded according to rounding rules in µg/m³.

Table 6. *Rounding rules*

Value size-range	Rule	Example	
		Before rounding	*After Rounding*
Tens: 10–50	Rounded to 5	13	15
Tens: 50–100	Rounded to tens	53	50
Hundreds	Rounded to fifties	123	100
Thousands	Rounded to hundreds	1568	1600
Ten thousands and twenty thousands	Rounded to thousands	17856	18000

Rounding rules:

- The EU-LCI calculation shall be rounded only at the end of the EU-LCI derivation process.
- Rounding is to be applied to EU-LCI values expressed as µg/m³
- All newly derived EU-LCI values shall be rounded as from the Table 6.

31) **Additional Comments:** additional relevant information from the data compilation sheet (e.g. odour, endocrine disrupting effects, known mixture effects).

32) **RATIONALE for derivation of the EU-LCI value:** The rationale section succinctly explains the the selection and use of key data in the derivation of the EU-LCI value, in particular the selection of the key study used to determine the point-of-departure value. It also, where necessary, explains

the use of particular assessment factors, especially non-default factors. The rationale normally comprises between half a page and a page of text.

2.5 Application of assessment factors in EU-LCI derivation

Assessment factors (AFs) are applied to the point of departure (POD) value to derive an EU-LCI value considered to be safe for humans (including children) following life-time exposure to VOCs emitted from a product. The selection of assessment factors is in accordance with REACH guidance on information requirements and chemical safety assessment (ECHA, 2012). The total assessment factor (TAF) value depends on whether the data are from human or animal studies, the duration of exposure in the study that supplies the POD, the type of POD used, and the completeness of the database that supports the POD. The TAF value may range from 1 to 3000 depending on the nature of the data used in the assessment.

2.5.1 Assessment factor for interspecies differences

This factor is applied when the POD is derived ***from experimental data*** from studies performed on animals. Assessment factors for interspecies differences cover uncertainties related to kinetic and dynamic differences between the studied species and humans. The dynamic differences can be related to anatomical differences, local metabolic effects and remaining species-specific differences. To account for differences in metabolic rate, allometric scaling factors as recommended in the ECHA Guidance are used (ECHA, Table R. 8.3) and for the remaining differences a default factor of 2.5 is applied.

Exposure to respiratory toxicants may cause adverse effects on the respiratory system (nose, pharynx, trachea, bronchi, and lungs). Respiratory toxicity includes a variety of acute and chronic pulmonary conditions, including local irritation, bronchitis, pulmonary edema, emphysema, and cancer.

In the case of ***respiratory toxicants***, only limited data are available for the purpose of quantitative interspecies comparison. However the small data set available has not produced any evidence of rodents being generally more sensitive to irritants than humans. Differences between rodent and human effect levels observed with some compounds may be interpreted as a tendency for somewhat greater sensitivity toward respiratory tract irritants in humans (Kalberlah *et al.,* 2002).

When the POD is derived ***from inhalation studies*** for systemic effects, no correction needs to be made for allometric differences (metabolic rate), because extrapolation is already based on the toxicological equivalence of concentration of a compound in the air: animals and humans breathe at a rate depending on their caloric requirements (allometric dose adjustment).

When the POD is related to ***local effects***, no correction has to be made for differences in systemic metabolism.

For remaining specific differences, a default value of 1 is used for effects on skin, eye and GI tract if the mode of action implies only a simple destruction of membranes, and a default value of 2.5 is used for effects on the skin, eye and GI tract if local metabolism or

receptor binding reactions are involved. A factor of 2.5 is also applied for local effects on the respiratory tract (ECHA, Table R. 8.6)

For compounds for which specific data are available, other values may be applied based on a case by case approach and expert judgment.

2.5.2 Assessment factor for intraspecies differences

The response of humans to exposure of xenobiotic compounds may vary because of a number of biological factors such as age, sex, genetic composition, disease status, etc. To account for this variability, a default factor of 10 is generally considered conservative enough for the general population but not always covering for very young children according to the ECHA guidance (Table R. 8.6). A case by case value would be thus preferred.

When the POD is derived from human occupational data, since some intraspecies variability between workers is already included (if the number of workers is sufficient to be representative of this population), the EU-LCI WG recommends applying a default factor of 5 to take into account vulnerable population including children. When the POD is derived from a single human study in a test chamber, as population variability is not covered, a factor of 10 should be applied as default. In the case of a sensory irritation chamber study with a sufficient number of subjects (men and women) a smaller factor of 5 might be selected, based on a case by case evaluation.

Concern has been raised about the special susceptibility of children to the toxicity of chemicals. To take into account the potential increased susceptibility of children to chemicals, due to their biological differences from adults, the application of an extra 10-fold inter individual factor is recommended by some organizations (e.g. US-EPA's Food Quality Protection Act, 1996). Concerning the susceptibility of some vulnerable populations such as elderly or early infancy in general, it is assumed that the default factor of 10 for intraspecies (human to human) variations is sufficient to account for differences between general population and vulnerable groups in most cases. Renwick *et al*. (2000), considers that available data do not provide a scientific rationale for an extra factor for children. Recently, Ginsberg *et al.* (2010) analysed information regarding child/adult intake and dosimetry differences for particles and gases for potential application to risk assessment. They concluded that these differences exist and are not usually captured by standard interspecies adjustment factors. However, for a life time risk assessment, incorporation of children's inhalation intake to the assessment would lead to an effective increase in exposure and risk of 1.6 fold. The EU-LCI WG considers that this value is already covered by the intraspecies assessment factor and no specific extra factor for children is by default needed.

If, for a specific compound, effects on the reproductive, endocrine, immune or nervous systems are suspected, then a specific assessment factor for children might be used, based on a case by case approach (Kemi, 2003; ECHA, 2012; RIVM report 613340005, 2002). Factors of 3 or 10 could then be used in those cases when there are reasons for concern for these severe effects in children.

A specific assessment factor for children might also be used in case the database for a compound is considered too poor for evaluation of the toxicity to children. In this case a factor of 1-10 may be applied to compensate.

For compounds for which specific data are available, other values may be applied based on a case by case approach and expert judgment. It is considered that information on intraspecies variation for local (concentration-dependent) effects is very scarce and no attempt has therefore been made to refine the default intraspecies factors already used for systemic effects.

For local effects, the assessment factors to be used for intraspecies differences are therefore the same as those proposed above for systemic effects.

It is to be noted that, as is the case for interspecies assessment factors, relevant substance-specific information on intraspecies variations should always be used to adjust or substitute the default factors (WHO/IPCS, 2005).

2.5.3 Extrapolation from short exposure periods to chronic exposure

LCIs are used to assess lifetime exposure to emitted compounds from a product, corresponding to a "chronic exposure". The EU-LCI WG considers that in this context of deriving EU-LCI values, an exposure of 10 years or more would be considered as a chronic exposure and no adjustment for time duration of the key study is required.

The assessment factor for study length concerns the adjustment for the study length, from short exposure periods to chronic exposure (subacute, subchronic, chronic). These latter terms are defined below (see also Table R.8-5 of the ECHA Guidance (ECHA, 2012)):

- Acute: Exposure by the oral, dermal, or inhalation route for 24 hours or less.

- Subacute: Repeated exposure (a) by the oral, dermal, or inhalation route for more than 24 hours, up to 30 days.

- Subchronic: Repeated exposure by the oral, dermal, or inhalation route for more than 30 days, up to approximately 10 percent of the life span in humans (b) (more than 30 days up to 90 days in typically used laboratory animal species(c)).

- Chronic: Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10 percent of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species).

When only subacute or subchronic data are available, an assessment factor is applied to take into account duration. The default values for this factor are based on Table R.8-5 of the ECHA Guidance (ECHA, 2012):

- Subacute to chronic: AF = 6
- Subchronic to chronic: AF = 2

For compounds for which specific data are available, other values may be applied based on a case by case approach and expert judgment. In particular, whether this assessment factor also applies to inhalation and dermal studies is questionable. It might be possible that the exposure period influences the toxicological effects that depend on the route of exposure. In the absence of compound-specific data, or in cases where the data cannot be readily assessed, available data supports default time extrapolation factors for local

(respiratory) effects similar to those proposed for systemic effects (Kalberlah *et al.,* 2002).

2.5.4 Assessment factor to adjust for exposure duration

Characterizing the hazards of inhaled toxicants generally includes extrapolation from observations on animals that are subjected to intermittent or subchronic exposures, to a human environmental context of usually continuous exposure.

Adjustment of duration to a lifetime continuous exposure is currently applied as a default assumption to derive inhalation non-cancer reference values in risk assessment. This accounts for differences in the exposure pathway (for example, in laboratory assays, rodents are usually exposed for several hours a day, five days a week for several months, whereas workers are exposed for 8 hours a day for five days a week). The exposure duration adjustment factor is calculated using a simple linear relationship. This assumes, for a given chemical compound, that the same calculated values of the concentration of exposure multiplied by the duration of exposure will yield the same biological response (Haber's rule) (Belkebir *et al*., 2011).

After duration adjustment, the POD will be converted into a human equivalent concentration (HEC) from the experimental animal dose. The HEC is a human equivalent for 24 hrs, 7 days a week of continuous exposure.

For compounds for which specific data are available, other adjustments may be applied based on a case by case approach and expert judgment. For example, where toxicity depends on the (peak) concentration rather than on the exposure duration, a time adjustment based on the experimental data for short term exposure could lead to an overestimation of risks. It may be assumed that the effects induced by direct contact with the respiratory tract are directly related to the concentration of exposure. Exposure duration would in this case exert a relatively weak influence on the induction of these lesions.

2.5.5 Assessment factor for dose-response

When no data are available to identify a clear NOAEL, a LOAEL may be used as a POD to derive an EU-LCI. An assessment factor may then be applied to the LOAEL to estimate the NOAEL. However, there is no guarantee that extrapolation of a LOAEL with any chosen factor will yield a true estimate of the NOAEL. The ratio between LOAEL and NOAEL is strongly linked to the dose spacing used. Therefore this factor can only be assigned using expert judgment in which the shape of the dose-response curve and the magnitude of the effect at the LOAEL is considered (Vermeire *et al*., 1999). By default and in line with REACH guidance, a tentative factor of 3 is applied in the EU- LCI setting process.

Besides the use of a LOAEL or NOAEL a benchmark dose approach (e.g. BMD_{10} as LOAEL and $BMDL_5$ as NOAEL) can be used to determine the POD (EFSA, 2009). The selection of the most appropriate POD is done by expert judgement.

2.5.6 Other assessment factors

Factors to consider with regard to missing data:

- In cases where animal bioassays are missing from a complete data base, the critical NOAEL needs to be adjusted to account for the impact of the missing bioassay(s). (Evans and Baird, 1998). Such adjustment depends on the definition of a "sufficient" database (and the quality of the data) in the context of deriving the EU-LCI, the data already available and those missing. Evans and Baird have shown that both the number of bioassays available and the specific bioassay(s) available may influence the estimate of the critical NOAEL from an incomplete data set. When it is considered necessary, the EU-LCI WG will apply a default value of 3 for this factor.

Severity of effects:

- Factors to consider concerning the severity of effect: The type of critical effect on which the EU-LCI is based should be taken into account. Depending on the severity of the effect for human health (e.g. severe and irreversible), extra assessment factors may be applied by expert judgment on a case by case approach. Therefore, the EU-LCI WG considers that no extra default correction factor is necessary.
- The extent and severity of the effects seen at the LOAEL in reproductive toxicity studies may in some cases be significant (e.g. extensive foetal or offspring death, major malformations, severe functional defects in the offspring, infertility or severe effects on the reproductive system). This should be reflected in the use of an appropriate assessment factor to account for the uncertainty related with the 'dose-response relationship' (ECHA section R.8.4.3.1).

An overview on the harmonised application of assessment factors in the context of the EU-LCI setting is given in Table 7 for the priority compounds treated by the EU-LCI WG and reported in chapter 3 of the present report.

Table 7. *Overview table on harmonised application of assessment factors in the context of the EU-LCI setting*

VERSION: 07 January 2013		Trimethyl-benzenes	Xylenes	Butoxyethanol	Acetaldehyde	Styrene	p-Dichlorobenzene	Toluene	Ethyl-benzene	n-Butanal	ε-Caprolactam	a-Pinene
		Compounds assessed with priority (1)								*Additionally assessed compounds (2)*		
STANDARDISED SUMMARY FACTSHEET'S PARAMETERS	**STANDARDISED SUMMARY FACTSHEET LINE**											
Critical effect	*15*	Neurotox and local effects on lungs	Irritation	Hematology, hemolysis, liver hemosiderin deposition	Nasal irritation, (olfact damage?)	Neurotox, genotox & hearing loss	Carcinogenic, respiratory effects/damage	Neurological effects (color vision impairment)	Ototoxicity (outer hair cells of the cochlear)	Irritation (squamous metaplasia of the nasal cavity)	Irritation of respiratory tissues	Bladder epithelial changes
LOAEL/NOAEL	*16*	NOAEC	LOAEC	NOAEC	NOAEC	LOAEC	NOAEC	LOAEC	LOAEC	NOAEC	NOAEC	NOAEC
Species	*11*	Rat	Human (workers)	F344-Rat	Rat	Human (workers)	Rodents	Human (workers)	Rat	Rat	Rat	Mouse
ASSESSMENT FACTORS												
Adjustment for exposure duration [h/d, d/w]	*19*	5.6	4.2	5.6	5.6	4.2	5.6	4.2	4.7	5.6	5.6	5.6
AF Study Length [sa --> sc --> c]	*20*	2	2	2	2				2	2	3	2
Route-to-route extrapolation factor	*21*											
AF Dose Response: reliability of dose-response LOAEL--> NOAEL	*22a*		3			3		2	3			
AF Dose Response: severity of effect	*22b*				2	3	5					
Interspecies: allometric metabolic rate	*23a*											

VERSION: 07 January 2013		Trimethyl-benzenes	Xylenes	Butoxyethanol	Acetaldehyde	Styrene	p-Dichlorobenzene	Toluene	Ethyl-benzene	n-Butanal	ε-Caprolactam	a-Pinene
		Compounds assessed with priority (1)								*Additionally assessed compounds (2)*		
STANDARDISED SUMMARY FACTSHEET'S PARAMETERS	**STANDARDISED SUMMARY FACTSHEET LINE**											
ASSESSMENT FACTORS												
Interspecies: kinetic+dynamic	*23b*	2.5					2.5		3.6			
Intraspecies: kinetic+dynamic / Worker - General Population	*24*	10	5	10	10	5	10	5	10	10	5	10
AF Sensitive population	*25*											
Other assessment factors: quality of whole database	*26*									2		
Total Assessment Factor (TAF)	*27*	**280**	**126**	**112**	**224**	**189**	**700**	**42**	**1015**	**224**	**84**	**112**
Point of Departure (POD) Value	*17*	123 mg/m³	14.2 ppm	25 ppm	275 mg/m³	10 ppm	20 ppm	123 mg/m³	200 ppm	50 ppm	24 mg/m³	50 ppm
EU-LCI Value [µg/m³]	*1 & 30*	**450**	**500**	**1100**	**1200**	**250**	**150**	**2900**	**850**	**650**	**300**	**2500**

(1) Compounds in the EU-LCI masterlist list which were assessed with priority and with 'derived interim' EU-LCI values

(2) Compounds in the EU-LCI masterlist with 'derived interim' EU-LCI values which were assessed additonally to those under (1)

2.6 Read-across guidance for EU-LCI derivation

For some chemicals, because of lack of adequate studies and experimental data, the EU-LCI value cannot be derived directly. In these cases hazard assessment within REACH may rely upon predictive approaches such as read-across and grouping of substances (ECHA, 2008). If test data are available on a range of chemicals with similar structure, it is possible to extrapolate, with confidence, from data-rich compounds to data-poor compounds provided that they are structurally closely related. As subtle changes in chemical structure can have a significant impact on biological activity, especially if the toxicity is mediated by binding to a receptor, certain minimum criteria need to be considered when undertaking hazard assessment using predictive approaches. It is important to be aware of the limitations of predictive approaches and the basic requirements associated with their use in human health hazard assessment (IGHRC, 2013).

2.6.1 General considerations

For data poor compounds, LCIs have been established by AgBB (60 compounds in 2012) and ANSES (50 compounds) by applying read-across on the basis of chemical structural similarity.

A major difference between the ANSES and the AgBB LCI lists is that AgBB applies molar adjustment to the read-across derived LCI values whereas ANSES does not. This results in different LCI values between these two lists as can be seen in Figure 1.

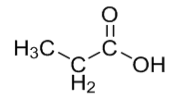
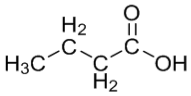
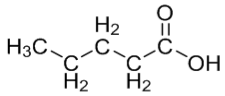
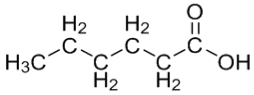
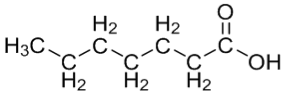
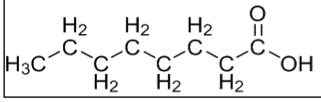
	NIK	CLI
	[µg m^{-3}]	
 propionic acid (**9-2**)	310	300
 butyric acid (**9-4**)	370	300
 n-pentanoic acid (**9-6**)	420	300
 n-hexanoic acid (**9-7**)	490	300
 n-heptanoic acid (**9-8**)	550	300
 n-octanoic acid (**9-9**)	600	300

Figure 1. *Differences of read-across derived LCIs in AgBB (NIK) and ANSES (CLI) due to molar adjustment*

When EU-LCIs are established for data-poor compounds by read-across, a justification is provided, including the argumentation for grouping or identification of homologue compounds – e.g. structural similarities between homologue compounds (common functional groups, or common precursors or breakdown products).

In the context of the EU-LCI work, derivation of an EU-LCI value for a data poor compound is thus based on read-across of information from one or several data- rich homologue compound(s). The justification shall contain a clear explanation to be transparent, consistent and traceable. Any points of uncertainty should be mentioned.

Application of read-across can only be justified if there is a reasonable indication that the homologue compounds have the same health endpoint(s). This is assessed and documented before the read-across is carried out. Although standardization of methods for read-across would benefit consistency, experience from read-across applied in similar contexts (e.g. LCI setting in the German AgBB scheme; use of read-across in setting OEL values[11]) has shown that the applicability of read-across methods needs to be evaluated on a case-by-case basis and requires expert judgment.

Nonetheless, a degree of standardization for read-across of EU-LCI values can be achieved by adopting the following approaches:

- Whenever possible, the EU-LCI value is derived by read-across from a compound with an existing EU-LCI value within the same chemical class.
- If no EU-LCI value is available for a homologue of the compound of interest then read-across is not possible, unless sufficient toxicological information is available to firstly derive a *de novo* EU-LCI value for a close homologue according to the EU-LCI procedure, which can then be used for the read-across process to derive an EU-LCI value for the compound of interest.
- When EU-LCI values are available for more than one compound within the same chemical class, read-across uses as a starting point the EU-LCI value for that homologous compound within the category which has the closest analogy in structure, functional groups and molecular weight and assuming the same endpoint as the compound for which the EU-LCI value is to be derived. Identification of the 'closest homologue' is based on expert judgment, preferably supported by existing tools and guidelines (e.g. by ECHA[12], Organisation for Economic Co-operation and Development (OECD) QSAR toolbox[13], European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), etc.) on how to undertake read-across. In the case that there is no unequivocal choice of compound having the 'closest homology to the compound for read-across' among the different compounds in the same category, read-across shall start from the compound with the lowest EU-LCI value. However, deviations from this rule of thumb may be possible, so long as a justification is provided.
- If QSAR analysis or specific functional groups indicate that the toxicity of the compound could be higher, or that endpoints different from those of the compounds on which the read-across might dominate, an additional uncertainty factor (AF) shall

[11] ECETOC Technical Report 101: Guidance for setting Occupational Exposure Limits (OELs): emphasis on data-poor substances.
[12] REACH – Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of chemicals
[13] http://www.oecd.org/env/existingchemicals/qsar

be applied, or the decision may be taken that no EU-LCI value by read-across can be derived.

- When performing read-across, the molar adjustment principle and rules shall be applied (see below).
- Certain quality criteria about the key study should be applied prior to carrying out read-across.

2.6.2 Molar adjustment

Molar adjustment in read-across accounts for the fact that the activity of a compound in air (or in solution) is driven by the number of molecules per unit air (or solution), rather than by the mass of the compound per unit air (or solution) (concentration – expressed as $\mu g/m^3$ or mg/m^3). Thus, read-across from one homologue to another should be done on a molarity basis, or, when read-across is on a $\mu g/m^3$ basis, by applying a molar adjustment factor accounting for differences in molecular weight (MW) between the two homologues. This approach recognizes that a common functional group(s) of the homologues is driving the health effect, and not – or to a lesser extent - the difference in (aliphatic saturated) chain length between the homologues.

In addition, the reactivity of functional groups may be counteracted by steric and electronic factors in larger molecules. Conversely, larger lipophilic residues may facilitate intracellular bioavailability and, hence, increase toxicological activities. Sometimes toxicological properties may be mediated by the whole molecule rather than by a prominent functional group (e.g. local irritation by hydrocarbons) and in such cases it may be inappropriate to extrapolate on a molar basis. The complexity of these issues indicates that the approach employed should not be too formalistic, and that read-across from compounds with a short aliphatic chain to a large aliphatic chain should be performed with caution.

The EU-LCI WG working group considers that if read-across is applied for homologues beyond two additional CH_2 groups per aliphatic chain, molar adjustment for larger molecules shall be confined to an arbitrary cut-off of two additional CH_2 groups per aliphatic chain compared to the homologue compound from which the read-across starts (cut-off rule).

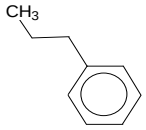
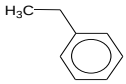
When applying read-across, the unrounded EU-LCI value of the homologue compound, which serves as the basis for the read-across, is used.

2.6.3 Examples of read-across used in the derivation of EU-LCI Values

Example 1: *n-Propylbenzene*

- Data poor compound: no adequate toxicological data for n-propylbenzene; *de novo* derivation of EU-LCI for n-propylbenzene is not possible.
- Read across from EU-LCI value of ethylbenzene: within the chemical class 'saturated aromatic hydrocarbons', ethylbenzene is the closest homologue compound with an EU-LCI value: one additional CH_2 group in the aliphatic side chain of n-propylbenzene.

- Toxicological critical endpoint for ethylbenzene: ototoxicity.
- The key assumption underlying the read across of the EU-LCI value from ethylbenzene to propylbenzene is that both compounds have the same critical endpoint (ototoxicity) and this is caused by the common functional group (and not by the additional CH_2 group).

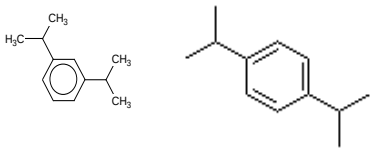
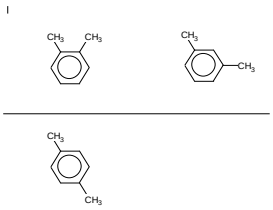
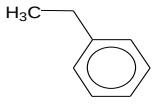
Compound	Structure	MW [g/mol]	EU-LCI value
n-Propylbenzene		120.19	? (read-across to be used) *950 µg/m³*
Ethylbenzene		106.17	850 µg/m³ (*de novo* protocol) Unrounded value: 860.6 µg/m³ or 197 ppb

- Unrounded EU-LCI value ethylbenzene: 197 ppb → to be used for read across EU-LCI of n-propylbenzene.

  No cut-off rule in place: difference in change length between the two homologue compounds is smaller than two CH_2 groups per aliphatic chain.
- Thus, EU-LCI value for n-propylbenzene is 197 ppb. After MW conversion: EU-LCI n-propylbenzene = 974.3 µg/m³ → rounded to 950 µg/m³.

Example 2: *Diisopropylbenzene (1,3-, 1,4-)*

- Data poor compound: no adequate toxicological data for diisopropylbenzene (1,3-, 1,4-); de novo derivation of EU-LCI diisopropylbenzene is not possible.
- Read-across candidate compounds for starting value: within the chemical class of 'saturated aromatic hydrocarbons' xylene and ethylbenzene are two compounds with EU-LCI values and having similar 'closest homologue' to diisopropylbenzene (1,3-, 1,4). Cumene (=isopropylbenzene) is another possible homologue, but it has no EU-LCI value.
- Toxicological critical endpoints for homologue compounds:
  - xylene: effects on central nervous system (CNS) (and irritation);
  - ethylbenzene: ototoxicity.
- Of these compounds, xylene has the lowest EU-LCI value (112.6 ppb). Thus, as a conservative approach, xylene is used as most appropriate homologue compound as starting point for the read across.
- The key assumption underlying the read across of the EU-LCI value from xylene to diisopropylbenzene (1,3-, 1,4-) is that both compounds have the same critical endpoint (CNS effects) and this endpoint is caused by the common functional group (and not by the additional CH_2 groups).

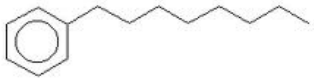
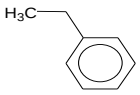
Compounds	Structure	MW [g/mol]	EU-LCI value
Diisopropylbenzene (1,3-, 1,4-)		162.27	? (read-across to be used) *750 µg/m³*
Xylene		106.17	500 µg/m³ (*de novo* protocol) Unrounded value: 491.9 µg/m³ or 112.6 ppb
Ethylbenzene		106.17	850 µg/m³ (*de novo* protocol) Unrounded value: 860.6 µg/m³ or 197 ppb

- No cut-off rule in place: difference in change length between the two homologue compounds is smaller than two CH_2 groups per aliphatic chain.

- Thus, the EU-LCI value for diisopropylbenzene (1,3-, 1,4-) is 112.6 ppb. After MW conversion : EU-LCI diisopropylbenzene (1,3-, 1,4-) = 751.8 µg/m^3 →to be rounded to 750 µg/m^3.

Example 3: *Phenyl octane and isomers*

- Data poor compound: no adequate toxicological data for phenyl octane; de novo derivation of phenyl octane not possible.
- Read-across candidate compounds for starting value: within the chemical class of 'saturated aromatic hydrocarbons' ethylbenzene is the closest homologue with an EU-LCI value; phenyl octane having additional $(CH_2)_6$ groups in the aliphatic chain compared to ethylbenzene. EU-LCI value for ethylbenzene: 197 ppb.
- Toxicological critical endpoints for homologue compounds:
  Ethylbenzene: ototoxicity, assuming the critical endpoint for phenyl octane is ototoxicity.

Compound	Structure	MW [g/mol]	EU-LCI value
Phenyl octane and isomers		190.32	? (read-across to be used) *1100 µg/m^3*
ethylbenzene		106.17	850 µg/m^2 (*de novo* protocol) Unrounded value: 860.6 µg/m^3 or 197 ppb

- The key assumption underlying the read across of the EU-LCI value from ethylbenzene to phenyl octane is that both compounds have the same critical endpoint (ototoxicity) and that this endpoint is caused by the common functional group (and not by the additional CH_2 groups).
- The cut-off rule on the molar adjustment factor is applicable: difference in change length between the two homologue compounds is larger than two CH_2 groups per aliphatic chain.
- Thus after applying the MW conversion: EU LCI phenyl octane= 1088.0 µg/m^3 → to be rounded to 1100 µg/m^3.

EU-LCI values were derived by applying read-across for the following compounds listed in the EU-LCI master list (table 9): n-propylbenzene, diisopropylbenzene (1,3-, 1,4-), phenyloctane and isomers, pentanal, hexanal, heptanal, octanal, nonanal, decanal, 2-ethylhexanal. The factsheets for these compounds are reported in Appendix A.

2.7 References

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3. EU-LCI DERIVATION FOR PRIORITY COMPOUNDS

To start with deriving EU-LCI values and also to support the harmonisation activities of DG ENTR's *ad hoc* group on classes and CEN/TC 351/WG 2, the EU-LCI WG treated with priority the compounds listed in Table 8.

Table 8. *Prioritised compounds for deriving EU-LCIs*

Compound	CAS No.
1,2,4-Trimethylbenzene	95-63-6
2-Butoxyethanol	111-76-2
Toluene	108-88-3
Xylene	1330-20-7
1,4-Dichlorobenzene	106-46-7
Ethylbenzene	100-41-4
Styrene	100-42-5
Acetaldehyde	75-07-0
Tetrachloroethylene	127-18-4
Formaldehyde	50-00-0
ε-Caprolactam	105-60-2
α-Pinene	80-56-8
n-Butanal	123-72-8

These 13 compounds (with their associated data) also served the purpose of testing, improving and finalising the protocol for the *de novo* derivation of EU-LCI values.

In Table 8, LCI values for the compounds shaded in *blue* are very similar (or equal) in the AgBB and ANSES lists. LCI values for the compounds shaded in *green* differ significantly between these two systems.

With regard to formaldehyde (shaded in *red* in Table 8), the *de novo* derivation of an EU-LCI value was postponed until a decision was made on its European harmonised classification and labelling. It is noted that based on a REACH Annex XV dossier, the ECHA Committee for Risk Assessment (RAC) in December 2012 (i.e. since the last meeting of the EU-LCI WG) adopted an opinion on a European harmonised classification and labeling for formaldehyde[14] classifying it as category 1B carcinogen and not as 1A category which proposed by France. The future *de novo* derivation of an EU-LCI value for formaldehyde will take into consideration the aforementioned ECHA opinion. Tetrachloroethylene is among the compounds for which their EU-LCI derivation is pending.

The compounds shaded in *orange* in Table 8 are compounds of recent concern in Germany (ε-caprolactam) and Belgium (α-Pinene). An EU-LCI value for n-butanal (shaded in *yellow*) was also derived as it served as starting value for read-across derivation of EU-LCIs for homologous aldehydes.

The data collection sheets and the summary factsheets of the compounds which were treated with priority by the EU-LCI WG are reported in Appendix A.

[14] http://echa.europa.eu/view-article/-/journal_content/c89bdb13-09e9-497c-8e73-ddae13a842c8

4. EU-LCI MASTER LIST

Following the principles and rationale for the establishment of EU-LCI values (chapter 2.3) and the application of the protocol for the *de novo* derivation of EU-LCI values (chapter 2.4) for the priority compounds (chapter 3), an EU-LCI master list was compiled by the EU-LCI WG in 2013.

The EU-LCI master list contains a total of 177 compounds and is subdivided into two groups, the first containing 82 compounds with agreed interim ('ascribed' or 'derived') EU-LCI values and the second containing 95 compounds for which EU-LCI values are still to be derived.

82 compounds with agreed interim ('*ascribed*' or '*derived*') EU-LCI values

- 21 compounds with interim 'derived' EU-LCI values according to the *de novo* EU-LCI protocol and the procedure for read-across.
- 61 compounds with interim 'ascribed' EU-LCI values according to the rationale for derivation of EU-LCIs (same or very similar (difference within 20%) NIK (Niedrigste Interessierende Konzentration) / CLI (Concentration Limite d'Intérêt) values in the German and French lists).

95 compounds with EU-LCI values '*with derivation pending*'

- 40 compounds for which EU-LCI values should be derived by read-across
- 29 compounds with different LCI values in AgBB and ANSES lists due to different derivation basis
- 24 compounds which are only present in either the AgBB or the ANSES list
- 1 compound with same key study for LCI derivation in both AgBB and ANSES but different LCI values due tothe application of different assessment factors (2-Ethylhexanoic acid)
- 1 compound for which an EU-LCI value currently cannot be derived (Benzaldehyde) due to limitations of underlying human and animal studies and lack of a sufficient and transparent database.

The composition of the EU-LCI master list (version as of July 2013) is graphically presented in Figure 2.

The content of the EU-LCI master list (as of July 2013) is reported in Table 9.

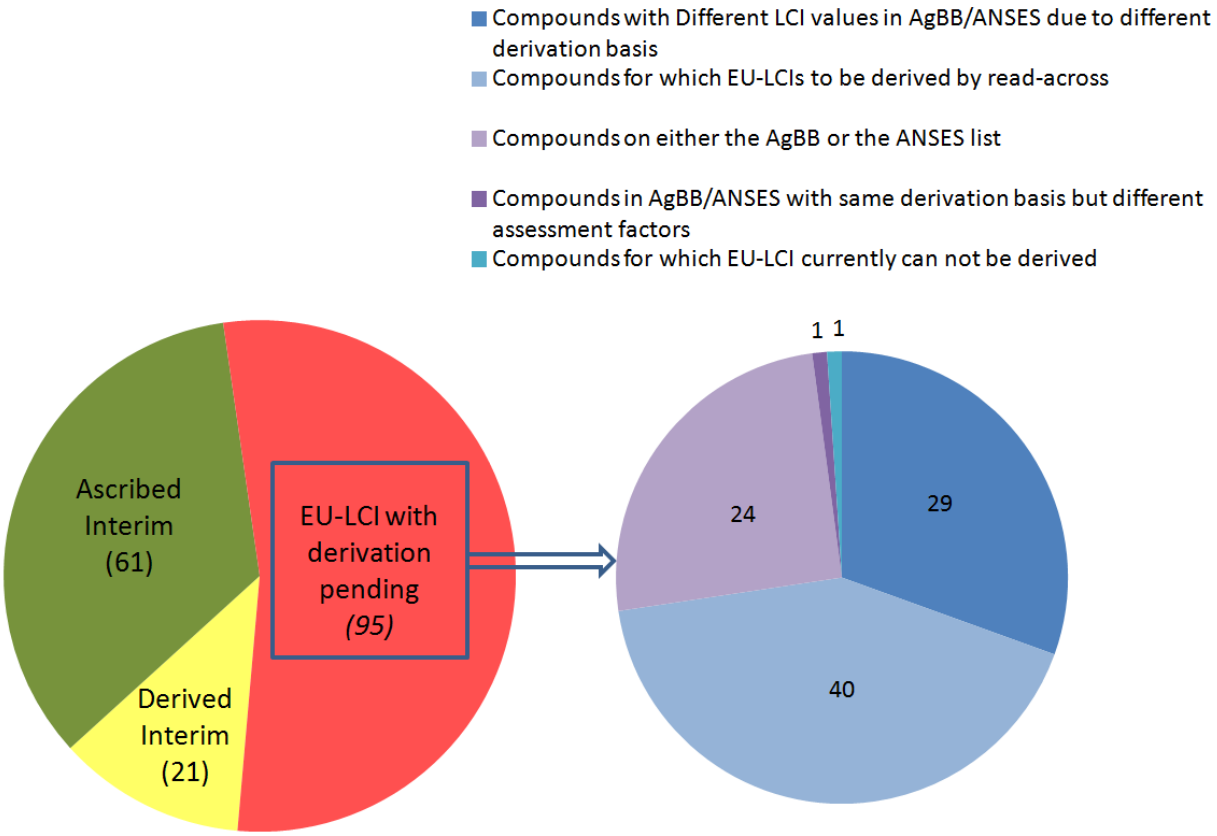

Figure 2. *The composition of the EU-LCI master list (as of July 2013)*

Table 9. *The content of the EU-LCI Master List (as of July 2013)*

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
1		**AROMATIC HYDROCARBONS**							
1-1	108-88-3	**Toluene**	**2900**	1900	EU: Repr. 2; Individ. substance evaluation	300	VG Index 2005; EU Repr. Cat. 3		'Derived' Interim EU-LCI
1-2	100-41-4	**Ethylbenzene**	**850**	880	OEL D	750	VTR RIVM		'Derived' Interim EU-LCI
1-3	1330-20-7 106-42-3 108-38-3 95-47-6	**Xylene (o-, m-, p-) and mix of o-, m- and p-xylene isomers**	**500**	2200	EU-OEL	200	VG Index		'Derived' Interim EU-LCI
1-4	98-82-8	**Isopropylbenzene (Cumene)**		1000	EU-OEL/OEL D	400	VTR IRIS US EPA		EU-LCI 'with derivation pending'
1-5	103-65-1	**n-Propylbenzene**	**950**	1000	cf. lowest LCI of saturated alkylbenzenes 1-6; EU-OEL/OEL D	200	Analogy xylene 1-3; VG Index	**Procedure for read-across applied**	'Derived' Interim EU-LCI
1-6	108-67-8 95-63-6 526-73-8	**Trimethylbenzene (1,2,3-;1,2,4-;1,3,5-)**	**450**	1000	EU-OEL/OEL D	1000	OEL F		'Derived' Interim EU-LCI
1-7	611-14-3	**2-Ethyltoluene**		1000	cf. lowest LCI of saturated alkylbenzenes 1-6; EU-OEL/OEL D	200	Analogy 1-3; VG Index	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
1-8	527-84-4 535-77-3 99-87-6 25155-15-1	**Cymene (o-,m-,p-) (1-Isopropyl-2(3,4)-methylbenzene) and mix of o-,m- and p-cymene**	**1000**	1100	cf. lowest LCI of saturated alkylbenzenes 1-6; conversion via molecular weight; EU-OEL/OEL D	1000	OEL Belgium	**Precautionary approach by adopting the lower value**	'Ascribed' Interim EU-LCI

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			Interim	AgBB		AFSSET/ ANSES			
			2012	2012		2009			
1		AROMATIC HYDROCARBONS							
1-9	95-93-2	1,2,4,5-Tetramethylbenzene		1100	cf. lowest LCI of saturated alkylbenzenes 1-6; conversion via molecular weight; EU-OEL/OEL D	200	Analogy 1-3; VG Index	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
1-10	104-51-8	n-Butylbenzene		1100	cf. lowest LCI of saturated alkylbenzenes 1-6; conversion via molecular weight; EU-OEL/OEL D	200	Analogy 1-3; VG Index	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
1-11	99-62-7 100-18-5	Diisopropylbenzene (1,3-;1,4-)	750	1400	cf. lowest LCI of saturated alkylbenzenes 1-6; conversion via molecular weight; EU-OEL/OEL D	200	Analogy 1-3; VG Index	Procedure for read-across applied	'Derived' Interim EU-LCI
1-12	2189-60-8	Phenyl octane and isomers	1100	1600	cf. lowest LCI of saturated alkylbenzenes 1-6; conversion via molecular weight; EU-OEL/OEL D	200	Analogy 1-3; VG Index	Procedure for read-across applied	'Derived' Interim EU-LCI
1-13	104-72-3	Phenyl decane and isomers		1800	cf. lowest LCI of saturated alkylbenzenes 1-6; conversion via molecular weight; EU-OEL/OEL D	200	Analogy 1-3; VG Index	Procedure for read-across to be applied	EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
1		**AROMATIC HYDROCARBONS**							
1-14	6742-54-7	**Phenyl undecane and isomers**		1900	cf. lowest LCI of saturated alkylbenzenes 1-6; conversion via molecular weight; EU-OEL/OEL D	200	Analogy 1-3; VG Index	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
1-15	4994-16-5	**4-Phenyl cyclohexene (4-PCH)**		1300	cf. styrene (1-16); conversion via molecular weight; OEL D	250	Analogy 1-3; VG Index	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
1-16	100-42-5	**Styrene**	**250**	860	OEL D	250	VG Index		'Derived' Interim EU-LCI
1-17	98-83-9	**2-Phenylpropene (α-Methylstyrene)**		2500	EU-OEL/OEL D	1200	OEL F		EU-LCI 'with derivation pending'
1-18	637-50-3	**1-Propenyl benzene (ß-methyl styrene)**		2400	EU-OEL for α-methyl styrene (1-17): 246000 µg/m³	1200	Analogy 1-17; OEL F	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
1-19	536-74-3	**Phenyl acetylene**		840	cf. Styrene (1-16); conversion via molecular weight; OEL D	250	Analogy 1-16; VG Index	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
1-20	611-15-4 100-80-1 622-97-9 25013-15-4	**Vinyl toluene (o-, m-, p-) and mix of o-,m- and p-vinyl toluene**		4900	OEL D	2400	OEL F		EU-LCI 'with derivation pending'
1-21	1074-17-5 1074-43-7	**1-Methyl-2(3)-propylbenzene**				200	Analogy 1-3; VG Index		EU-LCI 'with derivation pending'
1-22		**Other alkylbenzenes, as long as indiv. isomers have not to be evaluated differently**		1000	cf. lowest LCI of saturated alkylbenzenes 1-6; EU-OEL/OEL D				EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			Interim	AgBB		AFSSET/ ANSES			
			2012	2012		2009			
1		AROMATIC HYDROCARBONS							
1-23	91-20-3	Naphthalene		5	EU: Carc. 2; OEL D; LCI value changed	10	VG AFSSET; EU Carc. Cat. 3		EU-LCI 'with derivation pending'
1-24	91-17-8	Decahydronaphthalene				1000	OEL Poland		EU-LCI 'with derivation pending'
1-25	95-13-6	Indene	450	450	OEL Denmark, F: 45000 µg/m³	450	OEL F		'Ascribed' Interim EU-LCI
2		SATURATED ALIPHATIC HYDROCARBONS (n-, iso- and cyclo-)							
2-1	110-54-3	n-Hexane		72	EU-OEL; EU: Repr. 2	700	VTR IRIS US EPA; EU Repr. Cat. 3		EU-LCI 'with derivation pending'
2-2	110-82-7	Cyclohexane	6000	7000	EU-OEL/OEL D	6000	VTR IRIS US EPA	Precautionary approach by adopting the lower value	'Ascribed' Interim EU-LCI
2-3	108-87-2	Methyl cyclohexane	8100	8100	OEL D	8100	MAK-DFG		'Ascribed' Interim EU-LCI
2-4	142-82-5	n-Heptane		21000	EU-OEL				EU-LCI 'with derivation pending'
2-5		Other saturated aliphatic hydrocarbons until C8		15000	OEL D	10000	OEL F		EU-LCI 'with derivation pending'
2-6		Other saturated aliphatic hydrocarbons higher than C9	6000	6000	OEL D	6000	MAK-DFG		'Ascribed' Interim EU-LCI
3		TERPENES							
3-1	498-15-7	3-Carene	1500	1500	cf. 3-2 to 3-5; OEL Sweden	1500	OEL Sweden		'Ascribed' Interim EU-LCI
3-2	80-56-8	α-Pinene	2500	1500	OEL Sweden: 150000 µg/m³	450	VG Index		'Derived' Interim EU-LCI

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
3		**TERPENES**							
3-3	127-91-3	**β-Pinene**	**1400**	1500	OEL Sweden: 150000 µg/m³	1400	OEL Denmark	**Precautionary approach by adopting the lower value**	'Ascribed Interim EU-LCI
3-4	138-86-3	**Limonene**		1500	OEL Sweden: 150000 µg/m³	450	VG Index		EU-LCI 'with derivation pending'
3-5		**Other terpene hydrocarbons**	**1400**	1500	OEL Sweden: 150000 µg/m³ (This group includes all mono-terpenes, sesquiterpenes and their oxygen containing derivatives)	1400	OEL Denmark	**Precautionary approach by adopting the lower value**	'Ascribed' Interim EU-LCI
4		**ALIPHATIC ALCOHOLS**							
4-1	75-65-0	**2-Methyl-2-propanol (tert-butanol)**	**620**	620	OEL D	600	MAK-DFG	**MAK value already rounded, no double rounding**	'Ascribed' Interim EU-LCI
4-2	78-83-1	**2-Methyl-1-propanol**		3100	OEL D	1500	OEL F		EU-LCI 'with derivation pending'
4-3	71-36-3	**1-Butanol**	**3000**	3100	OEL D	3000	OEL USA; PEL OSHA	**Precautionary approach by adopting the lower value**	'Ascribed' Interim EU-LCI

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
4		**ALIPHATIC ALCOHOLS**							
4-4	71-41-0 30899-19-5 94624-12-1 6032-29-7 584-02-1 137-32-6 123-51-3 598-75-4 75-85-4 75-84-3	**1-Pentanol (all isomers)**	**730**	730	MAK-DFG: 73000 µg/m³	700	MAK-DFG	**MAK value already rounded, no double rounding**	'Ascribed' Interim EU-LCI
4-5	111-27-3	**1-Hexanol**	**2100**	2100	OEL D	2100	OEL D		'Ascribed' Interim EU-LCI
4-6	108-93-0	**Cyclohexanol**	**2000**	2100	TLV (ACGIH): 206000 µg/m³	2000	OEL F	**Precautionary approach by adopting the lower value**	'Ascribed' Interim EU-LCI
4-7	104-76-7	**2-Ethyl-1-hexanol**		540	MAK-DFG; LCI value changed due to changed MAK-DFG value	1100	MAK-DFG		EU-LCI 'with derivation pending"
4-8	111-87-5	**1-Octanol**	**1100**	1100	OEL D	1100	OEL D		'Ascribed' Interim EU-LCI
4-9	123-42-2	**4-Hydroxy-4-methyl-pentane-2-on (diacetone alcohol)**	**960**	960	OEL D	950	MAK-DFG	**Precautionary approach by adopting the lower value**	'Ascribed' Interim EU-LCI

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
4		**ALIPHATIC ALCOHOLS**							
4-10		**Other C4 - C13 saturated alcohols n- and iso-**		1100	cf. 4-7 and 4-8; saturated cyclic alcohols are excluded; OEL D				EU-LCI 'with derivation pending'
5		**AROMATIC ALCOHOLS**							
5-1	108-95-2	**Phenol**		10	EU: Muta. 2; Individ. substance evaluation	20	VTR RIVM; EU: Mut. Cat. 3		EU-LCI 'with derivation pending'
5-2	128-37-0	**BHT (2,6-di-tert-butyl-4-methylphenol)**	**100**	100	OELs Denmark, Finland, France, Great Britain: 10000 µg/m³	100	OEL F		'Ascribed' Interim EU-LCI
5-3	100-51-6	**Benzyl alcohol**	**440**	440	WEEL (AIHA): 44000 µg/m³	450	TWA WEEL (AIHA)	**No rounding**	'Ascribed' Interim EU-LCI
6		**GLYCOLS, GLYCOETHERS**							
6-1	107-21-1	**Ethandiol (Ethylenglycol)**		260	OEL D	400	VTR OEHHA		EU-LCI 'with derivation pending'
6-2	96-49-1	**Ethylene carbonate**		370	cf. Ethanediol (6-1); conversion via molecular weight; OEL D	400	Analogy 6-1; VTR OEHHA	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
6-3	7397-62-8	**Butyl glycolate**		550	cf. glycolic acid, metabolite of ethanediol (6-1); conversion via molecular weight; OEL D	1300	OEL Denmark	**Procedure for read-across to be applied or derive new EU-LCI ?**	EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
6		**GLYCOLS, GLYCOETHERS**							
6-4	111-46-6	**Diethylene glycol**	**440**	440	OEL D	450	MAK-DFG/OEL D	**MAK value already rounded, no double rounding**	'Ascribed' Interim EU-LCI
6-5	57-55-6	**Propylene glycol (1,2-Dihydroxypropane)**		2500	Individ. compound evaluation	100	TWA WEEL (AIHA)		EU-LCI 'with derivation pending'
6-6	108-32-7	**Propylene carbonate**		250	Individ. compound evaluation				EU-LCI 'with derivation pending'
6-7	623-84-7	**Propylene glycol diacetate**		5300	cf. propylene glycol (6-5); conversion via molecular weight	6500	OEL Denmark	**Procedure for read-across to be applied or derive new EU-LCI ?**	EU-LCI 'with derivation pending'
6-8	110-98-5 25265-71-8	**Dipropylene glycol**	**670**	670	OEL D; (CAS 25265-71-8)	650	OEL D	**No rounding**	'Ascribed' Interim EU-LCI
6-9	110-63-4	**1,4-Butanediol**	**2000**	2000	OEL D	2000	OEL D		'Ascribed' Interim EU-LCI
6-10	107-41-5	**Hexylene glycol (2-methyl-2,4-pentanediol)**		490	MAK-DFG: 49000 µg/m³				EU-LCI 'with derivation pending'
6-11	6846-50-0	**2,2,4-Trimethylpentanediol diisobutyrate (TXIB)**	**450**	450	Individ. compound evaluation	450	NIK AgBB		'Ascribed' Interim EU-LCI
6-12	109-86-4	**Ethylene glycol monomethyl ether (2-Methoxyethanol)**		3	EU: Repr. 1B; EU-OEL	20	VTR IRIS US EPA; EU: Repr. Cat. 2		EU-LCI 'with derivation pending'
6-13	110-49-6	**2-Methoxyethyl acetate**		5	EU: Repr. 1B; EU-OEL	90	VTR OEHHA; EU: Repr. Cat. 2		EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
6		**GLYCOLS, GLYCOETHERS**							
6-14	110-71-4	**1,2-Dimethoxyethane**		4	EU: Repr. 1B; cf. 2-methoxyethanol 6-12 (metabolite methoxyacetic acid); conversion via molecular weight; EU-OEL	20	Analogy 6-12; VTR IRIS US EPA; EU: Repr. Cat. 2	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
6-15	111-96-6	**Diethylene glycol dimethyl ether (1-Methoxy-2-(2-methoxy-ethoxy)-ethane)**	**28**	28	EU: Repr. 1B; OEL D	30	MAK-DFG/OEL D EU: Repr. Cat. 2	**MAK value already rounded, no double rounding**	'Ascribed' Interim EU-LCI
6-16	25265-77-4	**2,2,4-Trimethyl-1,3-pentanediol monoisobutyrate (Texanol®)**	**600**	600	Individ. compound evaluation	600	NIK AgBB		'Ascribed' Interim EU-LCI
6-17	109-59-1	**Ethylene glycol isopropylether (2-Methylethoxyethanol)**	**220**	220	OEL D	200	MAK-DFG/OEL D	**MAK value already rounded, no double rounding**	'Ascribed' Interim EU-LCI
6-18	112-49-2	**Triethylene glycol-dimethyl ether**		7	EU: Repr. 1B; cf. 2-methoxy-ethanol 6-12 (metabolite methoxyacetic acid); conversion via molecular weight; EU-OEL	20	Analogy 6-12; VTR IRIS US EPA; EU: Repr. Cat. 2	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
6-19	110-80-5	**Ethylene glycol monoethyl ether (2-Ethoxyethanol)**		8	EU: Repr. 1B; EU-OEL;	70	VTR OEHHA; EU: Repr. Cat. 2		EU-LCI 'with derivation pending'
6-20	111-15-9	**2-Ethoxyethyl acetate**		11	EU: Repr. 1B; EU-OEL;	300	VTR OEHHA; EU: Repr. Cat. 2		EU-LCI 'with derivation pending'
6-21	629-14-1	**1,2-Diethoxyethane**		10	cf. 2-ethoxyethanol 6-19 (metabolite ethoxyacetic acid); conversion via molecular weight; EU-OEL	70	Analogy 6-19; VTR OEHHA	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			Interim	AgBB		AFSSET/ ANSES			
			2012	2012		2009			
6		GLYCOLS, GLYCOETHERS							
6-22	111-90-0	Diethylene glycol monoethyl ether (2-(2-ethoxyethoxy)ethanol)	350	350	OEL D	350	OEL D		'Ascribed' Interim EU-LCI
6-23	2807-30-9	Ethylene glycol monoisopropyl ether (2-Propoxyethanol)	860	860	OEL D	850	MAK-DFG/OEL D	MAK value already rounded, no double rounding	'Ascribed' Interim EU-LCI
6-24	111-76-2	Ethylene glycol monobutylether (2-butoxyethanol)	1100	490	OEL D	1000	VTR ATSDR		'Derived' Interim EU-LCI
6-25	112-07-2	2-Butoxyethyl acetate		1300	EU-OEL/OEL D	150	OEL F		EU-LCI 'with derivation pending'
6-26	112-34-5	Diethylene glycol monobutylether	670	670	EU-OEL	650	EU-OEL	EU-OEL value already rounded, no double rounding	'Ascribed' Interim EU-LCI
6-27	124-17-4	Diethylene glycol monomethyl ether acetate (Butyldiglykolacetate, 2-(2-butoxyethoxy) ethyl acetate)	850	850	MAK-DFG: 85000 µg/m³	850	MAK-DFG		'Ascribed' Interim EU-LCI
6-28	122-99-6	2-Phenoxyethanol	1100	1100	OEL D	1100	MAK-DFG/OEL D		'Ascribed' Interim EU-LCI
6-29	112-25-4	Ethylene glycol n-hexyl ether (2-Hexoxyethanol)		1200	cf. ethylene glycol monobutyl ether 6-24; conversion via molecular weight; EU-OEL	1000	Analogy 6-24; VTR ATSDR	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
6-30	112-59-4	Diethylene glycol n-hexyl ether (2-(2-Hexoxyethoxy)-ethanol)		740	cf. diethylene glycol-monobutyl ether 6-26; conversion via molecular weight; EU-OEL	650	Analogy 6-26; EU-OEL	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
6-31	107-98-2	Propylene glycol monomethyl ether (1-Methoxy-2-propanol)		3700	EU-OEL/OEL D	2000	VTR IRIS US EPA		EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
6		**GLYCOLS, GLYCOETHERS**							
6-32	1589-47-5	**1-Propylene glycol 2-methyl ether (2-Methoxy-1-propanol)**	**19**	19	EU: Repr. 1B; OEL D	20	MAK-DFG/OEL D EU: Repr. Cat. 2	**MAK value already rounded, no double rounding**	'Ascribed' Interim EU-LCI
6-33	70657-70-4	**1-Propylene glycol 2-methyl ether acetate (2-Methoxy-1-propyl acetate)**	**28**	28	EU: Repr. 1B; OEL D	30	MAK-DFG/OEL D EU: Repr. Cat. 2	**MAK value already rounded, no double rounding**	'Ascribed' Interim EU-LCI
6-34	7777-85-0	**1,2-Propylene glycol dimethyl ether**		25	cf. 2-methoxy-1-propanol 6-32 (metabolit methoxypropionic acid); conversion via molecular weight; OEL D	20	Analogy6-32; MAK-DFG/OEL D	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
6-35	34590-94-8	**Dipropylene glycol monomethyl ether**	**3100**	3100	EU-OEL/OEL D	3100	EU-OEL		'Ascribed' Interim EU-LCI
6-36	88917-22-0	**Dipropylene glycol monomethyl ether acetate**		3900	cf. dipropylene glycol monomethyl ether 6-35; conversion via molecular weight; EU-OEL	3100	Analogy 6-35; EU-OEL	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
6-37	29911-27-1	**Dipropylene glycol mono-n-propylether**		740	cf. diethylene glycol monobutyl ether 6-26; conversion via molecular weight; EU-OEL	650	Analogy 6-26; EU-OEL	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
6-38	29911-28-2 35884-42-5 132739-31-2	**Dipropylene glycol mono-n(t)-butylether**		810	cf. diethylene glycol monobutyl ether 6-26; conversion via molecular weight; EU-OEL	650	Analogy 6-26; EU-OEL	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
6-39	20324-33-8 25498-49-1	**Tripropylene glycol mono-methylether**		2000	Individ. compound evaluation; LCI value changed	1000	NIK AgBB		EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
6		**GLYCOLS, GLYCOETHERS**							
6-40	63019-84-1 89399-28-0 111109-77-4	**Dipropylene glycol dimethyl ether**	**1300**	1300	Individ. compound evaluation	1300	NIK AgBB		'Ascribed' Interim EU-LCI
6-41	2517-43-3	**3-Methoxy-1-butanol**		500	Individ. compound evaluation; New LCI value				EU-LCI 'with derivation pending'
6-42	1569-01-3 30136-13-1	**1,2-Propylene glycol n-propylether**		1400	Individ. compound evaluation; New LCI value				EU-LCI 'with derivation pending'
6-43	5131-66-8 29387-86-8 15821-83-7 63716-40-5	**1,2-Propylene glycol n-butylether**		1600	Individ. compound evaluation; New LCI value				EU-LCI 'with derivation pending'
6-44	104-68-7	**Diethylene glycol phenylether**		1450	cf. 2-Phenoxy-ethanol; conversion via molecular weight; New LCI value				EU-LCI 'with derivation pending'
6-45	126-30-7	**Neopentyl glycol**		1000	Individ. compound evaluation; New LCI value				EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			Interim	AgBB		AFSSET/ ANSES			
			2012	2012		2009			
7		ALDEHYDES							
7-1	50-00-0	Formaldehyde			VVOC	10	VGAI AFSSET; EU: Carc. Cat. 3		EU-LCI 'with derivation pending'
7-2	75-07-0	Acetaldehyde	1200		VVOC	200	VG Index; NF 16000-3; EU: Carc. Cat. 3		'Derived' Interim EU-LCI
7-3	123-38-6	Propanal			VVOC	8	VTR US EPA; NF 16000-3		EU-LCI 'with derivation pending'
7-4	123-72-8	Butanal	650	640	VVOC; OEL D: 64000 µg/m³	650	MAK-DFG/OEL D NF 16000-3		'Derived' Interim EU-LCI
7-5	110-62-3	Pentanal	800	1700	OEL Denmark, F; TLV (ACGIH): 175000 µg/m³	1700	OEL F	Procedure for read-across applied	'Derived' Interim EU-LCI
7-6	66-25-1	Hexanal	900	890	cf. Butanal 7-4; conversion via molecular weight; OEL D	650	Analogy 7-4; MAK-DFG/OEL D	Procedure for read-across applied	'Derived' Interim EU-LCI
7-7	111-71-7	Heptanal	900	1000	cf. Butanal 7-4; conversion via molecular weight; OEL D	650	Analogy 7-4; MAK-DFG/OEL D	Procedure for read-across applied	'Derived' Interim EU-LCI
7-8	123-05-7	2-Ethyl-hexanal	900	1100	cf. Butanal 7-4; conversion via molecular weight; OEL D	650	Analogy 7-4; MAK-DFG/OEL D	Procedure for read-across applied	'Derived' Interim EU-LCI
7-9	124-13-0	Octanal	900	1100	cf. Butanal 7-4; conversion via molecular weight; OEL D	650	Analogy 7-4; MAK-DFG/OEL D	Procedure for read-across applied	'Derived' Interim EU-LCI

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
7		**ALDEHYDES**							
7-10	124-19-6	**Nonanal**	**900**	1300	cf. Butanal 7-4; conversion via molecular weight; OEL D	650	Analogy 7-4; MAK-DFG/OEL D	**Procedure for read-across applied**	'Derived' Interim EU-LCI
7-11	112-31-2	**Decanal**	**900**	1400	cf. Butanal 7-4; conversion via molecular weight, OEL D	650	Analogy 7-4; MAK-DFG/OEL D	**Procedure for read-across applied**	'Derived' Interim EU-LCI
7-12	4170-30-3 123-73-9 15798-64-8	**2-Butenal (Crotonaldehyde)**		1	EU: Muta. 2; former OEL D	6	OEL F EU. Mut. Cat. 3; NF 16000-3		EU-LCI "with derivation pending"
7-13	1576-87-0 764-39-6 31424-04-1	**2-Pentenal**		12	cf. 2-butenal 7-12, but no EU classification as mutagen; conversion via molecular weight; OEL D	6	Analogy 7-12; OEL F	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
7-14	6728-26-3 505-57-7 16635-54-4 1335-39-3 73543-95-0	**Hexenal**		14	cf. 2-pentenal 7-13; conversion via molecular weight; OEL D	6	Analogy 7-13; OEL F	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
7-15	2463-63-0 18829-55-5 57266-86-1 29381-66-6	**2-Heptenal**		16	cf. 2-pentenal 7-13; conversion via molecular weight; OEL D	6	Analogy 7-13; OEL F	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
7-16	2363-89-5 2548-87-0 25447-69-2 20664-46-4	**2-Octenal**		18	cf. 2-pentenal 7-13; conversion via molecular weight; OEL D	6	Analogy 7-13; OEL F	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
7		**ALDEHYDES**							
7-17	2463-53-8 18829-56-6 60784-31-8	**2-Nonenal**		20	cf. 2-pentenal 7-13; conversion via molecular weight; OEL D	6	Analogy 7-13; OEL F	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
7-18	3913-71-1 2497-25-8 3913-81-3	**2-Decenal**		22	cf. 2-pentenal 7-13; conversion via molecular weight; OEL D	6	Analogy 7-13; OEL F	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
7-19	2463-77-6 53448-07-0 1337-83-3	**2-Undecenal**		24	cf. 2-pentenal 7-13; conversion via molecular weight, OEL D	6	Analogy 7-13; OEL F	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
7-20	98-01-1	**Furfural**		20	EU: Carc. 2; Individ. compound evaluation	8	OEL ACGIH; EU: Carc. Cat. 3		EU-LCI 'with derivation pending'
7-21	111-30-8	**Glutaraldehyde**		2	OEL D	0.08	Sensitizer, VTR OEHHA; NF 16000-3		EU-LCI 'with derivation pending'
7-22	100-52-7	**Benzaldehyde**		90	WEEL (AIHA): 8800 µg/m³	90	TWA WEEL (AIHA)		EU-LCI 'with derivation pending'
8		**KETONES**							
8-1	78-93-3	**2-Butanone (ethylmethylketone)**	**5000**	6000	EU-OEL/OEL D	5000	VTR IRIS US EPA		'Ascribed' Interim EU-LCI
8-2	563-80-4	**3-Methyl-2-butanone**	**7000**	7000	OELs Denmark, F: 705000 µg/m³	7000	OEL F		'Ascribed' Interim EU-LCI
8-3	108-10-1	**4-Methyl-2-pentanone (methylisobutylketone)**		830	EU-OEL/OEL D	3000	VTR IRIS US EPA		EU-LCI 'with derivation pending'
8-4	120-92-3	**Cyclopentanone**	**900**	900	OEL Denmark: 90000 µg/m³	900	OEL Denmark		'Ascribed' Interim EU-LCI
8-5	108-94-1	**Cyclohexanone**	**410**	410	EU-OEL	410	OEL F		'Ascribed' Interim EU-LCI

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			Interim	AgBB		AFSSET/ ANSES			
			2012	2012		2009			
8		KETONES							
8-6	1120-72-5	2-Methylcyclopentanone		1000	cf. Cyclopentanone 8-4; conversion via molecular weight; OEL Denmark	900	Analogy 8-4; OEL Denmark	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
8-7	583-60-8	2-Methylcyclohexanone	2300	2300	OELs Denmark, F, Finland: 230000 µg/m³	2300	OEL F		'Ascribed' Interim EU-LCI
8-8	98-86-2	Acetophenone	490	490	TLV (ACGIH): 49000 µg/m³	500	TLV ACGIH	No rounding	'Ascribed' Interim EU-LCI
8-9	116-09-6	1-Hydroxyacetone (1-hydroxy-2-propanone)		2400	oxidation product of propylene glycol 6-5; conversion via molecular weight	400	Analogy VTR OEHHA	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
9		ACIDS							
9-1	64-19-7	Acetic acid		1250	Individ. compound evaluation; LCI value changed	250	EU-OEL		EU-LCI 'with derivation pending'
9-2	79-09-4	Propionic acid	310	310	EU-OEL/OEL D	300	OEL F	OEL values already rounded, no double rounding	'Ascribed' Interim EU-LCI
9-3	79-31-2	Isobutyric acid		370	cf. propionic acid 9-2; conversion via molecular weight; EU-OEL/OEL D	300	Analogy 9-2; OEL F	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
9-4	107-92-6	Butyric acid		370	cf. propionic acid 9-2; conversion via molecular weight; EU-OEL/OEL D	300	Analogy 9-2; OEL F	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
9-5	75-98-9	2,2-Dimethylpropanoic aicd (pivalic acid)		420	cf. propionic acid 9-2; conversion via molecular weight; EU-OEL/OEL D	300	Analogy 9-2; OEL F	Procedure for read-across to be applied	EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			Interim	AgBB		AFSSET/ ANSES			
			2012	2012		2009			
9		ACIDS							
9-6	109-52-4	n-Pentanoic acid (valeric acid)		420	cf. propionic acid 9-2; conversion via molecular weight; EU-OEL/OEL D	300	Analogy 9-2; OEL F	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
9-7	142-62-1	n-Hexanoic acid (caproic acid)		490	cf. propionic acid 9-2; conversion via molecular weight; EU-OEL/OEL D	300	Analogy 9-2; OEL F	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
9-8	111-14-8	n-Heptanoic acid		550	cf. propionic acid 9-2; conversion via molecular weight; EU-OEL/OEL D	300	Analogy 9-2; OEL F	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
9-9	124-07-2	n-Octanoic acid		600	cf. propionic acid 9-2; conversion via molecular weight; EU-OEL/OEL D	300	Analogy 9-2; OEL F	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
9-10	149-57-5	2-Ethylhexanoic acid		50	EU: Repr. 2; TLV (ACGIH): 5000 µg/m³	5	TLV (ACGIH); EU: Repr. Cat. 3		EU-LCI 'with derivation pending'
10		ESTERS							
10-1	108-21-4	Propyl acetate (n-, iso-)	4200	4200	OEL Finland, MAK-DFG: 420000 µg/m³	4200	MAK-DFG		'Ascribed' Interim EU-LCI
10-2	108-65-6	2-Methoxy-1-methylethyl acetate	2700	2700	EU-OEL/OEL D	2700	MAK-DFG/OEL D		'Ascribed' Interim EU-LCI
10-3	107-31-3	Methylformiate	1200	1200	OEL D	1200	MAK-DFG		'Ascribed' Interim EU-LCI
10-4	592-84-7	n-Butyl formiate		2000	cf. Methylformiate 10-3; conversion via molecular weight; OEL D	1200	Analogy 10-3; MAK-DFG/OEL D	Procedure for read-across to be applied	EU-LCI 'with derivation pending'
10-5	80-62-6	Methyl methacrylate		2100	EU-OEL/OEL D	50	VTR Canada		EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
10		**ESTERS**							
10-6		**Other methacrylates**		2100	cf. Methyl methacrylate 10-5; OEL D	50	Analogy 10-5; VTR Canada	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
10-7	110-19-0	**Isobutyl acetate**	**4800**	4800	OEL D;	4800	MAK-DFG/OEL D		'Ascribed' Interim EU-LCI
10-8	123-86-4	**n-Butyl acetate**	**4800**	4800	OEL D;	4800	MAK-DFG/OEL D		'Ascribed' Interim EU-LCI
10-9	103-09-3	**2-Ethylhexyl acetate**		690	cf. 2-ethyl-1-hexanol 4-7; conversion via molecular weight; MAK-DFG; LCI value changed	1100	Analogy 4-7; MAK-DFG/OEL D	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
10-10	96-33-3	**Methyl acrylate**	**180**	180	EU-OEL/OEL D	200	MAK-DFG/OEL D	**MAK/EU-OEL value already rounded, no double rounding**	'Ascribed' Interim EU-LCI
10-11	140-88-5	**Ethyl acrylate**	**200**	210	EU-OEL/OEL D	200	OEL F	**Precautionary approach by adopting the lower value**	'Ascribed' Interim EU-LCI
10-12	141-32-2	**n-Butyl acrylate**	**110**	110	EU-OEL/OEL D	100	OEL F	**Same value of origin, no rounding**	'Ascribed' Interim EU-LCI
10-13	103-11-7	**2-Ethylhexyl acrylate**	**380**	380	OEL D	400	MAK-DFG/OEL D	**MAK value already rounded, no double rounding**	'Ascribed' Interim EU-LCI
10-14		**Other acrylates (acrylic acid esters)**	**110**	110	cf. n-butyl acrylate 10-12; EU-OEL/OEL D	110	Analogy 10-12; OEL D		'Ascribed' Interim EU-LCI

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
10		**ESTERS**							
10-15	627-93-0	**Dimethyl adipate**	**50**	50	Dicarbonic acid (C4-C6)-dimethylester, mixture MAK-DFG: 5000 µg/m³; Individ. compound evaluation	50	NIK AgBB		'Ascribed' Interim EU-LCI
10-16	106-65-0	**Dimethyl succinate**	**50**	50	Dicarbonic acid (C4-C6)-dimethylester, mixture MAK-DFG: 5000 µg/m³; Individ. compound evaluation	50	NIK AgBB		'Ascribed' Interim EU-LCI
10-17	1119-40-0	**Dimethyl glutarate**	**50**	50	Dicarbonic acid (C4-C6)-dimethylester, mixture MAK-DFG: 5000 µg/m³; Individ. compound evaluation	50	NIK AgBB		'Ascribed' Interim EU-LCI
10-18	71195-64-7	**Diisobutyl glutarate**		100	Individ. compound evaluation				EU-LCI 'with derivation pending'
10-19	925-06-4	**Diisobutyl succinate**		100	Individ. compound evaluation				EU-LCI 'with derivation pending'
10-20	105-75-9	**Dibutyl fumarate**	**50**	50	Individ. compound evaluation	50	NIK AgBB		'Ascribed' Interim EU-LCI
10-21	105-76-0	**Maleic acid dibutylester**	**50**	50	Individ. compound evaluation	50	NIK AgBB		'Ascribed' Interim EU-LCI
10-22	13048-33-4	**Hexamethylene diacrylate**	**10**	10	WEEL (AIHA) 1000 µg/m³	10	TWA WEEL (AIHA)		'Ascribed' Interim EU-LCI
10-23	96-48-0	**Butyrolactone**		2700	Individ. compound evaluation	1800	OEL Denmark		EU-LCI 'with derivation pending'

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			**Interim**	**AgBB**		**AFSSET/ ANSES**			
			2012	**2012**		**2009**			
10		**ESTERS**							
10-24	115-95-7	**Linalool acetate**				200	Analogy vinyl acetate; OEL D		EU-LCI 'with derivation pending'
11		**CHLORINATED HYDROCARBONS**							
11-1	127-18-4	**Tetrachloroethene**[15]			Compound has been deleted from the German list, no relevance	250	AQG WHO; EU Carc. Cat. 3		EU-LCI 'with derivation pending'
11-2	56-23-5	**Tetrachloromethane**				35	VTR AFSSET; EU Carc. Cat. 3		EU-LCI 'with derivation pending'
11-3	106-46-7	**1,4-Dichlorobenzene**	**150**			60	VTR ATSDR; EU Carc. Cat. 3		'Derived' Interim EU-LCI
12		**OTHERS**							
12-1	123-91-1	**1,4-Dioxane**		73	EU: Carc. 2; OEL D	3000	VTR OEHHA; EU Carc. Cat. 3		EU-LCI 'with derivation pending'
12-2	105-60-2	**ε-Caprolactam**	**300**	240	Individ. compound evaluation	100	OEL Denmark		'Derived' Interim EU-LCI
12-3	872-50-4	**N-Methyl-2-pyrrolidon**	**400**	400	EU: Repr. 1B; EU-OEL; Individ. compound evaluation	400	EU-OEL; EU: Repr. Cat. 2		'Ascribed' Interim EU-LCI
12-4	556-67-2	**Octamethylcyclotetrasiloxane (D4)**	**1200**	1200	EU: Repr. 2; Individ. compound evaluation	1200	NIK AgBB; EU: Repr. Cat. 3		'Ascribed' Interim EU-LCI
12-5	541-02-6	**Decamethylcyclopentasiloxane (D5)**		1500	cf. Octamethylcyclo-tetrasiloxane; conversion via molecular weight				EU-LCI 'with derivation pending'

[15] Compound otherwise known, and frequently referred to, as tetrachloroethylene

EU-LCI no.	CAS no.	Compound	EU-LCI	NIK (µg/m³)	Remarks / derived from	CLI (µg/m³)	Remarks / derived from	Explanatory note	Status of EU-LCI values
Version: July 2013			Interim	AgBB		AFSSET/ ANSES			
			2012	2012		2009			
12		OTHERS							
12-6	540-97-6	Dodecamethylcyclohexa-siloxane (D6)		1200	cf. Octamethylcyclo-tetrasiloxane; Individ. compound evaluation				EU-LCI 'with derivation pending'
12-7	100-97-0	Hexamethylenetetramine	30	30	OEL Norway, Sweden: 3000 µg/m³	30	Sensitizer; OEL Sweden		'Ascribed' Interim EU-LCI
12-8	96-29-7	2-Butanonoxime		20	EU: Carc. 2; Individ. compound evaluation	90	OEL Denmark; EU Carc. Cat. 3		EU-LCI 'with derivation pending'
12-9	126-73-8	Tributyl phosphate			SVOC, no LCI value EU: Carc. 2	2	OEL F		EU-LCI 'with derivation pending'
12-10	78-40-0	Triethyl phosphate		75	cf. tributyl phosphate 12-9; MAK: 11000 µg/m³; conversion via molecular weight; LCI value changed	2	Analogy 12-9; OEL France	**Procedure for read-across to be applied**	EU-LCI 'with derivation pending'
12-11	26172-55-4	5-Chloro-2-methyl-2H-isothiazol-3-one (CIT)	1	1	Individ. compound evaluation	1	NIK AgBB		'Ascribed' Interim EU-LCI
12-12	2682-20-4	2-Methyl-4-isothiazolin-3-one (MIT)	100	100	Individ. compound evaluation	100	NIK AgBB		'Ascribed' Interim EU-LCI
12-13	121-44-8	Triethylamine		42	OEL D	7	VTR US EPA		EU-LCI 'with derivation pending'
12-14	109-99-9	Tetrahydrofuran		1500	EU-OEL/OEL D New LCI value				EU-LCI 'with derivation pending'
12-15	68-12-2	Dimethylformamide		15	EU: Repr. 1B; MAK-DFG; New LCI value				EU-LCI 'with derivation pending'

Note: the French list was filed in 2009, classifications given in the corresponding column are based on the dangerous substances directive (67/548/EEC), and not according to the CLP regulation (Regulation (EC) No 1272/2008).

COLOUR CODING	DEFINITION	STATUS OF EU-LCI VALUES
Yellow	- Compounds for which EU-LCI were derived according to the de novo protocol (11) and the procedure for read across (10)	'Derived' Interim EU-LCI
Red	- Compounds with different LCI values in AgBB/ANSES due to different derivation basis (29) - Compounds for which EU-LCIs to be derived by read across (40)	EU-LCI 'with derivation pending'
Green	Compounds in AgBB/ANSES with same/similar (within 20% difference) LCI values (61)	'Ascribed' Interim EU-LCI
Blue	- Compounds on either the AgBB-list or the ANSES-list (24) - Compounds in AgBB/ANSES for which same derivation basis for the LCIs but different values due to different safety/extrapolation factors (1 case, see No 9-10)	EU-LCI 'with derivation pending'
Grey	Limitations of underlying human and animal studies and lack of a sufficient and transparent database currently does not allow the *de novo* derivation of an EU-LCI value (1)	EU-LCI 'with derivation pending'

5. PRACTICAL APPLICATION OF EU-LCIs AND THE NECESSARY CONSIDERATION OF MULTIPLE SOURCES

As previously explained, EU-LCI values are, by definition, health-based values used to evaluate emissions after 28 days from a single product during a laboratory test chamber procedure (as defined in the Technical Specification TS 16516 of the horizontal testing method developed by CEN TC 351/WG 2). EU-LCIs are applied in product safety assessment with the ultimate goal to avoid health risks from long-term exposure[16] for the general population.

EU-LCI values serve a different purpose from IAQ guideline values. They are intended only for evaluating emissions from single products, not for evaluating indoor air quality.

It is clear that achieving appropriate low levels of hazardous compounds in any particular indoor environment through the control of emissions requires account to be taken of the presence of all sources of those compounds.

Thus whenever a product is selected and used in a building it must always be kept in mind that the resulting indoor air concentrations of a particular volatile organic compound will depend upon the amounts emitted from that product as well as from other possible sources of that compound. The resulting indoor air concentration in buildings will also depend on the ventilation rate and any other processes such as chemical reactions, sorption to surfaces, and air temperature. Compared with the test chamber scenario the real room situation is complex and more dynamic in nature. Therefore the selection of 'approved' construction products with emissions satisfying the EU-LCI criteria does not necessarily guarantee good indoor air quality in buildings.

There are several conceivable ways of addressing the multiple sources issue:

1. Determine the appropriate emission rate of a compound from a particular product based on the likely presence of other sources of that compound in typical use conditions. In this case the EU-LCI value could be adjusted by application of a 'multiple sources factor' to give the target highest product emission rate.[17]
2. Provide quantitative emission information on product approval documents (i.e. specifying the R_i value[18]) or limit the emission for a single compound to 50% of the R-value[19] (ceiling value) for example.
3. When selecting a particular construction product with a determined and declared emission rate of a compound, consider the possible presence of other emitting sources of that same compound in a given environment. In this situation the consideration (and

[16] By inhalation in indoor environments, not taking into consideration other exposure routes (dietary, dermal etc.)

[17] It is suggested that in this scenario the default multiple sources factor (MSF) applied to the EU-LCI should be 2, which would effectively halve the LCI value in the default situation. In the situation where the compound is rare/unusual then this factor might be changed to 1. Where it is known, or there is good reason to believe, that there are likely to be numerous sources of that compound then the MSF could be raised to 5.

[18] R_i value: Ratio C_i/LCI_i where C_i is the mass concentration of the compound in air and LCI_i is the LCI value of compound i.

[19] R value: sum of all R_i values

avoidance) of multiple sources of the same compound would be done by planning/building professionals.

The knowledge of, and access to, construction product emission information within the approval process is beyond the remit of the EU-LCI Working Group. The Working Group will derive EU-LCI values solely on a toxicological basis with no inherent consideration of possible multiple sources or other modifying factors.

It is recommended that the decision on approving a particular construction product and providing appropriate information on emission behaviour (e.g. emission classes) should rest with the approving agencies, and that the selection of products and/or technical solutions within a building process should rest with the planner, who must be given access to adequate information to make these decisions.

6. POTENTIAL HARMONISATION ISSUES

Concerning the overall evaluation of chemical emissions from construction products, certain additional aspects are considered to require further development and potential harmonisation. These are related to:

(a) The evaluation of compounds for which currently no LCI values can be derived ("not-yet-assessable" compounds)

(b) Assessment concept for semi-volatile organic compounds (SVOCs), very volatile organic compounds (VVOCs) and carcinogens.

(c) Reviewing the EU-LCI concept by considering combined effects of chemicals

(d) Common criteria and threshold values for total volatile organic compounds (TVOC) and sensory evaluation

Once these potential harmonisation issues have been addressed, the health-based evaluation of emissions from construction products using the EU-LCI approach can be broadened by considering, for example, common criteria and threshold values for TVOC, SVOC, sensory evaluation and the sum of "not-yet-assessed" compounds) and R-value <1.

6.1 Evaluation of "not-yet-assessable" compounds

The central goal of the EU-LCI concept is to assess as many emitted compounds as possible in order to enable a real health-based evaluation of product emissions. This can reduce uncertainty for consumers and for product manufacturers. A limitation of this concept is that there are still remaining gaps due to lack of approaches and adequate data for other potentially relevant compounds to derive EU-LCI values. Also, compounds whose health effects are poorly understood and compounds which cannot be identified with existing analytical capabilities cannot be evaluated using the EU-LCI concept. Additional criteria and measurement methods are needed to tackle this problem.

Some compounds are currently measured, at least semi-quantitatively by the sampling and analytical methods currently prescribed but not assessed according to EU-LCI values. Two strategies have been used to limit the potential problems with these compounds:

- The AgBB and ANSES schemes restrict "not-yet-assessable" compounds to 10% of the threshold value for the TVOC amount (ECA report 18, 1997).
- The M1-scheme in Finland has a low allowed total amount of VOC emission (TVOC 0.2 mg/m^2.h) including assessed and "not-yet-assessable" compounds. The idea behind this approach is the following: low TVOC assumes low emission of the individual compounds that constitute the TVOC.

More toxicological information about the "not-yet-assessable" compounds is expected in the course of the REACH process. However, degradation or reaction products and odorous compounds – not falling under the REACH regulation – will still need to be tackled.

6.2 Health-based evaluation of emissions for SVOCs, VVOCs and carcinogens

Besides the VOCs that have already been accommodated in the EU-LCI harmonisation framework and the “not-yet-assessable” compounds, there is a need to consider the inclusion and development of protocols for assessing carcinogens, SVOC (e.g. phthalates, flame retardants) and VVOCs for which European harmonised test methods are not yet available.

The Technical Specification TS 16516 of the horizontal testing method developed by CEN TC 351/WG 2 provides emission data for carcinogens within the VOC range, for some of the most volatile of SVOCs and some VVOCs including formaldehyde.

6.3 Considering the EU-LCI in relation to combined effects of chemicals

The application of NIK/LCI-values in the registration of construction products relates to the concentration of VOCs obtained in emission chamber testing. In general construction product emissions contain several VOCs from different chemical classes.

The existing schemes in Germany (AgBB) and France (ANSES) make use of the R-value approach (Risk-value) to determine whether the concentration of multiple compounds emitted from a construction product is in compliance with the approval requirements. The R-value is derived by summarizing the individual R_i-values. The R_i value is the ratio of the emission concentrations of individual compounds in the mixture divided by the corresponding LCI value (C_i/LCI_i).

R-value = $\Sigma R_i + \ldots R_n$

While the limitations of the current R-value approach assuming dose additivity of all compounds in a chemical mixture irrespective of their health effects is recognised in the EU-LCI work, current knowledge does not allow the practical use of health end-point dedicated R-values.

At this stage of development of the EU-LCI harmonization exercise, therefore, the R-value approach shall be adopted as it is currently used by the AgBB and ANSES schemes (i.e. as a

pragmatic approach). However, in the light of any new evidence, the definition and/or application of the R-value concept should be re-considered. In this perspective, the outcome of EU activities (DG ENV and DG SANCO)[20] on a new approach to assessing combined health effects of chemicals, as well as of other international initiatives such as those being taken by the World Health Organisation (WHO)/International Programme on Chemical Safety (IPCS) and the OECD, need also to be considered[21].

In conclusion, at present, applying the existing R-value concept - as opposed to several health end-point dedicated R-values - is considered to provide a pragmatic and, from a toxicological perspective, conservative approach.

6.4 Harmonisation needs for TVOC and sensory evaluation

TVOC is an air pollution parameter that summarises the amounts of VOCs collected by an air sampler containing the sorbent Tenax TA that is determined by thermal desorption and gas chromatography (TD/GC) analysis. It refers to those compounds defined as VOCs that elute during the GC analysis between the C_6 to C_{16} chromatographic retention window. TVOC is determined as the total integrated peak area that is calibrated with use of toluene as reference compound.

Alternatively, the sum of VOCs ($TVOC_{SUM}$) may be determined by summing the individual concentrations of every identified and unidentified component eluting between n-hexane and n-hexadecane inclusively, at a concentration above 5 $\mu g.m^{-3}$, after subtracting non-interfering VOC artefacts.

It can be deduced from the aforementioned definition of TVOC/ $TVOC_{SUM}$ that TVOC is not a health based indicator. Any assumption that all VOCs within the TVOC window have the same health endpoint and thus can be treated in the same manner and be added together, cannot be supported from a toxicological standpoint. Moreover, TVOC cannot reflect perceived intensity of olfaction by nature of the diversity of the odor thresholds of VOCs.

As far as the relevance of using TVOC in assessing the emissions of construction products is concerned, the following points should be underlined:

- TVOC represents a narrow chromatographic window that excludes, for example, the lower aldehydes, e.g. formaldehyde
- Poly-oxygenated VOCs may be underestimated, i.e. low detector response
- Certain biologically reactive VOCs are not measured
- VOCs with low odour thresholds may not be measured
- A high TVOC value may be harmless, while a low TVOC value may result in poor IAQ, e.g. as a result of strong odour perception.

[20] At request of DG ENV, the DG SANCO's Scientific Committee on Health and Environmental Risks (SCHER), the Scientific Committee on Emerging and Newly Identified Risks (SCENIR) and the Scientific Committee on Consumer Products (SCCP) prepared an opinion on mixture toxicity/combination effects of chemicals.

[21] "RISK ASSESSMENT OF COMBINED EXPOSURES TO MULTIPLE CHEMICALS: A WHO/IPCS FRAMEWORK." The project was conducted within the WHO-IPCS project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals.

The EU-LCI WG recognises that TVOC is widely established and accepted in Europe in connection with product emissions and indoor air quality. Although TVOC has no direct relevance to health, it is used as an indicator to quantify VOC emissions and often as one of the criteria when assessing indoor air quality. Assessing the emission behaviour of products via TVOC as the one and only criterion is certainly unacceptable. However, when evaluating the emissions of construction products, TVOC does provide supplementary information when combined with the health-based evaluation using the EU-LCI concept and the limitation of CMR compounds.

Harmonisation of the TVOC concept and the setting of a possible upper concentration limit was not within the remit of the EU-LCI WG but will be the responsibility of a new group which was recommended to be established by European Commission according to the resolutions of ECA WG 27 (ECA report no. 27, 2012).

As far as the sensory evaluation (sensory irritation and odour perception) of the emissions is concerned, this is considered to be an important aspect of the assessment of construction product emissions. Results have shown that chemical characterisation of emissions is not a good predictor of sensory effects. Therefore it is important to complement the chemical assessment of product emissions with sensory evaluation. ECA WG 27 (ECA report no. 27, 2012) supports the work of ISO TC 146/SC6 in creating a standard for sensory evaluation. The ISO 16000-28 on "Indoor Air - Determination of odour emissions from construction products using test chambers" includes both acceptability evaluation using an untrained panel and perceived intensity measurement with a trained panel. It also combines the odour evaluation chamber technique with Technical Specifications TS 16516 of the horizontal testing method developed by CEN TC 351/WG 2(reference room).

6.5 References

CEN TC 351/WG 2 technical specification TS 16516. (http://www.cen.eu/CEN/Sectors/TechnicalCommitteesWorkshops/CENTechnicalCommittees/Pages/WP.aspx?param=510793&title=CEN%2FTC+351).

ECA report no. 27 (2012). "Harmonisation framework for indoor products labelling schemes in the EU". EUR 25276 EN, ISBN 978-92-79-22535-2. Publications Office of the European Union, Luxembourg.

ECA report no. 18 (1997). Evaluation of VOC emissions from building products – Solid flooring materials. EUR 17334/EN, ISBN 92-828-0384-8, Office for Official Publications of the European Communities, Luxembourg.

ISO 16000-28:2012. "Indoor air – Part 28: Determination of odour emissions from building products using test chambers".

7. EU-LCI IN RELATION TO EXISTING POLICIES

The EU-LCI harmonisation framework cuts across a number of EU legislative mandates and standardization activities, and its implemention is to be seen strictly in relation to them. It is important to implement the EU-LCI framework in a wider and integrated context of safe, healthy, energy efficient and sustainable buildings in EU. This, in line with the Europe 2020 Strategy, implies the efficient alignment and implementation of various legislative mandates the Construction Products Regulation (Regulation (EU) No 305/2011), the Energy Performance of Buildings Directive – EPBD (2002/91/EC), the EC Lead Market Initiative (COM(2007)860), the Integrated Product Policy (IPP), the Chemicals Policy (REACH), Green Public Procurement, and the Integration of Environmental Aspects into European Standardisation (COM(2004)206).

In the following sections of chapter 7, developments concerning some of the policies which have explicitly or implicitly considered and/or referred to the EU-LCI work are reported.

7.1 EU-LCI in relation to CE marking

Since 2013-07-01, the European Construction Products Regulation (Regulation (EU) No 305/2011) replaced the former Construction Products Directive (CPD, 89/106/EEC). The goal of the CPR is to facilitate cross-border trade and over-come trade barriers in the form of national rules and standards. The CPR aims to provide a common technical language in harmonised European product performance standards, for use by both manufacturers and regulators.

The CPR contains a chapter defining the framework of European or national requirements for hygiene, health and the environment for construction works. Amongst other things, the giving-off of toxic gas, or the presence of dangerous particles or gases in the air has been identified as specific criteria. The translation into limit values for relevant compounds is left to each EU Member State and is currently implemented on a mandatory basis only in France and Germany, while Belgium has recently notified a similar mandatory regulation.

The purpose of the CPR is not to influence the level of protection but to harmonise the technical description of products and to facilitate cross-border trade. CE marking could (wherever relevant) be accompanied by performance classes that cover all national regulations in Europe. Then each EU Member State could specify which performance classes a product shall fulfil for being accepted into that national market. The intention is that this CE marking will substitute any national law.

This topic acquired high relevance for Europe when the French system was recently introduced, as this system is based on performance classes whereas the German system and the upcoming Belgium system is based on pass/fail criteria. The German system with its pass/fail scheme defines a product as being safe or not safe for an assumed concentration according to the exposure scenario in a standard room described in the technical specification. Moreover, it applies to indoor environments which are commonly occupied by people for a prolonged time. In the construction sector in general, the principle of classes (stability, durability, fire resistance, etc.) is applied depending on the type of building that is

constructed. It is not always necessary to use the best performing material. Products belonging to different performance classes can be combined. However, it should be underlined that a product cannot be considered as being unsafe or safe *per se*. It depends on the use of the product. Products could in principle be safe, *per se*. It depends on the use of the product. Products could in principle be safe, as long as they are used correctly in relation to the exposure scenario defining appropriate use in a given building. Moreover, the issue of potential multiple sources for a given compound opens the possibility of classes below that deemed 'safe' according to the single material exposure scenario used. Therefore, the challenge is how the information about a given product can be most effectively applied to fit-for-purpose, safe and cost-optimised building constructions.

The current effort by DG ENTR's Expert Group on Dangerous Substances (EGDS) is to bring both systems into an EU harmonised classification system which should be transparent in the communication to end users in the market, require less expert knowledge for interpretation, and be consistent with the EU-LCI harmonisation work. This will decrease existing burdens for the construction industry in producing and certifying safe construction materials and products and will also help remove barriers to trade across the European market.

7.2 EU-LCI in relation to the REACH process

In the derivation of the EU-LCI values information from the European chemical substances information system, the Annex VI on hazardous substances of the Classification, Labelling and Packaging Directive ((EC) No 1272/2008)) and the REACH process is fully considered. Via the European Chemicals Agency (ECHA) website (http://echa.europa.eu), a vast amount of registration data is published, where DNELs (Derived No Effect Levels) are also included. As mentioned in section 2.4.1 the EU-LCI WG considers only information from published reports (e.g. already published info for compounds of very high concern/SVHC), or if access to registration dossiers can be arranged (via the respective EU competent bodies or the registrant on a voluntary basis) so that the derivation of particular DNELs could be fully comprehended.

Comparing the long-term inhalation DNELs for workers ($DNEL_w$) with the DNELs for the general population ($DNEL_p$) for 120 compounds relevant to indoor air (Figure 3), it can be seen that on average the $DNEL_w$ is four times greater than the $DNEL_p$, with minimum and maximum ratios being in the range 1 to 23.

Table 10 shows wide differences between DNELs and the EU-LCI values derived for several compounds emitted from construction products in the context of the EU-LCI harmonisation framework, even though the REACH Guidance on information requirements and the chemical safety assessment (Chapter R.8) was used as the basis in the derivation of the EU-LCI values. This may be due to a number of reasons, such as non-harmonised application of assessment factors and read-across, assumption of short-term exposure scenarios for consumers, etc. The reasons for such discrepancies should be explored and alignment of DNELs and EU-LCIs should be sought where appropriate. Disclosure of the approach and associated data used for the derivation of DNELs would greatly facilitate this. The importance of the findings of the EU-LCI work in relation to the requirements of the REACH legislation is reflected in the Commission's Staff Working document (SWD(2013)0025, page 16) companion to the EC's report "Review of REACH".

(COM(2013)0049)(http://ec.europa.eu/enterprise/sectors/chemicals/documents/reach/review2012/index_en.htm).

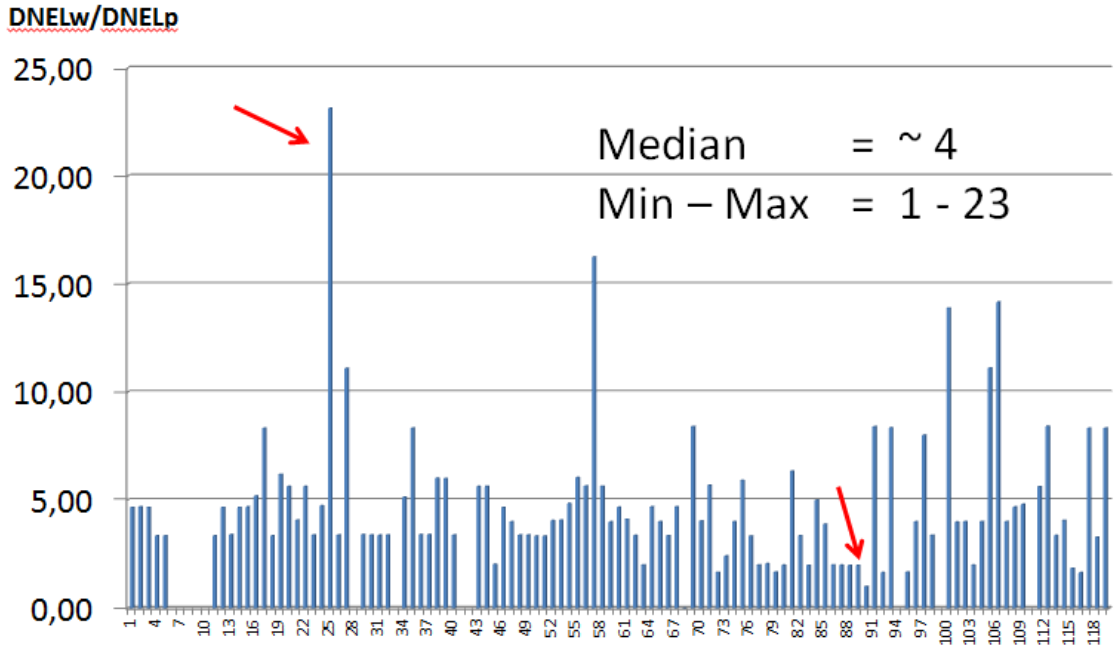

Figure 3. *DNELs for workers versus DNELs for general population*

Table 10. *Comparison of EU-LCI, NIK, CLI and DNEL values for some compounds in the EU-LCI master list*

Compound	**EU-LCI** [µg/m³]	**NIK** [µg/m³]	**CLI** [µg/m³]	**DNEL*** [µg/m³]
Trimethylbenzenes	450	1000	1000	29400
Xylenes**	500	2200	200	14800
2-Butoxyethanol	1100	490	1000	49000
Styrene	250	860	250	10200
Toluene	2900	1900	300	56500
Ethylbenzene	850	880	750	15000

* Long-term inhalation DNEL, general population: systemic effects
** CAS 1330-20-7

Moreover, it would be useful to revise chapter R.8 of the ECHA guidance on information requirements and chemical safety assessment concerning sensory irritation, and also to have additional data requirements concerning odour threshold as part of the REACH documentation according to a harmonised test.

7.3 EU-LCI in relation to consumer product policies

There are a number of EU policies that impact on the use of ingredients in consumer products, either by prohibiting the use of certain compounds or by imposing restrictions on the content of chemicals in product composition: the REACH regulation (EC 1907/2006), the General Product Safety Directive (GPSD, 2001/95/EC), the regulation on classification, labelling and packaging of substances and mixtures ((EC) No 1272/2008) and the Biocidal Products Regulation (BPR, 2012). Specific sectorial policies exist for various categories of consumer products such as cosmetics (Cosmetics Products Regulation EC 1223/2009), detergents and toys (Toys Safety Directive 2009/48/EC), etc. In terms of health risk assessment, most existing product policies focus on chemical content rather than emissions. Risk health assessment in relation to emissions, exposure patterns and health effects of consumer products in the EU was recently undertaken in the context of the EU funded EPHECT project (Emissions, Exposure Pattern and Health Effects of Consumer products in the EU, https://sites.vito.be/sites/ephect). The outcome of EPHECT shows that many of the compounds emitted from the products studied in this project (i.e., personal care products, air fresheners, cleaning agents and sprays, etc.) are common with those emitted from construction products and are considered in the EU-LCI harmonisation framework. From a health risk assessment point of view, a new holistic approach for health based evaluation of emissions from construction products (based on the EU-LCI concept) and consumer products is considered a challenging development. Such an approach should account for differences between construction and consumer products in terms of typologies of pollution sources and emissions (constant sources and long term emissions as opposed to short and temporary emissions), different use and exposure patterns and risk assessment procedures.

7.4 EU-LCI in relation to national legislation

The development of the EU-LCI harmonisation framework has been positively received and supported by a wide range of stakeholders (European Commission, EU Member States and the European Chemicals Industry). However, in terms of its implementation into national policies in the EU Member States, there is a need for further discussion and definition of how the on-going work and procedures of national committees (e.g., the German NIK Committee) will be aligned to the outcome of the EU-LCI work (i.e. adopting the harmonised protocol for deriving EU-LCI values and the master list of EU-LCI values). This requires a transition phase in which the EU Member States that do not have in place a national procedure for deriving LCI values may wish to proactively adopt the EU-LCI framework even if it is not formally required by the European legislation. An example of such a proactive adoption of the EU-LCI framework (with interim solution the German NIK values) is the stated intention of Belgium via its Belgian

Royal Decree which aims at establishing threshold levels for the emissions to the indoor environment from construction products.

(http://ec.europa.eu/enterprise/tris/pisa/app/search/index.cfm?fuseaction=pisa_notif_overview&sNlang=EN&iyear=2012&inum=568&lang=en&iBack=3).

7.5 References

Biocidal Products Regulation (BPR, 2012). Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products.

Construction Products Directive (CPD, 1989). Council Directive 89/106/EEC of 21 December 1988 on the approximation of laws, regulations and administrative provisions of the Member States relating to construction products; Official Journal L 040, 11/02/1989 P. 0012 – 0026.

Construction Products Regulation (CPR, 2011). REGULATION (EU) No 305/2011 of the European Parliament and of the Council of 9 March 2011 laying down harmonised conditions for the marketing of construction products and repealing Council Directive 89/106/EEC.

Cosmetics Products Regulation (CPR, 2009). Regulation (EC) no. 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (recast).

(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.

General Products Safety Directive (GPSD). Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety.

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

Toys Safety Directive 2009/48/EC of the European Parliament and of the Council of 18 June 2009 in the safety of toys.

8. GLOSSARY

AFSSET: Agence Francaise de Sécurité Sanitaire de l'Environment et du Travail (French agency for environmental and occupational health and safety; now ANSES).

ANSES: Agence nationale de sécurité sanitaire de l'alimentation, de l'environment et du travail (French agency for food, environmental and occupational health and safety).

AgBB: Ausschuss zur gesundheitlichen Bewertung von Bauprodukten (Committee for Health-related Evaluation of Building Products).

Assessment Factor: A numerical factor (multiplier) used at various stages of the extrapolation from an experimentally determined toxicological point-of-departure to the estimated level of exposure below which an adverse effect is unlikely to occur. Sometimes referred to as an 'uncertainty factor' or, historically, a 'safety factor'.

ATSDR: [US] Agency for Toxic Substances and Disease Registry.

BMD: Benchmark Dose – The dose or exposure of a compound associated with a specified low incidence of risk, generally in the range of 1% to 10%, of a health effect, or the dose associated with a specified measure or change of a biological effect. Thus BMD_{10}, for example, is the dose of the test material that leads to a 10% increase in effect. The BMD approach provides a more quantitative alternative to the first step in the dose-response assessment than the NOAEL/LOAEL process for non-cancer health effects.

Category 1A and 1B carcinogens and mutagens: Compounds that are classified in accordance with the provisions of Regulation (EC) No 1272/2008 as a carcinogen or mutagen category 1A or 1B (based on the Globally Harmonized System). A Category 1 compound is known or presumed to have carcinogenic/mutagenic potential for humans. For Category 1A the assessment is based primarily on human evidence; for Category 1B the assessment is based primarily on animal evidence.

CEN/TC 351 horizontal standard: Horizontal testing procedure being developed by the CEN/TC 351 working group 2 and published as Technical Specification TS 16561 for the determination of emissions into indoor air of regulated dangerous substances from construction products that can be used for all types of substances and construction products deemed relevant under the essential requirements of the Construction Products Directive (89/106EEC).

CLI: Concentration Limite d'Intérêt– the French (Afsset/Anses) LCI.

CLP: Classification, Labelling and Packaging. The classification, labeling and packaging of substances in the EU is regulated under EU Regulation 1272/2008 on Classification, Labelling and Packaging and, until 1st June 2015, Directive 67/548 EEC on Classification, Labelling and Packaging.

CMR: Carcinogenic, mutagenic or toxic to reproduction – meeting the criteria for classification in category 1 or 2 in accordance with Directive 67/548/EEC. This directive was recently replaced by the new EU regulation (EC) No 1272/2008 on classification, labelling and packaging of chemical substances and mixtures, the so-called CLP Regulation. According to the new CLP Regulation these substances shall be classified as 1A or 1B (see definition above).

CPD: The 'Construction Products Directive' 89/106/EEC of 21 December 1988 on the approximation of laws, regulations and administrative provisions of the member states relating to construction products. The 'Construction Products Directive' (CPD) aims to ensure the free movement of all construction products within the European Union by introducing a common technical language, consisting of harmonised standards and European technical approvals, in which manufacturers can express the performance of the products that they place on the market. This Directive will be replaced by the Construction Products Regulations (CPR) on 1st July 2013.

CPR: The Construction Products Regulation (EU) No 305/2011 of the European Parliament and of the Council of 9 March 2011 laying down harmonised conditions for the marketing of construction products and repealing Council Directive 89/106/EEC. This regulation aims to ensure reliable information on construction products in relation to their performance. This is achieved by providing a "common technical language" offering uniform assessment methods of the performance of construction products. The Construction Products Regulation entered into force on the 24th of April 2011 and will replace the Construction Products Directive (CPD) completely on 1st July 2013.

Critical effect: The first adverse effect that appears when the threshold (critical) concentration or dose is reached in the critical organ.

Critical dose: The dose of a substance at and above which adverse functional changes, reversible or irreversible, occur in a cell or an organ. In the EU-LCI process it may also refer to the lowest dose or exposure level at which the identified important (critical) toxic effect occurs in the chosen study(ies).

CSR: Chemical Safety Report (produced as part of the substance registration process under REACH).

DG ENTR: The European Commission's Directorate General for Enterprise and Industry.

DG JRC: The European Commission's Joint Research Centre.

DG SANCO: The European Commission's Directorate General for Health and Consumers.

DIBT: Deutsches Institut für Bautechnik (German Institute for Building Technology).

DNEL: Derived No-Effect Level – in REACH, the level of exposure below which no adverse effects are expected to occur and therefore the level above which humans should not be exposed. A DNEL is a derived level of exposure because it is normally calculated on the basis of available dose descriptors such as NOAELs or BMDs from animal studies.

ECETOC: European Centre for Ecotoxicology and Toxicology of Chemicals.

ECHA: The European Chemicals Agency.

EFSA: The European Food Safety Agency.

EGDS: The DG Enterprise Expert Group on Dangerous Substances.

Emission rate: The mass of chemical emitted from a specific unit area of product surface per unit time – [mg/m^2/h] or [mg/item/h].

Endpoint: In biological and clinical research, a disease, symptom or sign that constitutes one of the target outcomes of the experiment or trial.

EU-LCI: The EU-LCI value for a compound ('ascribed interim', 'derived interim', 'with derivation pending') agreed by the EU-LCI working group or formally endorsed by the EU Member States ('confirmed').

EU-LCI 'ascribed interim' value: The EU-LCI value given to a compound that, for whatever reason, has identical or very similar (differing by 20% or less) LCI values in the ANSES and AgBB lists.

EU-LCI 'candidate' compound: A compound under consideration for inclusion into the EU-LCI master list and subsequent evaluation (e.g. compounds identified by EU national authorities).

EU-LCI 'derived interim' value: The EU-LCI value of a compound derived *de novo* using the EU-LCI protocol.

EU-LCI 'interim' value: The 'ascribed' or 'derived' EU-LCI value in the EU-LCI master list to be used as the harmonised value by the EU Member States, as long as no formal process is underway to transform it into a 'confirmed' EU-LCI value.

EU-LCI 'with derivation pending': The EU-LCI value (for compounds with different LCI values in AgBB and ANSES lists) for which *de novo* derivation (by applying the EU-LCI protocol) has not been initiated.

EU-LCI WG: The expert group (established by the European Commission's DG JRC in the context of the PILOT INDOOR AIR MONIT administrative arrangement with DG SANCO) responsible for developing the EU-LCI framework, deriving EU-LCI values and preparing the EU-LCI master list.

EU-LCI master list: a list comprising compounds with 'confirmed' and 'interim' EU-LCI values, EU-LCI values 'with derivation pending' and EU-LCI 'candidate' compounds.

EU-RAR: European Union Risk Assessment Report. These reports were produced in accordance with Council Regulation (EEC) 793/93 on the evaluation and control of the risks of "existing" substances - chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances.

HEC: The human equivalent concentration represents the equivalent human exposure concentration adjusted to a continuous basis.

IAQG: Indoor Air Quality Guideline(s).

LOAEL: Lowest Observed Adverse Effect Level - the lowest dose or exposure level at which there is a statistically or biologically significant increase in the frequency or severity of an adverse effect compared with the unexposed control group.

LCI: Lowest Concentration of Interest - The LCI concept was first developed by the 'European Collaborative Action on 'Indoor Air Quality and its Impact on Man' when considering the best way to evaluate emissions from solid flooring materials. It was defined (see ECA Report No.18, 1997) as "the lowest concentration above which, according to best professional judgement, the pollutant may have some effect on people in the indoor environment".

Molar adjustment: The multiplicative factor, based on relative molecular weight, applied to the value derived by read-across, generally from a smaller molecular entity to a larger molecule, assuming the same active moiety. When applying molar adjustment in a homologous series of compounds, the molar adjustment factor rapidly increases. It is considered appropriate, therefore, to apply a cap or 'cut-off' (e.g. 1.5 x base value; two CH2 group per aliphatic chain) to limit the maximum adjustment made and achieve an appropriate level of safety in the risk assessment procedure.

MRL (Chronic Minimal Risk Level): An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a lifetime of exposure (based on chronic studies of 365 or more days). Used by ATSDR.

NIK: Niedrigste Interessierende Konzentration – the German (AgBB) LCI.

NOAEL: No Observed Adverse Effect Level - An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects compared to those observed in the control group; some effects may be produced at this level, but they are not considered as adverse or precursors to adverse effects. The NOAEL is thus generally taken as the highest exposure without adverse effect.

OECD: Organization for Economic Co-operation and Development.

OEL: Occupational Exposure Limit.

PBPK: Physiologically based pharmacokinetic [modelling] - Mathematical modeling of the kinetic behavior of a substance in the body, based on measured physiological parameters (*Also known as physiologically based toxicokinetic modelling*).

Point-of-departure value: The point on a toxicological dose-response curve established from experimental data generally corresponding to an estimated low effect level, based for example on the benchmark dose or a LOAEL or NOAEL.

Primary emission: The release of volatile compounds contained in the material from manufacture in free form. The rate of emission will normally decay continuously up to and beyond the standard 28-day chamber testing period.

QSAR: Quantitative Structure-Activity Relationship - The relationship between the physical and/or chemical properties of a substance and its ability to cause a particular effect. 'QSARs', as commonly referred to, are the mathematical models developed to predict the properties of a substance from its molecular structure. In toxicology the aim of QSARs is to predict the toxicity of a substance by analogy with the properties of other toxic substances of known structure and toxic properties.

R-Value: R is the sum of the ratio of individual VOC_i concentrations to their respective LCI_i values, i.e. $R = \Sigma (C_i/LCI_i)$ of assessable VOCs. In both the AgBB scheme and the ANSES protocol, the limit value of "exposure concentration" is $R \leq 1$ after 28 days.

Read-across: The technique used to predict endpoint information for one chemical by using data on the same endpoint from another chemical which is considered to be similar - e.g. on the basis of structural similarity and similar properties and/or activities. The approach can be qualitative or quantitative.

REACH: Registration, evaluation, authorisation and restriction of chemicals – the European regulatory framework for chemicals (Regulation (EC) No 1907/2006).

RfC (Reference Concentration)/RfD (Reference Dose): An estimate of the daily exposure concentration/dose to/of a substance for a human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious effects during a lifetime.

RIVM: Rijksinstituut voor Volksgezondheid en Milieu (Dutch national institute for public health and the environment).

Risk value (inhalation): A concentration of chemical (usually expressed as $\mu g/m^3$) that for noncancer toxicity is generally considered to be without adverse effects in populations of humans (including sensitive subpopulations) for the duration of exposure specified. Examples include: MRL, RfC, TC, TCA, WHO Air quality guidelines, DNEL).

SCOEL: EC Scientific Committee on Occupational Exposure Limits

Secondary emission: The release of volatile compounds formed by a continuous process (sometimes only after induction by an external influence) – for example by oxidation, hydrolysis or other chemical reaction – after the material is produced. This can result in an unusually prolonged emission phase or even an increase in emissions during the 28-day chamber testing period.

SVOC: Semi-Volatile Organic Compound – An organic compound whose boiling point is in the range from (240 °C to 260 °C) to (380 °C to 400 °C).[22]

TC (TCA): Tolerable Concentration (or Tolerable Concentration in Air), used by Health Canada and RIVM.

TRV: Toxicological Reference Value (or "reference dose"); see RfD.

TVOC: Total Volatile Organic Compounds – TVOC is a simple parameter that summarizes on Tenax TA adsorbed VOCs following GC elution between the C_6 to C_{16} chromatographic retention window. TVOC is

[22] This classification has been defined by the World Health Organization. Boiling points of some compounds are difficult or impossible to determine because they decompose before they boil at atmospheric pressure. Vapour pressure is another criterion for classification of compound volatility that may be used for classification of organic chemicals.

determined as the total integrated peak area, calibrated with use of toluene as reference compound[23]. Alternatively, the sum of VOCs ($TVOC_{SUM}$) may be determined by summing the individual concentrations of every identified and unidentified component eluting between n-hexane and n-hexadecane inclusively, at a concentration above 5 $\mu g.m^{-3}$, after subtracting non-interfering VOC artefacts[24].

UBA: Umweltbundesamt – the German Federal Environment Agency

VOC: Volatile Organic Compound – An organic compound whose boiling point is in the range from (50 °C to 100 °C) to (240 °C to 260 °C)[1].

VVOC: Very Volatile Organic Compound – An organic compound whose boiling point is in the range from <0 °C to (50 °C to 100 °C)[1].

WHO: World Health Organization

[23] ISO 16000-6 (2004) Indoor Air – Part 6: Determination of volatile organic compounds in indoor and test chamber air by active sampling on Tenax TA sorbent, thermal desorption and gas chromatography using MS/FID, Geneva, Switzerland, International Organization for Standardization.

[24] As in the German AgBB scheme.

APPENDIX A: *Data collection sheets and the summary factsheets of the compounds which were treated with priority by the EU-LCI WG*

A.1 Acetaldehyde

Compound	ACETALDEHYDE	*Data collection sheet*
N° CAS: 75-07-0	**EU classification:** 67/548/EEC: F+; R12 Carc. Cat. 3; R40, Xi; R36/37 **CLP:** Flam. Liqu. 1, Carc. 2, Eye Irrit. 2 STOT SE 3 **EU:** no risk assessment report **ECHA:** no DNEL derived	
1 ppm = 1.83 mg/m³	Supporting studies for inhalatory repeated toxicity on website available	

Organization Name	**OEHHA**	**Santé Canada**	**US EPA**
Risk Value Name	Inhalation REL	TC	RfC
Risk Value (µg/m³)	140	390	9
Risk Value (ppb)	80	220	5
Reference period	Chronic	Chronic	Chronic
Year	2008	2000	1991
Key Study	Appleman et al., 1982; 1986; supported by Saldiva et al., 1985; Woutersen et al., 1986, 1984; Woutersen and Feron, 1987	Appleman et al. (1982, 1986).	Appleman, L.M., et al., 1986. Effect of variable versus fixed exposure levels on the toxicity of acetaldehyde in rats
Study type	4-weeks study on rats	4-weeks study on rats	4-weeks study on rats
Species	Wistar rats	Wistar rats	Wistar rats
Duration of exposure in key study	Inhalation exposure 6 h/d, 5 d/w, 4 w	Inhalation exposure 6 h/d, 5 d/w, 4 w	Inhalation exposure 6 h/d, 5 d/w, 4 w
Critical effect	respiratory system: degenerative, inflammatory ans hyperplasic changes of the nasal mucosa in animals	no neoplasic effects in respiratory system	Degeneration of olfactory epithelium
Critical dose value	NOAEL: 270 mg/m³ (150 ppm)	CA (acceptable concentration): 218 mg/m³ (120 ppm)	NOAEL: 275 mg/m³ (150 ppm)
	LOAEL: 720 mg/m³ (400 ppm)		LOAEL: 728 mg/m³ (400 ppm)
Adjusted critical dose	BMC_{05}: 178 mg/m³ (99 ppm)	Temporal	Temporal + HEC
	Human equivalent concentration: 242.1 mg/ m³ (134.6 ppm)	218 x 6/24 x 5/7 = 39 mg/m³ (0.20 ppm)	NOAEL(ADJ): 48.75 mg/cu.m (26 ppm) = 273 mg/m³ x 6/24 x 5

			d/7 d
	Time-adjusted exposure: 43.2 mg/m³ (24 ppm) = (134.6*6/24*5/7)		NOAEL(HEC): 8.7 mg/m³ *
Single assessment factors (see table R.8.6)	UF_A √10 x UF_S √10x UF_H (10 x √10) = 300	UF_A 10 x UF_H 10 = 100	UF_S 10 x UF_A 10 x UF_H 10 = 100
Other effects			
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies			
* The NOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.23 m³/day, MVh = 20 m³/day, Sa(ET) = 11.6 sq. cm, Sh(ET) = 177 sq. cm. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.18. NOAEL(HEC) = NOAEL(ADJ) x RGDR = 8.7 mg/m³			

Compound	**ACETALDEHYDE**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m³]	1200
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	12 December 2012
General Information			
CLP-INDEX-Nr.	4	INDEX	605-003-00-6
EC-Nr.	5	EINECS – ELINCS - NLP	200-836-8
CAS-Nr.	6	Chemical Abstracts Service number	75-07-0
Harmonised CLP classification	7	Human health risk related classification	Flam. Liq. 1 Eye Irrit. 2 STOT SE 3 Carc. 2
Molar mass	8	[g/mol]	44.1
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Appelman et al., (1982) Toxicol.23, 293-307
Read across compound	10	Where applicable	
Species	11	Rat,… human	Rat (also hamster inhalation studies available which show lower sensitivity)

Route/type of study	12	Inhalation, oral feed,…	Inhalation
Study length	13	Days, subchronic, chronic	28 days
Exposure duration	14	Hrs/day, days/week	6 hrs/ day, 5 days a week
Critical endpoint	15	Effect(s), site of	Nasal irritation
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	NOAEC
POD Value	17	[mg/m^3] or [ppm]	275 mg/m^3
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
AF Study Length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	2
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	10
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	224
POD/TAF	28	Calculated value (µg/m^3 and ppb)	……1227.6 µg/m^3 …… 676.6 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m^3]	1200
Additional Comments	31		
Rationale Section	32		

Canada (TC: 390 µg/m^3) and US-EPA (Inhalation reference concentration: RfC: 800 µg/m^3), all evaluations are based on the studies by Appleman et al., 1982 and 1986:

POD and assessment factors

The key study (Appleman et al., 1982) shows the key effect (nasal irritation) and the NOAEC in the course of a 28 days study. For acetic aldehyde and also for other aldehydes is has been experimentally consistently shown that the NOAECs for this local effect don't change much with exposure time. Hence, the time extrapolation factor for length of study could be confined to 2. A factor of 2 is proposed for severity of effects. This has been made with regard to the carcinogenic effect (nasal tumors in rats if concentrations were driven into a massive irritating

state). Aldehydes react directly without metabolic activation, hence enzyme polymorphism is not considered to play a significant role. However, interindividual defense mechanisms may vary and this is considered by an intraspecies factor of 10.

References:

Acetaldehyde: CASRN 75-07-0. IRIS Risk information system. US-EPA: http://www.epa.gov/iris/subst/0290.htm

OEHHA: Office of Environmental Health Hazard Assessment, California: Acetaldehyde Reference Exposure Levels: Acetaldehyde: http://oehha.ca.gov/air/toxic_contaminants/pdf_zip/acetaldehyde_112508.pdf

Canadian Canadian Environmental Protection Act, 1999 Priority assessment substance list assessment report: Acetaldehyde: http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl2-lsp2/acetaldehyde/acetaldehyde_fin-eng.pdf

A.2 Toluene

Compound	TOLUENE	*Data collection sheet (1/3)*
N°CAS 108-88-3		
1 ppm (in air, 25 °C) = 3.76 mg/m³		

Organization Name	**OMS**	**US EPA IRIS**	**Santé Canada**	**RIVM**	**OEHHA**	**ATSDR**
Risk Value Name	Guide Value	RfC	CJA	TCA	REL	MRL
Risk Value (mg/m³)	**0.26**	**5**	**3.75**	**0.4**	**0.3**	**0.3**
Risk Value (ppm)	0.07	1.3	1	0.1	0.07	0.08
Reference period	Chronic	Chronic	Chronic	Chronic	Chronic	Chronic
Year	2005	2005	1992	2001	2003	2000
Key Study	Foo et al., 1990, Chronic neurobehavioural effects of toluene	Abbate *et al.*, 1993, Boey *et al.*, 1997, Cavalleri *et al.*, 2000, Eller *et al.*, 1999, Foo *et al.*, 1990, Murata *et al.*, 1993, Nakatsuka *et al.*, 1992, Neubert *et al.*, 2001, Vrca *et al.*, 1995, Zavalic *et al.*, 1998a	Andersen *et al.*, 1983, Human response to controlled levels of toluene in 6-h exposures	Foo *et al.*, 1990, Chronic neurobehavioural effects of toluene	Hillefors-Berglund *et al.*, 1995 supported by Foo *et al.*, 1990, Orbaek et Nise 1989 (human)	Zavalic *et al.*, 1998, Assessment of colour vision impairment in male workers exposed to toluene generally above occupational exposure limits
Study type	Neurobehavioural tests: measuring manual dexterity (grooved peg board), visual scanning (trail making, visual reproduction, Benton visual retention, and digit symbol), and verbal memory (digit	see below	Human response to controlled levels of toluene in six-hour exposures	Neurobehavioural tests: measuring manual dexterity (grooved peg board), visual scanning (trail making, visual reproduction, Benton visual retention, and digit symbol),	Subchronic inhalation study	Colour vision was evaluated by Lanthony-D-15 desaturated test

	span)			and verbal memory (digit span)		
Species	Human (30 female workers)	Human (occupationally-exposed workers)	Human	Human	Rat	Human (45 male workers occupationally exposed to toluene, employed in a printing press)
Duration of exposure in key study	Average of 5.7 years	see below	6-h exposures to clean air and to 10, 40 or 100 ppm of toluene	Average of 5.7 years	6 h/d, 5 d/w, 4 weeks, followed by 29-40 days recovery	Average of 16.8 years (mean value of [toluene] in ambient air = 119.96 ppm)
Critical effect	Decrease in performance at neuropsychological tests	Neurological effects (impaired color vision, impaired hearing, reduced performance in neuropsychological tests, sensations of concentration difficulties, headaches, dizziness)	Decrease in neuroligal function as measured by various tests, increased neurological symptoms ans respiratory irritation	Decrease performance in neuropsychological tests	Neurological effects (decrease the weight of the subcortical limbic area of the brain and alteration of dopamine receptors)	Neurological effects (dysfunctions of color vision)
Critical dose value		Average NOAEC = 128 mg/m^3 (34 ppm)	NOAEC 150 mg/m^3 *(40 ppm)*		NOAEC 150 mg/m^3 (40 ppm)	
	LOAEC 332 mg/m^3 (88 ppm)			LOAEC 332 mg/m^3 (88 ppm)	LOAEC 306.4 mg/m^3 (80 ppm)	LOAEC 134 mg/m^3 (35 ppm)
Adjusted critical dose	Temporal	Temporal	Temporal	Temporal	Temporal	Temporal

	80 mg/m³ (21 ppm)= 332 mg/m³ x 8h/24h x 5j/7j	46 mg/m³ (12 ppm) = 128 mg/m³ x10m³/20m³ x 5j/7j	38 mg/m³ (10 ppm)= 150 mg/m³ x 6h/24h	119 mg/m³ (30 ppm)= 332 mg/m³ x 10m³/20m³ x 5j/7j	26.8 mg/m³ (7 ppm)= 150 mg/m³ x 6h/24h x 5j/7j	32 mg/m³ (8.3 ppm)= 134 mg/m³ x 5j/7j x 8h/24h
Single assessment factors (see table R.8.6)	UF_L 10 x UF_H 10 x UF(for potential effects on the developing CNS) 3 = 300	UF_H 10	UF_H 10	UF_L 10 x UF_H 10 x UF_D (on neurotoxicity and respiratory irritation on animal) 3 = 300	UF_S 10 x UF_H 10 = 100	UF_L 10 x UF_H 10 = 100
Other effects						
Confidence		High		High		
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies						

Compound	TOLUENE	*Data collection sheet (2/3)*
N°CAS 108-88-3		
1 ppm (in air, 25 °C) = 3.76 mg/m³		

Organization Name	**Afsset**	**German IAQ**	**Austrian IAQ**	**EU-RAR- based***	**EU-RAR-based***	**ECHA Registered Substances**
Risk Value Name	VTR	IAG (I)	IAG	DNEL consumer	DNEL consumer	DNEL
Risk Value (mg/m³)	**3**	**0.3**	**0.075**	**1.40**	**2.5**	**56**
Risk Value (ppm)	0.8	0.07	0.02	0.37	0.66	14.75
Reference period	Chronic	Chronic	Chronic	Chronic	Chronic	Chronic
Year	2010	1996	2006	2011	2011	2011
Key Study	Zavalic *et al.,* 1998	Echeverria et al. 1989 supported by various studies, including long term occupational exposure	Campagna et al. 2001	Thiel and Chahoud In RAR, 2003	Pryor et al. in RAR, 2003	
Study type	Colour vision was evaluated by Lanthony-D-15 desaturated test	Cognitive tests	Colour Confusion Index, Lanthony D-15 desaturated panel	Developmental toxicity	Multisensory conditioned avoidance response test	
Species	Human (45 male workers occupationally exposed to toluene, employed in a printing press)	Human volunteers	72 Human workers, occupationally exposed		Male fisher rats	
Duration of exposure in key study	Average of 16.8 years (mean value of [toluene] in ambient air = 119.96 ppm)	3 days, 7 hours, 281 and 562 mg Toluol/m^{-3}			14 weeks treatment	

Critical effect	Neurological effects (disorders of color vision)	CNS effects	CNS-effects: color vision loss	Effects on fertility and reproduction (dev.): reduced foetal weights and birth weights in r in the offspring of exposed mothers. Long-lasting developmental neurotoxicity, manifest as impaired learning ability.	Hearing loss	No information about DNEL derivation
Critical dose value	NOAEC 123 mg.m^{-3} *(32 ppm)*			NOAEC 2250 mg/m^3	NOAEC 2660 mg/m^3	Long-term inhalation DNEL (systemic effects) for the general population derived from industry
		LOAEL: 281 mg/m^3 *(73 ppm)*	LOAEL 35 mg/m^3 *(9 ppm)*			
Adjusted critical dose	Temporal	Chronic	Chronic	Chronic	Subchronic	No information about DNEL derivation
	29 mg/m^3 (7.5 ppm)= 123 mg/m^3 x 5j/7j x 8h/24h		35 mg/m^3 / 4.2 = 8 mg/m^3	401.8 mg/m^3 = 2250 mg/m^{3}x 5j/7j x 6h/24h		
Single assessment factors (see table R.8.6)	UF_H 10	Toxicokin: 5x Intrasp. 10x UF (sens) 2x 10x = 1000	UF LOAEL-NOAEL 10x UF Intrasp. 10 =100	UF 2x Intersp. 2.5x4 Intrasp. 10x UF (sens) 2x =600	Intersp. 2.5x4 Intrasp. 10x Exp.dur:3x UF (sens) 2x =600	Total AF: 1.7
Other effects						

Confidence						
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies						

*DNELs derived based on key studies selected for risk characteriszation in the EU RAR (risk characterization in the RAR is based on the margin of safety MOS concept for defined consumer scenarios (e.g. spray painting).

Compound	TOLUENE	*Data collection sheet (3/3)*

STUDIES supporting the US EPA RfC						
Study number and reference	**Number of workers and duration of exposure (average years ± SD)**	**NOAEL (ppm)**	**LOAEL (ppm)**	**Effect/test**	**Response level at the LOAEL (statistically significant response compared to controls)[a]**	**Noted potential limitations**
1. Abbate et al., 1993	Reference (n=40), exposed (n=40) (12-14 years; no SD reported)	None	97	Brainstem response auditory-evoked potential	28% increase of the latency shift for wave-I during passage from 11 to 90 repetitions.	
2. Boey et al., 1997	Reference (n = 29) exposed (n = 29) (4.9 ± 3.5 years; range of 1-13 years)	None	91	Neuropsychological examination; digit span, visual reproduction, Benton visual retention test, trail making test, symbol digit modality test, grooved pegboard test, and finger tapping tests	Increased time to complete the grooved pegboard test 7% and 6% for dominant and non-dominant hands respectively, increase in time to complete trail-making test parts A&B, 31% & 28%, respectively; 15% decrease in backward digit span test; 12% and 10% decrease in symbol digit modality test for written and oral sections, respectively.	Control workers were exposed to 12 ppm toluene

3. Cavalleri et al., 2000	Reference (n=16), exposed (n=33) (9.75 years; no SD reported)	None	42	Colour vision impairment (Lanthony D-15)	29% increase in CCI and 49% increase in total confusion index (TOCI) (reported as mean of both eyes).	Exposure measured from urinary excretion of toluene: on the basis of previous data, air concentrations estimated to be 42 ppm.
4. Eller et al., 1999	Reference (n=19), low exposure (n=30), high exposure (n=49) low exposure (1-12 years; no SD reported) high exposure (>12 years)	20	>100	Neuropsychological examination (Cognitive Function Scanner); verbal and nonverbal learning and memory, visuomotor function, computerized neurological examination (CATSYS, TREMOR, and SWAY), subjective assessment	13% increase in performance time on Bourdon Wiersma Test but no increase in the number of missed or incorrect detections; 33% of exposed population reported concentration difficulties.	The high exposure classification was based on historical exposures which may have exceeded 100 ppm for up to 27 years.
5. Foo et al., 1990	Reference (n=30), exposed (n=30) (5.7 ± 3.2 years)	None	88	Neurobehavioral tests: Benton visual retention test, visual reproduction, trail making, grooved pegboard, digit span, digit symbol, finger tapping, and simple reaction time	Increased time to complete the trail-making test parts A&B, 51% & 63%, respectively; 25% decrease in digit symbol test performance; 16% decrease in total digit span test scores (both forward and backward).	Control workers were exposed to 13 ppm toluene for 2.5 ± 3.2 years. The education level was lower in the exposed group. As a result, data from the neurobehavioral tests were adjusted for years of education using a generalized linear model.

6. Murata et al., 1993	Reference (n=10), exposed (n=10) (11 years; range of 1-36 years; no SD reported)	None	83	Electrophysiological analysis of maximial motor and sensory nerve conduction velocity (MCV & SCV)	9% reduction in the MCV in the forearm and 6% reduction in the SCV in the palm.	Exposed workers were matched for age but not alcohol consumption.
7. Nakatsuka et al., 1992	Reference (n=120), exposed (n=174)	44-48	None	Color vision impairment (Lanthony's new colour test and Ishihara's color vision test)	No measured effect on colour vision.	In lieu of determining exposure duration, groups were age-matched to control for effects of aging on colour vision.
8. Neubert et al., 2001	Ref-ex (n=109), ref-int (n=48), exp gp I (n=316), exp gp II (n=535), exp gp III (n=308), exp gp IV (n=65)	39 (exp gp 1)	81 (ex gp IV)	Psychophysiological and psychomotor testing: verbal memory span, visuomotor performance, immediate visual memory, self-rating of feeling, biosensory vigilance, critical flicker fusion frequency test, personality dispositions	5% reduction in ascending flicker fusion frequency.	Exposure was identified as chronic but the duration was not reported.

9. Vrca et al., 1995	Reference (n=59), exposed (n=49) (21.4 ± 7.4 years)	None	40-60	Visual evoked potentials	The amplitudes of visual evoked brain potentials were 24, 43, and 55% higher for N75, P100, and N145, respectively.	Exposure levels were estimated based on urinary levels of metabolites and toluene levels in blood.
10. Zavalic et al., 1998a	Reference (n=90), low exposure (n=46), high exposure (n=37) low exposure (16.21 ± 6.1 years) high exposure (18.34 ± 6.03 years)	32	132	Color vision impairment (Lanthony D-15)	10-14% increase in CCI (both eyes).	The results from this investigation were reported in several publications (Zavalic et al., 1998 a, b ,c); some reporting discrepancies exist regarding the number of workers in the exposed and control groups and the statistical analyses.

Compound	TOLUENE		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	2900
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	29 August 2012
General Information			
CLP-INDEX-Nr.	4	INDEX	R2B
EC-Nr.	5	EINECS – ELINCS - NLP	203-625-9
CAS-Nr.	6	Chemical Abstracts Service number	108-88-3
Harmonised CLP classification	7	Human health risk related classification	Flam. Liq. 2 Asp. Tox. 1 Skin. Irrit. 2 STOT SE 3 Rep. 2 STOT RE 2
Molar mass	8	[g/mol]	92.14
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Zavalic et al., 1998
Read across compound	10	Where applicable	
Species	11	Rat,… human	Human
Route/type of study	12	Inhalation, oral feed,…	Inhalation, occupational
Study length	13	Days, subchronic, chronic	17 years
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	Neurological effects (colour vision impairment)
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose,….	LOAEC
POD Value	17	[mg/m^3] or [ppm]	123 mg/m^3
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	4.2
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	2
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	

	23 b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	5
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	42
POD/TAF	28	Calculated value (µg/m³ and ppb)	……2928.57 µg/m³ ….. 772.58 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	2900
Additional Comments	31		
Rationale Section	32		

Rationale for critical effects

Neurological effects have been demonstrated in rodents and in humans exposed by the respiratory route during chronic exposure. Toluene like many other organic solvents can impair colour vision, even at concentrations below 50 ppm. Reprotoxic and developmental effects have also been shown, particularly in animals. However, the neurological effects were reported at lower concentrations than those for effects on fertility or development.

WHO, RIVM, ATSDR, US-EPA, ANSES, German IAQ, Austria IAQ, based their values on human studies showing neurologic effects (could be neurobehavioural, vision impairment, …).

Rationale for key study

The reference value is based on the Zavalic´et al. (1998) study. In this study, colour vision was examined in two groups of workers occupationally exposed to toluene and in a control group. The authors referenced standard methods for measuring both ambient air concentrations and individual blood toluene levels. Significantly higher values of colour confusion index and alcohol intake-adjusted colour confusion index in exposed groups in comparison to the non-exposed group were reported. The colour confusion index scores were adjusted for alcohol consumption. A LOAEC of 134 mg/m³ (35 ppm) could be derived from this study.

ATSDR (2000) and Anses (2010) also based their toxicological reference value on this study. US-EPA (2005) considered several human studies as key studies, including the Zavalic´et al. (1998). An average NOAEC from these studies was used.

The study from Zavalic´was selected as the key study as it is an epidemiological study on workers exposed for many years and a dose-response relationship for neurological effects was observed in this study.

Rationale for starting point

In the study of Zavalic´ et al. (1998), two groups of exposed workers to toluene and a control group have been evaluated:

- the first exposed group, Group E1, comprised 41 workers (toluene exposure ranged from 11.3 to

49.3 ppm; median 32.0 ppm)
- the second exposed group, Group E2, comprised 32 workers (toluene exposure ranged from 66.00 to 250.00 ppm; median 132.00 ppm).
- the non-exposed group, Group NE, comprised 83 subjects.

Each group was divided into two subgroups; alcohol consumers and non-consumers. Colour vision loss was expressed as a colour confusion index (CCI) and as an age and alcohol intake-adjusted colour confusion index (AACCI).

The AACCI value was significantly higher in Group E2 compared to Group NE (t-test, P <0.0001) and Group E1 (t-test; P <0.05), and in Group E1 compared to Group NE (t-test; P < 0.05). Difference was not established in CCI value between groups E1 and NE. No statistically significant correlation was established between AACCI and any marker of toluene exposure in Group E1, or in the subgroups of alcohol consumers and non-consumers. Significant correlation was established between the AACCI value and toluene in air, between AACCI and orthocresol in urine and between AACCI and hippuric acid in urine in this Group.

The authors concluded that age and alcohol intake, play a role in colour vision impairment. Alcohol intake plays a role as an additive cofactor with toluene.

Based on the evidence that the AACCI value was significantly higher in Group E1 (median toluene exposure 32.0 ppm) compared to Group NE, 32 ppm could be considered as a LOAEC.

Rationale for Uncertainty factors

- *AF Dose response*: An assessment factor of 2 is applied to account for extrapolating from a LOAEC to a NOAEC. This low factor is justified by the fact that numerous human studies have identified NOAELs in the range of 25-50 ppm toluene for individual neurological effects and also by the fact that US-EPA considered 34 ppm as a NOAEC (US-EPA, 2005) .
- *Adjusted study length factor*: an assessment factor to account for extrapolating from less than chronic results was not necessary. Most of the studies used in the analysis were of chronic duration.
- *Adjusted exposure duration factor*: The LOAEL (average) of 32 ppm (123 mg/m^3) was adjusted from an occupational exposure scenario to continuous exposure conditions as follows:

NOAEL (adj) = NOAEL (average) x 8 hours /24 hours x 5 days/7 days = 123 mg/m^3 x 10m^3/20m^3 x 5 days/7 days = 30 mg/m^3

- *Interspecies differences*: an assessment factor to account for laboratory animal-to-human interspecies differences was not necessary because the point of departure is based on human exposure data.
- *Intraspecies differences*: a 5-fold assessment factor for was used to account for potentially susceptible human subpopulations and life stages. Differences in human susceptibility may also be due to life stage (e.g., childhood or advanced age), differences among the adult population, genetic polymorphisms, decreased renal clearance in disease states, and unknown pharmacodynamic variations in response to toluene exposure.

References

Echeverria D, Fine L, Langolf G, Schork A, Sampaio C. Acute neurobehavioural effects of toluene. Br J Ind Med. 1989 Jul; 46(7):483-95.

Foo SC, Jeyaratnam J, Koh D. (1990) Chronic neurobehavioural effects of toluene. British Journal if Industrial Medicine. 1990 Jul; 47(7):480-4.

Zavalić M, Mandić Z, Turk R, Bogadi-Sare A, Plavec D. (1998a) Quantitative assessment of color vision impairment in workers exposed to toluene. American journal of industrial medicine. 1998 Mar; 33(3):297-304.

A.3 Xylenes

Compound	XYLENES	*Data collection sheet (1/2)*
N°CAS 1330-20-7	**EU- Classification:** 67/548/EEC: R10, Xn; R20/21, Xi; R38 **CLP:** Flam. Liq. 3 Acute Tox. 4, Acute Tox. 4 *Skin Irrit. 2	

Organization Name	**INDEX Project**	**ATSDR**	**OEHHA**	**U.S. EPA**
Risk Value Name	Chronic exposure limit	Chronic inhalation MRL	REL	RfC
Risk Value (µg/m³)	200	175	700 for mixed xylenes or for total of individual isomers	100
Risk Value (ppb)	57	50	200	29
Reference period	Chronic	Chronic	Chronic	Chronic
Year	2005	2007	2000	2003
Key Study	Uchida et al., 1993	Uchida et al., 1993	Uchida et al., 1993	Korsak et al., 1994
Study type	Epidemiologic study on workers (175 exposed/241 control)	Epidemiologic study on workers (175 exposed/241 control)	Epidemiologic study on workers (175 exposed/241 control)	3 months animal study
Species	Human	Human	Human	Male Rats
Duration of exposure in key study	Occupational exposure for an average of 7 years	Occupational exposure for an average of 7 years	Occupational exposure for an average of 7 years	6h/d, 5d/w at 0 or 100 ppm for 6 months or 1000 ppm for 3 months

Critical effect	Dose related increase in the prevalence of eye irritation, sore throat, floating sensation, and poor appetite.	neurotoxicity (anxiety, forgetfulness, floating sensation) and respiratory toxicity (nasal irritation and sore throat) and eye irritation.	Dose related increase in the prevalence of eye irritation, sore throat, floating sensation, and poor appetite.	CNS: impaired motor coordination (decreased rotarod performance) Subchronic inhalation study in male rats
Critical dose value				NOAEL: 50 ppm (217 $mg.m^{-3}$)
	LOAEL: 62 mg/m^3 (14.2 ppm)	LOAEL: 62 mg/m^3 (14.2 ppm)	LOAEL: 62 mg/m^3 (14.2 ppm)	LOAEL: 100 ppm *LOAEL(HEC): 78 mg/m^3*
Adjusted critical dose	Subchronic -> chronic	No duration adjustment	Temporal	Temporal
	22 mg/m^3 (5.03 ppm)		14.2 x 10/20 x 5/7 = 5.1 ppm (22.3 mg/m^3)	NOAEL = 217 x 6/24 x 5/7 = 39 mg/m^3 (9 ppm)
Single assessment factors (see table R.8.6)	UF_L 10 x UF_H 10 = 100	UF_L 10 x UF_H 10 x UF_S 3 = 300	UF_L 3 x UF_H 10 = 30	UFD 3 x UF_S 3 x UF_A 3* x UF_H 10 = 300
Other effects				
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies				
* A factor of 3 was applied because default NOAEL [HEC] dosimetric adjustments were used to calculate a human equivalent concentration (HEC), reducing the uncertainty involved with the extrapolation from the results of an animal study to a human exposure scenario (i.e., the toxicokinetic portion of the UF is 1; the toxicodynamic portion of the UF is 3).				

Compound	XYLENES	*Data collection sheet (2/2)*
N°CAS 1330-20-7	**EU- Classification:** 67/548/EEC: R10, Xn; R20/21, Xi; R38 **CLP:** Flam. Liq. 3 Acute Tox. 4, Acute Tox. 4 *Skin Irrit. 2	

	Reprotoxic effects	*Provisional*		
Organization Name	**RIVM**	**Health Canada**	**ECHA Registered substance**	**ICPS, 1997**
Risk Value Name	TCA	TC	DNEL	Guidance value
Risk Value (µg/m³)	870	180 (provisional)	14800	870
Risk Value (ppb)	250			200
Reference period	Chronic			Chronic
Year	1999	1991	2011	1997
Key Study	Hass and Jakobsen, 1993, Prenatal toxicity of xylene inhalation in the rat: A teratogenicity and postnatal study	Ungvary and Tatrai, 1985		Hass and Jakobsen, 1993
Study type	Teratology and postnatal study			Teratology and postnatal study
Species	Rats	Rats		Rats
Duration of exposure in key study	6 h/d on days 4 to 20 of gestation			6 h/d on days 4 to 20 of gestation
Critical effect	Developmental (the postnatal study, the xylene-exposed pups had a higher body weight and an impaired performance on a motor ability test (Rotarod))	Developmental	No information available*	Developmental (the postnatal study, the xylene-exposed pups had a higher body weight and an impaired performance on a motor ability test (Rotarod))

Critical dose value			Long-term inhalation DNEL for consumers (systemic effects) derived by industry (ECHA-website: registered substances), no information about derivation of DNEL	
	LOAEL: 870 mg/m^3 (250 ppm)			LOAEL: 870 mg/m^3 (250 ppm)
Adjusted critical dose	No duration adjustment			No duration adjustment
Single assessment factors (see table R.8.6)	UF_L 10 x UF_H 10 x UF_A 10 = 1000			UF_L 10 x UF_H 10 x UF_A 10 = 1000
Other effects				
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies				
* A factor of 3 was applied because default NOAEL [HEC] dosimetric adjustments were used to calculate a human equivalent concentration (HEC), reducing the uncertainty involved with the extrapolation from the results of an animal study to a human exposure scenario (i.e., the toxicokinetic portion of the UF is 1; the toxicodynamic portion of the UF is 3).				

Compound	XYLENES		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	500
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	30 November 2012
General Information			
CLP-INDEX-Nr.	4	INDEX	601-022-00-9
EC-Nr.	5	EINECS – ELINCS - NLP	215-535-7
CAS-Nr.	6	Chemical Abstracts Service number	1330-20-7
Harmonised CLP classification	7	Human health risk related classification	Flam. Liq. 3 Acute Tox. 4 (skin) Skin Irrit. 2 Acute Tox. 4 (inhalation)
Molar mass	8	[g/mol]	106.16
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Uchida et al., 1993
Read across compound	10	Where applicable	
Species	11	Rat,… human	Human
Route/type of study	12	Inhalation, oral feed, …	Inhalation/occupational exposure
Study length	13	Days, subchronic, chronic	7 years
Exposure duration	14	Hrs/day, days/week	Average 7 y, 8 h/d, 5 d/wk
Critical endpoint	15	Effect(s), site of	Sensory irritation* (eye irritation, sore throat) and CNS effects (floating sensation and poor appetite in humans); supported by neurological and developmental toxicity in rats
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	LOAEC
POD Value	17	[mg/m^3] or [ppm]	14.2 ppm
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	4.2
AF Study Length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		

AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	3
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	5
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	126
POD/TAF	28	Calculated value (µg/m³ and ppb)	…… 492.2 µg/m³ ……112.7 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	500
Additional Comments	31		
Rationale Section	32		

Xylene (CAS 1330-20-7) has three isomers:

- o-xylene (CAS: 95-47-6)
- m-xylene (CAS: 108-38-3)
- p-xylene (CAS: 106-42-3)

A risk value for xylenes was derived by US-EPA (RfC: 100 µg/m^2), RIVM (TCA: 870 µg/m^3), Health Canada (provisional TC: 180 µg/m^3), ICPS (guidance value: 870 µg/m^3), INDEX (chronic exposure limit: 200 µg/m^3), ATSDR (chronic inhalation MRL: 175 µg/m^3) and OEHHA (REL: 700 µg/m^3).

POD

The LCI derivation is based mainly on the key study of Uchida et al. (1993). The occupational study of Uchida et al. (1993), involved 175 xylene exposed workers and 241 non-exposed workers. The LOAEL of 14 ppm derived from the Uchida et al. (1993) study is based on the average exposure levels to the sum of the three isomers in the group of exposed workers. Health effects observed in this exposed group were an increased prevalence of subjective symptoms in the exposed workers which were apparently related to the effects on the central nervous system and to the local effects on the eyes, the nose, and the throat. Evidence of health effects of xylenes on the central nervous system is also supported by developmental neurotoxicity effects observed in rats exposed to xylenes (Hass & Jakobsen, 1993 and Korsak et al., 1994).

Evidence for local irritation effects caused by xylenes exposure is contradicted by additional data: In the Uchida et al. (1993) study, a LOAEL value of 14 ppm xylenes had been derived based on CNS effects and local irritation effects seen for a mixture of solvents, composed from 70 % xylenes and 30 % remaining, unidentified compounds. However, it is doubtful whether the observed irritating effect observed in the Uchida et al. (1993) have been caused by xylenes exposure, or rather by the 30 % remaining unidentified fraction. Based on the RD50 values (mice) for m- and p-xylene, respectively, and the Alarie algorithm

(Schaper et al. 1993) the threshold for sensory irritation is calculated to be about 40 ppm for workers. A human exposure study (4 hours) with toluene shows a LOAEL value of 100 ppm for sensory irritation (Bælum et al., 1990). In addition, based on RD50 values from mice exposed to xylenes, and applying the Kuwabara et al. algorithm (2007), which extrapolates animal test RD50 values to LOAEL a LOAEL of 88 ppm xylene for sensory irritation for the general population, was predicted (Wolkoff, 2012). Summing up this information, there are strong indications that there is no causal relationship between sensory irritating effects observed in the Uchida et al. (1993) study and exposure to 14 ppm xylenes.

Assessment Factors

Standard default assessment factors for:

1) *reliability of dose-response* (extrapolation from LOAEL to NOAEL; note 21a): a factor of 3 is applied.

2) *adjustment of study length* (note 22), a factor of 2 is applied considering that in the key study, the workers are exposed during 7 years (subchronic exposure).

3) *exposure duration* (note 19, a time adjustment factor of 4.2 is applied considering the exposure duration in the key study compared to the exposure in the general population.

4) *intraspecies AF* (note 24) were applied: a factor of 5 is applied to take into account the variability among the general population.

References

Bælum, J., Lundquist, G.R., Mølhave, L., Andersen, I., 1990. Human response to varying concentrations of toluene. Int. Arch. Occup. Environ. Health 62, 65–71.

Hass U, Jakobsen BM, Prenatal toxicity of xylene inhalation in the rat. A tetatogenicity and postnatal study. 1993. Pharmocology and Toxicilogy. 73:1:20-23.

Korsak Z, Wisniewska-Knypl J, Swiercz, R. 1994. Toxic effects of subchronic combined exposure to n-butyl alcohol and m-xylene in rats. Int J Occup Med Environ Health 7:155-166.

Schaper, M. 1993 Development of a database for sensory irritants and its use in establishing occupational exposurelimits, American Industrial Hygiene Association Journal, 54,

Uchida Y, Nakatsuka H, Ukai H, Watanabe T, Liu YT, Huang MY *et al.* 1993. Symptoms and signs in workers exposed predominantly to xylenes. Int. Arch. Occup. Environ. Health 64:597-605.

Wolkoff, P., 2012 Indoor air pollutants in office environments: Assessment of comfort, health, and performance. Int. J. Hyg. Environ. Health (2012), (in press) http://dx.doi.org/10.1016/j.ijheh.2012.08.001

A.4 Trimethylbenzenes

Compound	**Trimethylbenzenes**		***Data collection sheet***
N°CAS 95-63-6 25551-13-7	**EU- Classification:** R 10; Xn; R20, Xi; R36/37/38 67/548/EEC annex 1 **CLP:** Flam. Liq. 3 Acute Tox. 4, Skin Irrit. 2 Eye Irrit. 2 Asp. Tox. 1		
	Alkylbenzenes	*Trimethylbenzenes*	*1,2,4-Trimethylbenzene*
Organization Name	**RIVM**	**Ontario Ministry of Environment**	**ECHA: Registered substances**
Risk Value Name	TCA	AAQC	DNEL
Risk Value (µg/m³)	870	220	29400
Risk Value (ppb)			
Reference period	Chronic	Chronic	Chronic
Year	2007	2007	2013
Key Study	based on Isopropylbenzene EU (2001) Risk Assessement Report – Cumene. European Chemicals Bureau, Existing Substances.	Korsak and Rydzynski, 1996; Gralewicz and Wiaderna, 2001; Wiaderna *et al.*, 2002	Clark DG, et al. 1989
Study type	Chronic	Subchronic inhalation	Chronic inhalation
Species	Rats	Rats	Rats
Duration of exposure in key study	6h/day, 5 days/week chronic	6h/day, 5 days/week	6h/day, 5 days/week, 1 yr
Critical effect	Neurotoxicity	Neurotoxicity	Irritation (respiratory tract)
Critical dose value			Long-term inhalation DNEL for consumers (systemic effects) derived by industry (ECHA-website: registered substances), no transparent information about derivation of DNEL
	NOAEL 490 mg/m³	NOAEL 123 mg/m³	NOAEC 1800 mg/m³

Adjusted critical dose	5.6	5.6	
Single assessment factors (see table R.8.6)	UF_H 10 x UF_A 10 = 100	UFs 3 x UF_H 3 x UF_A 10 = 100	1.7 (Overall assessment factor)
Other effects			

Compound	TRIMETHYLBENZENES		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	450
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	22 November 2012
General Information			
CLP-INDEX-Nr.	4	INDEX	601-025-00-5 601-043-00-3 601-025-00-5
EC-Nr.	5	EINECS – ELINCS - NLP	247-099-9 202-436-9 203-604-4 208-394-8
CAS-Nr.	6	Chemical Abstracts Service number	25551-13-7 95-63-6 108-67-8 526-73-8
Harmonised CLP classification	7	Human health risk related classification	Not harmonised
Molar mass	8	[g/mol]	120.19
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Korsak and Rydzynski, 1996, 1997, 2000a, 2000b
Read across compound	10	Where applicable	
Species	11	Rat,… human	Rat
Route/type of study	12	Inhalation, oral feed, …	Inhalation
Study length	13	Days, subchronic, chronic	Subchronic
Exposure duration	14	Hrs/day, days/week	6h/24h / 5d/7d
Critical endpoint	15	Effect(s), site of	Neurotoxicity and local effects on lungs
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	NOAEC
POD Value	17	[mg/m^3] or [ppm]	123 mg/m^3
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
AF Study Length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	

Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic Worker - General population	10
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	280
POD/TAF	28	Calculated value (µg/m³ and ppb)	……439.29 µg/m³ ….. 88.84 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	450
Additional Comments	31		
Rationale Section	32		

Trimethylbenzene (CAS 25551-13-7) has three isomers:

- 1,3,5-trimethylbenzene (synonym: mesitylene; CAS 108-67-8)
- 1,2,4-trimethylbenzene (synonym: pseudocumene; CAS 95-63-6)
- 1,2,3-trimethylbenzene (synonym: hemimellitene; CAS 526-73-8)

None of the agencies (WHO, EPA, ATDSR, EU RAR, INDEX) provide a human health risk assessment for TMB exposure in indoor environments, but the Ontario Ministry of Environment [2007] and RIVM [Dusseldorp et al. 2007] reviewed the compound and derived a 24-hour Ambient Air Quality Criterion (AAQC) of 220 µg/m³ for trimethylbenzenes and a chronic air limit value (TCA) of 870 µg/m³ respectively. An industry sponsored study (Firt 2007) derived an RfD of 3 mg/m³ using standard USEPA methods.

POD

The LCI derivation is based mainly on the key studies by Korsak et al. [1996, 2000a, b] and Wiaderma et al. (2002). In accordance with Ontarion Ministry of Environment (2007) CNS effects were chosen as the critical effect observed in 5 subchronic inhalation studies on rats. In subchronic inhalation studies of 1,2,3 and 1,2,4-trimethylbenzene (Korsak et al., 2000a and 2000b; Korsak and Rydzynski, 1996) rats were exposed to 123 mg/m³, 492 mg/m³ and 1230 mg/m³, 6 h/day, 5 days/week for 3 months. The same neurotoxic effects were observed as in the subacute studies. A NOAEC of 123 mg/m³ and a LOAEC of 492 mg/m³ was identified for TMB which includes also local effects in the lung and is below the exposure concentration (1476 mg/m³) at which reprotoxic effects were observed (Sallenfait et al. 2005). A comparison of the available toxicity data for 1,2,4-TMB and 1,3,5-TMB suggests similar toxicity.

Assessment factors

Standard default assessment factors for adjustment for exposure duration (note 19), study length (note 22), interspecies AF (note 23b) and intraspecies AF (note 24) were applied.

No additional factor for combined effects was introduced, because according to Clark et al. (1989), the NOAEL

for a mixture of high aromatic naphtha was without systemic toxicity with a NOAEC of 1800 mg/m^3 in a 12 month rat study.

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TMB is listed by ECHA: http://apps.echa.europa.eu/registered/registered-sub.aspx#search

A.5 Dichloro-(1,4)-benzene

Compound	DICHLORO-(1,4)-BENZENE	*Data collection sheet*
N°CAS 106-46-7	**Classification:** Carc. Cat. 3; R40, Xi; R36, N; R50-53 **CLP:** Carc. 2, Eye Irrit. 2, Aquatic Acute 1, Aquatic Chronic 1	
1 ppm (in air, 25 °C) = 6.0 mg/m³	**EU Registered Substances:** No DNEL published	

Organization Name	**ATSDR**	**OEHHA**	**US EPA**	**RIVM**	**EU-RAR based***
Risk Value Name	MRL	REL	Inhalation RfC	TCA	DNEL
Risk Value (mg/m³)	0.08	0.8	0.8	0.67	0.8
Risk Value (ppm)	0.013	0.1	0.1	0.11	0.13
Reference period	Chronic	Chronic	Chronic	Chronic	Chronic
Year	2006	1999	1996	1999	2011
Key Study	Aiso S, Takeuchi T, Arito H, et al. 2005b. Carcinogenicity and chronic toxicity in mice and rats exposed by inhalation to para-dichlorobenzene for two years.	Chlorobenzene Producers Association, 1986. Parachlorobenzene: Two-generation reproduction study in Sprague-Dawley rats.	Chlorobenzene Producers Association, 1986. Parachlorobenzene: Two-generation reproduction study in Sprague-Dawley rats.	Riley et al., 1980. Para-dichlorobenzene: Long-term inhalation study in the rat.	JBRC (1995). Toxicology and carcinogenesis studies of 1,4-dichlorobenzene in F344/DuCrj rats and Crj:BDF1 mice (two years inhalation studies). Japan Bioassay Center Research (JBRC), November 1995.
Study type	2-years inhalation study	10-weeks multigeneration reproductive study: whole-body inhalation exposures (0, 50, 150 or 450 ppm)	10-weeks multigeneration reproductive study: whole-body inhalation exposures (0, 50, 150 or 450 ppm)	76-weeks inhalation study	Inhalation study
Species	Male and female F344/DuCrj rats + 50 male and female Crj:BDF1 mice	Sprague-Dawley rats (28 rats/sex/group)	Sprague-Dawley rats (28 rats/sex/group)	Rats	Mice and rats

Duration of exposure in key study	6 h/d, 5 d/w for 104 weeks	6 h/d, 7 d/w for 10 weeks	6 h/d for 7 d/w for 10 weeks	5h/d, 5d/w for 76 weeks	5h/d, 5d/w for 104 weeks
Critical effect	Moderate or severe eosinophilic changes in the nasal olfactory epithelium in female rats	General effects (reduced body weights and food consumption), CNS effects (tremors), Respiratory/dermal effects (nasal and ocular discharge), Liver effects (increased liver weight), and Kidney effects (increased kidney weight)	Increased liver weights in P1 males	Increased kidney and liver weights in the high dose group. (500 ppm)	Liver toxicity (increased liver enzyme: AST, ALT, LDH, alkalinephosphatases; increased liver weight in both sexes and histological findings: slight local necrosisin both sexes, central hepatocellular hypertrophy in males)
Critical dose value	NOAEL: 158.4 mg/m^3 (19.8 ppm)	NOAEL: 300 mg/m^3 (50 ppm)	NOAEL: 301 mg/m^3 (50 ppm)	NOAEL: 450 mg/m^3 (75 ppm)	NOEL: 450 mg/m^3 (75 ppm)
	LOAEL: 598 mg/m^3 (74.8 ppm)	LOAEL: 900 mg/m^3 (150 ppm)	LOAEL: 902 mg/m^3 (150 ppm)	LOAEL: 3000 mg/m^3 (500 ppm)	
Adjusted critical dose	$BMCL_{10}$: 57 mg/m^3 (9.51 ppm)	Temporal	$NOAEL_{HEC}$: 75 mg/m^3 (12.5 ppm)	$NOAEL_{ADJ}$: 67 mg/m^3 (11 ppm)	$NOAEL_{ADJ:}$ 80 mg/m^3(13 ppm)
	$BMCL_{ADJ}$: 9.51 x 6/24 x 5/7 = 1.70 ppm (10 mg/m^3)	$NOAEL_{HEC}$: 78 mg/m^3 (50 x 6/24 = 13 ppm)	$LOAEL_{HEC}$: 225 mg/m^3 (37 ppm)		
Single assessment factors (see table R.8.6)	UF_A 3 x UF_H 10 = 30	UF_S 3 x UF_A 3 x UF_H 10 = 100	UF_S 3 x UF_A 3 x UF_H 10 = 100	UF_A 10 x UF_H 10 = 100	UF_A2.5x4xUF_H10 =25
Other effects					
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies *DNEL derived based on key studies selected for risk characteriszation in the EU RAR (risk characterization in the RAR is based on the margin of safety MOS concept.					EU Risk Assessment Report (RAR). 2004France. http://ecb.jrc.ec.europa.eu/risk-assessment/REPORT/14dichlorobenzenereport001.pdf

Compound	1,4-DICHLOROBENZENE		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	150
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	27 November 2012
General Information			
CLP-INDEX-Nr.	4	INDEX	602-035-00-2
EC-Nr.	5	EINECS – ELINCS - NLP	203-400-5
CAS-Nr.	6	Chemical Abstracts Service number	106-46-7
Harmonised CLP classification	7	Human health risk related classification	Carc. 2 Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1
Molar mass	8	[g/mol]	147.0
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Aiso S, Takeuchi T, Arito H, et al. 2005 Carcinogenicity and chronic toxicity in mice and rats exposed by inhalation to para-dichlorobenzene for two years. The Journal of Veterinary Medical ScienceVol. 67, p1019–1029
Read across compound	10	Where applicable	
Species	11	Rat,… human	Rodent male and female F344/DuCrj rats + 50 male and female Crj:BDF1 mice
Route/type of study	12	Inhalation, oral feed, …	Inhalation
Study length	13	Days, subchronic, chronic	Chronic 104 weeks
Exposure duration	14	Hrs/day, days/week	6 hrs/day, 5 days/week
Critical endpoint	15	Effect(s), site of	The nasal olfactory epithelium moderate or severe eosinophilic changes in the nasal olfactory epithelium in female rats, respiratory metaplasia
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	NOAEC
POD Value	17	[mg/m^3] or [ppm]	20 ppm

Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	5
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic Worker - General population	10
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	700
POD/TAF	28	Calculated value (µg/m³ and ppb)	……..172.78 µg/m³ …….28.57 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	150
Additional Comments	31		
Rationale Section	32		

The most recent reliable chronic inhalation study was conducted by the Japan Bioassay Research Center (Aiso et al. 2005) and was selected as key study of the ATSDR risk assessment as well as of this assessment.

50 BDF1 mice and 50 F344 rats of both sexes were exposed to p-DCB by vapour with 0, 20, 75 and 300 ppm for 6 hours/day, 5 days/week and 2 years. Clear evidence of carcinogenicity for male and female mice as shown in increased incidences of hepatocellular carcinomas and hepatoblastomas and histiocytic sarcomas in the 300 ppm exposed male mice and in the increased incidences of hepatocellular adenomas and carcinomas and hepatoblastomas in the 300 ppm exposed female mice was found. In rats no tumor induction was reported. The most sensitive endpoint of the chronic inhalation toxicity was the nasal lesion characterized by treatment- and age-related increases in the incidences of the eosinophilic globules of the respiratory and olfactory epithelia in female rats and the incidence of the respiratory metaplasia of the nasal gland epithelium of female rats and in the olfactory epithelium of mice. The lesions were increased in the female rats exposed to 75 – 300 ppm, therefore the NOAEL 20 ppm was taken forward as the POD.

POD

Due to the carcinogenicity of the compound, which is also observed when laboratory rodents were exposed to p-DCB via the oral route a factor of 5 for severity of effect was applied. At present there is no evidence for carcinogenicity of p-DCB in humans. IARC classified p-DCB as possibly carcinogenic to humans, Group 2B.

The Federal Institute for Occupational Safety and Health (BAuA) derived an occupational exposure limit and calculated a theoretical cancer risk of 4 in 100,000 at 0.1 ppm. The EU-LCI value of 150 µg/m³ (0.025 ppm)

would account for an almost similar risk for the general population. Morbt et al. (2011) found that exposition of human lung-cells to chlorinated benzenes (CB, o-DCB) yield to altered protein expression and oxidative stress response at very low concentrations (CB 2.2 ppm, o-DCB 0.17 ppm). Therefore an interspecies factor for local effects seemed to be justified.

References

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A.6 2-Butoxyethanol

Compound	2-BUTOXYETHANOL	*Data collection sheet*		
N° CAS: 111-76-2				
1 ppm = 4.91 mg/m³				
Organization Name	**ATSDR**	**US EPA**	**Santé Canada**	**ECHA: registered substances**
Risk Value Name	Chronic Inhalation MRL	Inhalation RfC	CA	DNEL
Risk Value (mg/m³)	1	1.6	11	49
Risk Value (ppm)	0.2	0.3	2.2	
Reference period	Chronic	Chronic	Chronic	
Year	1998	2010	1999	
Key Study	Haufroid et al., 1997	NTP (2000), NTP technical report on the toxicology and carcinogenesis studies of 2 butoxyethanol	NTP 1998	
Study type	chronic study in workers	Chronic (rat and mouse) inhalation study	Chronic inhalation study	
Species	Human (31 male workers)	F344/N rats and $B6C3F_1$ mice	F344 Rats	
Duration of exposure in key study	1 to 6 years	6 h/d, 5 d/w for 2 years	6 h/d, 5 d/w for 2 years	
Critical effect	Decrease in haematocrit values and increase in mean corpuscular haemoglobin concentration	Hemosiderin deposition in the liver	Haemolytic anemia (macrocytic and normochromic)	

Critical dose value	NOAEL: 0.6 ppm	NOAEL: 31 ppm		Long-term inhalation DNEL for consumers (systemic effects) derived by industry (ECHA-website: registered substances), no transparent information about derivation of DNEL
		LOAEL: 62.5 ppm	LOAEL: 150 mg/m^3 (31 ppm)	
Adjusted critical dose		PBPK and $BMCL_{10}$		
		$BMCL_{HEC}$: 16 mg/m^3		
Single assessment factors (see table R.8.6)	UF_H 3 = 3	UF_H 10 = 10	0.5 x 0.1 x 3.2 x 3.2 = 0.5	No information on DNEL derivation
Other effects				
Confidence		Medium/High	Medium	
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies				

Compound	2-BUTOXYETHANOL		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	1100
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	27 November 2012
General Information			
CLP-INDEX-Nr.	4	INDEX	603-014-00-0
EC-Nr.	5	EINECS – ELINCS - NLP	203-905-0
CAS-Nr.	6	Chemical Abstracts Service number	111-76-2
Harmonised CLP classification	7	Human health risk related classification	Acute Tox 4 (H302) Acute Tox 4 (H312) Skin Irrit. 2 Eye Irrit. 2 Acute Tox 4 (H332)
Molar mass	8	[g/mol]	118.2
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Dodd et al. 1983
Read across compound	10	Where applicable	
Species	11	Rat,… human	F344-Rat
Route/type of study	12	Inhalation, oral feed, …	Inhalation
Study length	13	Days, subchronic, chronic	90d
Exposure duration	14	Hrs/day, days/week	6h/d, 5d/w
Critical endpoint	15	Effect(s), site of	Haematology, haemolysis, Liver hemosiderin deposition
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L,	NOAEC

		Benchmark dose, ….	
POD Value	17	[mg/m^3] or [ppm]	122.8 mg/m^3
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
AF Study Length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	10
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	112
POD/TAF	28	Calculated value (µg/m^3 and ppb)	……1096.43 µg/m^3 ……. 225.48 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m^3]	1100
Additional Comments	31		

Rationale Section	32		

Existing risk assessments for EGBE: EPA has derived a chronic reference concentration (RfC) of 1.6 mg/m^3 (0.3 ppm), Health Canada derived a tolerable concentration (TC) of 11 mg/m^3 and ATSDR derived a chronic minimal risk level (MRL) of 0.96 mg/m^3 (0.2 ppm), and there exists a MOS evaluation in the EU-RAR (2006).

Dodd et al. (1983) performed a 90-day subchronic inhalation study on F344 rats. Male and female rats were exposed to EGBE for 6 hours/day, 5 days/week at concentrations of 0, 5, 25, and 77 ppm. After 6 weeks, the 77 ppm exposed female rats had slight but statistically significant decreases in RBC counts (13% below control value) and Hb concentrations, accompanied by an 11% increase above the control value in MCH. At the end of the 90-day study (66 exposures), the haematologic effects seen in the 77 ppm exposed animals had either lessened or returned to the ranges of control values and were no longer statistically significant. The NOAEL was determined to be 25 ppm, and the LOAEL was 77 ppm.

NTP (2000) did a two-species, 2-year inhalation study on EGBE in both genders of rats and mice. Animals were exposed to EGBE 6 hours/day, 5 days/week at concentrations of 0, 31, 62.5, and 125 ppm (0, 150, 302, and 604 mg/m^3) for groups of 50 F344/N rats and 0, 62.5, 125, and 250 ppm (0, 302, 604, and 1,208 mg/m^3) for groups of 50 B6C3F1 mice.

Non-neoplastic effects in rats (males and females) included hyaline degeneration of the olfactory epithelium and Kupffer cell pigmentation in the livers, the latter a secondary effect of the EGBE related hemolysis. In rats, a NOAEL could not be determined, and a LOAEL of 31 ppm was determined for hemosiderin deposition.

Incidences of hyaline degeneration of the olfactory epithelium were significantly increased in all exposed groups of males and in females exposed to 62.5 or 125 ppm. The severity of this lesion was not affected by exposure. In exposure-related cases, this change has been proposed to have an adaptive/protective role (St Clair and Morgan 1992).

POD

Available data indicate haemolysis as the primary and critical response. The increased incidence of hyaline degeneration of the olfactory epithelium observed in rodents appears to be an adaptive response typical for the species and was unaffected by increasing exposure concentrations. The subchronic inhalation study with the NOAEC of 25 ppm for haematologic effects that described by Dodd et al. (1983) provides an appropriate POD for derivation of the LCI, which is supported by the chronic NTP study LOAEC of 31 ppm for haemosiderin deposition.

AF Study length

The study length is appropriately considered by a factor of 2 for subchronic → to chronic exposure.

AF Interspecies

It can be assumed that humans are less sensitive to nasal effects and haemolysis by butoxyacetic acid (BAA, the active metabolite causing haemolysis), also sensitive human sub-populations, including the children, the elderly and those with sickle cell anaemia are also equally resistant (Ghanayem et al. 1993, Udden 1994). An AF interspecies between 0.1 - 1 could thus be considered as defensible, a factor of 1 was selected.

AF intraspecies
A value of 10 was selected to account for variation in sensitivity within the human population.

AF sensitive individuals and other adjustment factors
It can be assumed that developmental toxicity due to EGBE in humans could not be expected without maternal toxicity. Consequently, there is no concern for this endpoint and no need for an additional AF.

References

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A.7 Styrene

Compound	STYRENE	*Data collection sheet (1/3)*
N°CAS 100-42-5		

Organization Name	EU-INDEX Project	OEHHA	U.S. EPA	ATSDR
Risk Value Name	long-term exposure limit	REL	RfC	MRL
Risk Value (µg/m³)	250	900	1000	900
Risk Value (ppb)	55	200	222	200
Reference period	chronic	Chronic	Chronic	Chronic
Year	2005	2000	1993	2010
Key Study	Mutti et al. 1984, Neuroendocrine effects of styrene on occupationally exposed workers	Mutti et al. (1984)., Exposure-effect and exposure-response relationships between occupational exposure to styrene and neurophychological functions	Mutti et al. (1984). Exposure-effect and exposure-response relationships between occupational exposure to styrene and neuropsychological functions	Benignus VA, Geller AM, Boyes WK, et al. 2005. Human neurobehavioral effects of long-term exposure to styrene: a meta-analysis
Study type	chronic study in workers (study for levels of substances associated with neuroendocrine function), inhalation exposure	Inhalation	Cross-sectional study in workers (Occupational)	Benignus et al. used data from occupational exposure studies examining color vision impairment (Campagna et al. 1996; Eguchi et al. 1995; Gobba et al. 1991; Gong et al. 2002; Kishi et al. 2001) and delays in choice reaction time (Jegaden et al. 1993; Mutti et al. 1984a; Triebig et al. 1989; Tsai and Chen 1996).
Species	Human (30 females)	Human (occupational, 50 workers)	Human (occupational, 50 workers)	Human

Duration of exposure in key study	8 hours/day, 5 days/week	8.6 years (average years at work)	8.6 years (average years at work)	20 ppm for 8 work-years would result in a 6.5% increase in choice reaction time and a 2.23% increase in CCI score.
Critical effect	CNS; neuropsychological tests: reaction time, s/l term logic memory, s/l term verbal memory, digit-symbol association, block design and figure identification	Neuropsychological deficits in humans as measured by memory and sensory/motor function tests	CNS effects	Colour vision impairment and delays in choice reaction time
Critical dose value			NOAEL: 94 mg/m³ (25 ppm)	
	LOAEL: 107 mg/m³ (25 ppm)	LOAEL: 15 ppm	LOAEL: >94 mg/m³ (>22 ppm)	LOAEL = 20 ppm based on the findings of Triebig et al. (2001)
Adjusted critical dose	Occupationnal -> continuous pattern of exposure (factor of 4.2)	BMC_{05} = 1.7 ppm		
	$LOAEL_{ADJ}$: 107/4.2 = 25 mg/m³	HEC = 1.7 x 10/20 x 5/7 = 0.61 ppm	NOAEL(HEC): 34 mg/m³	$LOAEL_{ADJ}$ = 20 ppm x 8h/24h x 5 d/7 d = 4.8 ppm
Single assessment factors (see table R.8.6)	UF_L 10 x UF_H 10 = 100	UF_H 3 = 3	UF_S 3 x UF_D 3 x UF_H 3 ≈ 30	UF_L 3 x UF_H 10 = 30
Other effects				
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies				

Compound	STYRENE	*Data collection sheet (2/3)*
N°CAS 100-42-5		

Organization Name	WHO	RIVM	Sw Criteria Group
Risk Value Name	Guideline value	TCA	n.a.
Risk Value (µg/m³)	260	900	n.a.
Risk Value (ppb)	58	200	n.a.
Reference period	Chronic	Chronic	Chronic
Year	2001	2000	2010
Key Study	Eguchi, T. et al., 1995, Impaired colour discrimination among workers exposed to styrene: relevance to a urinary metabolite		Several: Hanova 2011, Laffon 2001, Migliore 2006, Teixeira 2010, Wongvijitsuk 2011, Benignus 2005, Gong 2002, Kishi 2001, Mascagni 2007, Morata 2002, Sliwinska-Kowalska 2003, 2005
Study type		Intermittent occupational exposure of humans	Intermittent occupational exposure of humans
Species	Human	Human	Human
Duration of exposure in key study		8.6 years (average years at work)	8.6 years (average years at work)
Critical effect	Reductions in visuomotor accuracy, verbal learning skills and subclinical effects on colour vision, sensory effects or annoyance reactions	Minor effects on the central neural system: verbal learning skills	Genotoxicity, hearing loss and effects on colour vision
Critical dose value		NOAEL = 107 mg/m³	LOAEL approx. 10 ppm

	LOAEL = 107 mg/m³ (25 ppm)		
Adjusted critical dose	Occupationnal -> continuous pattern of exposure (factor of 4.2)	Occupationnal -> continuous pattern of exposure (factor of 4.2)	Occupationnal -> continuous pattern of exposure (factor of 4.2)
		26 mg/m³	2.4 ppm
Single assessment factors (see table R.8.6)	UF_L 10 x UF_H 10 = 100	UF_S 3 x UF_H 10 = 100	n.a.
Other effects			
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies			

Compound	STYRENE	*Data collection sheet (3/3)*
N°CAS 100-42-5		

Organization Name	German IAQ	Austrian IAQ	EU-TDR	EU: TRD based*	ECHA: Registered Substances
Risk Value Name	IAG	IAG	DNEL	DNEL	DNEL
Risk Value (µg/m³)	30	40	34640	2300	10200
Risk Value (ppb)	6.90	10	8000	520	2356
Reference period	Chronic	chronic	exp. Scen. (DIY tasks*)	chronic	chronic
Year	2004	2004	2008	2011	2011
Key Study	Chia et al. Impairment of colour vision among workers exposed to low concentrations of styrene .AmJ.Ind. Med. 26 (1994) supported by various other studies	Mutti A, Mazzucchi A, Rustichelli P, Friger G, Arfini G, Franchini I (1984a): Exposureeffect and exposure-response relationships between occupational exposure to styrene and neuropsychological functions. Am J Ind Med 5, pp 275-286	In EU-RAR, 2008-UK EU-TRD, UK, RCruzan G, Faber WD, Johnson KA, Roberts LS, Hellwig J, Carney E, Yarrington JT and Stump DG (2005a) Two generation reproduction study of styrene by inhalation in Crl-CD rats. Birth Defects Research (Part B) 74: 211-220.	In EU-RAR, 2008-UK EU-TRD, UK, RCruzan G, Faber WD, Johnson KA, Roberts LS, Hellwig J, Carney E, Yarrington JT and Stump DG (2005a) Two generation reproduction study of styrene by inhalation in Crl-CD rats. Birth Defects Research (Part B) 74: 211-220.	No information on DNEL derivation; DNEL derived by industry
Study type	Occupationnal exposure	Occupational exposure	2-generation study	2-generation study	
Species	Human	Human	Rat	Rat	
Duration of exposure in key study					

Critical effect	Effects on CNS, colour vision	Effects on CNS, colour vision	Developmental effects	Developmental toxicity	
Critical dose value	LOAEL: 34 mg/m^3	NOAEL: 1.3 mg/m^3	NOAEC: 150 ppm	NOEC= 150 ppm (649.5)	Long-term inhalation DNEL for consumers (systemic effects) derived by industry (ECHA-website: registered substances), no transparent information about derivation of DNEL
Adjusted critical dose	Occupationnal -> continuous pattern of exposure (factor of 5)	Occupationnal -> continuous pattern of exposure (factor of 5)	x 0.75 x 3.5 = 394 ppm (8-hour)	Animal exp. - human consumer 649.5*0.25*0.71 115.29	
Single assessment factors (see table R.8.6)	5 (exp. Time)x Intrasp. 10x UF (sens.) 2x x10 =100	5 (exp. Time)x Intrasp. 3x UF (sens.) 2x =30	UF2x Intersp2.5 Intrasp10= 50	UF2x Intersp2.5 Intrasp5xUF2 = 50	Overall assessment factor: 1
Other effects					
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies					

* DNEL derived based on key studies selected for risk characteriszation in the EU RAR.

Compound	STYRENE		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	250
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	27 November 2012
General Information			
CLP-INDEX-Nr.	4	INDEX	601-026-00-0
EC-Nr.	5	EINECS – ELINCS - NLP	202-851-5
CAS-Nr.	6	Chemical Abstracts Service number	100-42-5
Harmonised CLP classification	7	Human health risk related classification	Flam. Liq. 3 Skin Irrit. 2 Eye Irrit. 2 Acute Tox. 4 (inhalation)
Molar mass	8	[g/mol]	104.15
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Several critical studies with effects at similar exposure levels. Single study cannot be identified since exposure measurements are uncertain in occupational studies
Read across compound	10	Where applicable	
Species	11	Rat,… human	Human
Route/type of study	12	Inhalation, oral feed, …	Inhalation/occupational exposure
Study length	13	Days, subchronic, chronic	Chronic
Exposure duration	14	Hrs/day, days/week	Several years, 8 h/d, 5 d/wk
Critical endpoint	15	Effect(s), site of	Genotoxicity, neurotoxicity and hearing loss
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	LOAEC
POD Value	17	[mg/m^3] or [ppm]	10 ppm
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	4.2
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF	22 a	Reliability of dose-response,	3

Dose-response		LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	3
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	5
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	189
POD/TAF	28	Calculated value (µg/m³ and ppb)	……226.66 µg/m³ …… 52.9 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	250
Additional Comments	31		

Rationale Section	32		

The following risk assessments were considered for styrene: EU-INDEX project (2005), OEHHA (2000), US EPA (1993), ATSDR (2010), WHO (2001), RIVM (2000), German IAQ (2004) and the Swedish Criteria Group (Montelius 2010). The latter report was chosen as it represents the most recent evaluation and also identified the lowest effect level. A Pubmed search (December 2011) was carried out to include more recent studies not cited in Montelius (2010).

According to the Swedish concensus report (Montelius 2010), the critical effects of styrene are genotoxicity, hearing loss and effects on colour vision. Styrene is probably genotoxic to humans and possibly also carcinogenic. Genotoxic effects (chromosomal aberrations, micronuclei, strand breaks, DNA repair) have been observed at occupational exposures down to about 10 ppm (Hanova 2011; Laffon 2001; Migliore 2006; Teixeira 2010; Wongvijitsuk 2011). Effects on colour perception and choice reaction time have also been documented at occupational exposures around 10 ppm (Benignus 2005; Gong 2002; Kishi 2001). Hearing loss (Mascagni 2007; Morata 2002; Sliwinska-Kowalska 2003, 2005) is presumed to occur at approximately the same level.

POD and assessment factors

An assessment of 3 was applied as the point of departure (POD) is a LOAEL and not a NOAEL. Another factor of 3 was applied to account for the severity of the genotoxic effect. As the data stem from several years of occupational exposure, a factor of 2 was applied to account for life-long exposure. No route extrapolation or interspecies extrapolation factors were needed. The adjustment for duration of exposure was set to 4.2, assuming 40 hours per week in the study group and continuous exposure in the target population. A factor of 5 was applied to account for the heterogeneity of the general population (including children), as compared to the small group of workers studied.

The resulting LCI value of 250 µg/m³ is similar to the lower odour threshold for styrene of 202 µg/m³ reported by Ruth (1986).

References

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A.8 Ethylbenzene

Compound	ETHYLBENZENE	*Data collection sheet (1/2)*
N°CAS 100-41-4		
1 ppm (in air, 25 °C) = 4.35 mg/m^3		

Organization Name	**WHO**	**ATSDR**	**US EPA (IRIS)**	**OEHHA**	**RIVM**	**AFSSET**
Risk Value Name	***on-going re-evaluation*** Guideline Value	MRL	RfC	inhalation REL	TCA	CLI (VTR RIVM)
Risk Value (mg/m^3)	22	*0.261*	1	2	0.77	0.75
Risk Value (ppm)	5	0.06	*0.23*	0.4	0.177	0.172
Reference period	Chronic	Chronic	Chronic	Chronic	Chronic	Chronic
Year	1996	2010	1991	2000	2001	2009
Key Study	NTP semi chronic study (13-week), 1992	NTP, 1999	Andrew et al., 1981, teratologic assessment of ethylbenzene and 2-ethoxyethanol Hardin et al., 1981, Testing of selected workplace chemicals for teratogenic potential (rats, rabbits)	NTP, 1999 and Chan et al., 1998 (lifetime toxicity/carcinogenesis study - discontinuous inhalation)	NTP semi chronic study, 1992	NTP semi chronic study, 1992
Study type	Inhalation studies	Inhalation studies	Teratologic assessment	Discontinuous inhalation	Inhalation studies	Inhalation studies
Species	Rats	Rats, mice	Rats, rabbits	Rats, mice	Rats, mice	Rats, mice
Duration of exposure in key study	6 h/d, 5 d/w for 13 weeks.	6 hours per day, 5 days per week, for 104 weeks.	6 (7)h/d, 7 d/w during days 1-19 (1-24) of gestation - rats (rabbits)	6 hours/day, 5 days/week, 103 weeks.	6 h/d, 5 d/w for 13 weeks.	6 h/d, 5 d/w for 13 weeks.

Critical effect	Increase in liver weight unassociated with any histopathological findings	Kidney effect: chronic progressive nephropathy in female rats increased	Increase in maternal liver, kidney, and spleen weights	Nephrotoxicity, body weight reduction (rats); hyperplasia of the puituiray gland; liver cellular alterations and necrosis (mice)	Liver and kidney effects	Liver and kidney effects
Critical dose value	NOEL 2150 mg/m^3 (500 ppm)		NOAEL 435 mg/m^3 (100 ppm)	NOAEL 325 mg/$^{-3}$ (75 ppm)	NOAEL 430 mg/m^3	NOAEL 430 mg/m^3
	NOAEL 4300 mg/m^3 (1000 ppm)	LOAEL 326 mg/m^3 (75 ppm)	LOAEL 4350 mg/m^3 (1000 ppm)	LOAEL 1087 mg/m^3 (250 ppm)		
Adjusted critical dose	No duration adjustment	PBPK model	No duration adjustment	Temporal	Temporal	Temporal
		75.7 mg/m^3 (17.45 ppm)		NOAEL 56.5 mg/m^3 (75 ppm x 6/24 x 5/7 = 13 ppm)	NOAEL 77 mg/m^3 (17.70 ppm)	NOAEL 77 mg/m^3 (17.70 ppm)
Single assessment factors (see table R.8.6)	UF_A 10 x UF_H 5 x UF_D 2 = 100	UF_A 3 x UF_H 10 x UF_L 10 = 300	UF_A 3 x UF_H 10 x UF_D 10 = 300 (D=absence of multigenerational reproductive and chronic studies)	UF_A 3 x UF_H 10 = 30	UF_A 10 x UF_H 10 = 100	UF_A 10 x UF_H 10 = 100
Other effects						
Confidence			Low			
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies						

COMPOUND	ETHYLBENZENE	*Data collection sheet (2/2)*
N°CAS 100-41-4		
1 ppm (in air, 25 °C) = 4.35 mg/m³		

Organization Name	**EU TRD-RRS**	**EU TRD-RRS based***	**ECHA Registered Substances**
Risk Value Name	Refv. workplace	DNEL consumer	DNEL
Risk Value (mg/m³)	16.4	1.08	15
Risk Value (ppm)	3.7	0.25	3.4
Reference period	Work exp.	Chronic	Chronic
Year	2008	2011	2011
Key Study	Faber In RAR, TRD-RRS, 2008	Faber In RAR, TRD-RRS, 2008	
Study type	Inhalation	Inhalation	
Species	Rats	Rats	
Duration of exposure in key study	6 h/d, 5 d/w	6 h/d, 5 d/w	
Critical effect	Dev. Tox.: ↓ pup survival un-til PND 4, dose-related mortality and signs of CNS depression in PND 22 exposed off-spring, ↓ weanling body weight on PND 34 in the PND 22 and in the PND 33 exposed off-spring at 500 (LOAEC) and 1000 ppm	Dev. Tox.: ↓ pup survival un-til PND 4, dose-related mortality and signs of CNS depression in PND 22 exposed off-spring, ↓ weanling body weight on PND 34 in the PND 22 and in the PND 33 exposed off-spring at 500 (LOAEC) and 1000	ECHA- homepage: long-term inhalation DNEL (systemic effects) for the general population derived from industry: limited information about DNEL derivation

		ppm	
Critical dose value	NOEC 441 mg.m-3	NOEC 441 mg.m-3	NOEC
Adjusted critical dose			
	441 (NOEC) • 0.45 / 0.65 • 6.7/10	441 (NOEC) • 0.45 / 0.65 * 0.25*0.71= 54.2mg/m^3	
Single assessment factors (see table R.8.6)	Intersp. 2.5x Intrasp. 5 =12.5	Intersp. 2.5x Intrasp. 10x UF (sens 2x) =50	Total AF: 5
Other effects			
Confidence			

* DNEL derived based on key studies selected for risk characteriszation in the EU RAR

Compound	ETHYLBENZENE		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	850
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	4 December 2012
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS - NLP	
CAS-Nr.	6	Chemical Abstracts Service number	100-41-4
Harmonised CLP classification	7	Human health risk related classification	Flam. Liq. 2 Acute Tox. 4 (inhalation)
Molar mass	8	[g/mol]	106.17
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Gagnaire F, Langlais C, Grossmann S, Wild P (2007). Ototoxicity in rats exposed to ethylbenzene and to two technical xylene vapours for 13 weeks. Arch. Toxicol. 81: 127-143
Read across compound	10	Where applicable	
Species	11	Rat,… human	Rat
Route/type of study	12	Inhalation, oral feed, …	Inhalation
Study length	13	Days, subchronic, chronic	13 weeks
Exposure duration	14	Hrs/day, days/week	6h/24 h, 5 d/7
Critical endpoint	15	Effect(s), site of	Ototoxicity
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	LOEAC
POD Value	17	[mg/m^3] or [ppm]	200 ppm
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	4.7
AF Study Length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	3
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	

	23 b	Kinetic + dynamic	1.44 x 2.5
Intraspecies differences	24	Kinetic + dynamic Worker - General population	10
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	1015
POD/TAF	28	Calculated value (µg/m³ and ppb)	……..860.63 µg/m³ …….197.04 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	850
Additional Comments	31		

Rationale Section	32		

ATSDR, RIVM, and US EPA have evaluated the non-cancer inhalation toxicity data for ethylbenzene. ATSDR derived a chronic-duration inhalation minimal risk level (MRL) of 0.26 mg/m³ using a human PBPK model. RIVM derived a tolerable concentration in air (TCA) of 0.77 mg/m³ based on liver and kidney effects observed in rats and mice. EPA derived a reference concentration (RfC) of 1 mg/m³ based on developmental effects observed in rats and rabbits. Using the 13-week study by NTP (1996), RIVM derived a tolerable concentration in air (TCA) of 0.77 mg/m³.

POD

According to several case reports, where hearing deficits were observed in humans occupationally exposed to organic solvents or from people after solvent abuse. The data from a subchronic rat study (Gagnaire et al., 2007) are considered most relevant for humans. In the key study selected (Gagnaire et al., 2007) male Sprague-Dawley rats were exposed to ethylbenzene (200, 400, 600 and 800 ppm) by inhalation, 6 h/day, 6 days/week for 13 weeks. Ethylbenzene produced moderate to severe ototoxicity in rats exposed to 200 ppm, which is close to the NOAEL from the RIVM risk assessment and taken as a LOAEL for ototoxicity. A NOAEL was not determined in that study.

Assessment factors

To derive a NOAEL from the LOAEL for ototoxicty a factor of 3 (2x1.5) for dose response and severity of effect is selected.

Standard AFs for study length and intraspecies extrapolation are used. For interspecies assessment factors, values as given in the EU risk assessment report are applied (2).

The difference in pulmonary absorption between rats and humans for ethylbenzene is considered by the ratio of the rat absorption percentage of 45%, divided by human absorption percentage after inhalation of 65%.

In the absence of clear carcinogenic evidence and ethylbenzene's carcinogenic mechanism being most likely not relevant for humans, and a NOAEL (500 ppm) for maternal reproductive toxicity, developmental toxicity, and developmental neurotoxicity, no further assessment factors are introduced.

References

Gagnaire F, Langlais C, Grossmann S, Wild P. 2007. Ototoxicity in rats exposed to ethylbenzene and to two technical xylene vapours for 13 weeks. Arch Toxicol. 2007 Feb; 81(2):127-43. Epub 2006 Jun 20.

EU-TRD-RRS. Ethylebenzene, Strategy For Limiting Risks, Human Health, November 2008, BAUA, Federal Institute for Occupational Safety and Health, Germany.

Hard G C. 2002. Significance of the Renal Effects of Ethyl Benzene in Rodents for Assessing Human Carcinogenic Risk. Toxicol. Sci. (2002) 69 (1): 30-41.

Faber WD, Roberts LS, Stump DG, Beck M, Kirkpatrick D, Regan KS, Tort M, Moran E, Banton M. 2007. Inhalation developmental neurotoxicity study of ethylbenzene in Crl-CD rats. Birth Defects Res B Dev Reprod Toxicol. 2007 Feb;80(1):34-48.

Faber WD, Roberts LS, Stump DG, Tardif R, Krishnan K, Tort M, Dimond S, Dutton D, Moran E, Lawrence W. 2006. Two generation reproduction study of ethylbenzene by inhalation in Crl-CD rats. Birth Defects Res B Dev Reprod Toxicol. 2006 Feb; 77(1):10-21.

A.9 ε-Caprolactam

Compound	ε-CAPROLACTAM	*Data collection sheet*
N°CAS 105-60-2		
1 ppm (in air, 25 °C) = 4.7 mg/m³		

Organization Name	**US EPA IRIS**	**OEHHA**	**ECHA Registered Substances**	**DFG**	**ACGIH**	**NIOSH**
Risk Value Name	RfC	REL	DNEL	MAK	TLV-TWA	REL-TWA
Risk Value	n.a.	**2.2 µg/m³**	**2.5 mg/m³**	**5 mg/m³**	**5 mg/m³**	**1 mg/m³**
Risk Value	n.a.	0.5 ppb	0.5 ppm	1.06 ppm	1.06 ppm	0.2 ppm
Reference period	Chronic	Chronic	chronic	Chronic (worker)	Chronic (worker)	Chronic (worker)
Year	1994	2011 (draft)	2010	2002	2003	1995
Key Study	Health effect data was determined to be inadequate for the derivation of an inhalation RfC	Reinhold et al., Toxicol.Sci. 44, 197-205; 1998	Ziegler et al., Int. Arch. Occup. Environ. Health 81:743–753; 2008	Ferguson & Wheeler, Am. Ind. Hyg. Ass. J. 34, 384-389; 1973	Ferguson & Wheeler, Am. Ind. Hyg. Ass. J. 34, 384-389; 1973	Ferguson & Wheeler, Am. Ind. Hyg. Ass. J. 34, 384-389; 1973
Study type		Subchronic inhalation study	Exposure chamber study, chemosensory effects in low concentration range.	Health surveillance	Health surveillance	Health surveillance
Species		Rat	Human	Human	Human	Human
Duration of exposure in key study		6 h/d, 5 d/w, 13 weeks, followed by 4 week recovery	6 h / 4d	Not specified	Not specified	Not specified
Critical effect		Respiratory tract irritation	Respiratory tract irritation	Respiratory tract irritation	Respiratory tract irritation	Respiratory tract irritation

Critical dose value		LOAEL 24 mg/m³ (14 ppm)	NOAEC > 5 mg/m³	NOAEC >32 mg/m³ (7 ppm)	NOAEC >32 mg/m³ (7 ppm)	NOAEC >32 mg/m³ (7 ppm)
		$BMCL_{05}$ 3 mg/m³ (1.13 ppm)				
Adjusted critical dose		Chronic	Chronic	Chronic	Chronic	
		Human equivalent concentration: 0.134 mg/m³ (3 mg/m³ x 6/24 x 5/7 x 0.25) (0.25 = "regional gas dose ratio")	No dose adjustment (conc. dependent local effect)			
Single assessment factors (see table R.8.6)		UF_A $\sqrt{10}$ x UF_H 10 x UF_S 2 = 60	Reliable human data Intrasp. 2x (worker - general)	Not indicated	Not indicated	
Other effects						
Confidence						
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies						

Compound	ε-CAPROLACTAM		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	300
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	18 June 2012
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS - NLP	
CAS-Nr.	6	Chemical Abstracts Service number	105-60-2
Harmonised CLP classification	7	Human health risk related classification	Acute Tox.4 (Swallow) Skin Irrit.2 Eye Irrit.2 Ecute Tox.4 (Inhalation) STOT SE 3
Molar mass	8	[g/mol]	113.6
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Critical study with lowest relevant effect subchronic study (Reinhold et al., Tox. Sci. 44, 197-205; 1998)
Read across compound	10	Where applicable	
Species	11	Rat,… human	Rat
Route/type of study	12	Inhalation, oral feed, …	Inhalation
Study length	13	Days, subchronic, chronic	90 days (subchronic)
Exposure duration	14	Hrs/day, days/week	6 hrs/day, 5 days a week
Critical endpoint	15	Effect(s), site of	Irritation of respiratory tissues
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	NOAEC
POD Value	17	[mg/m^3] or [ppm]	24 mg/m^3
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
AF Study Length	20	sa→ sc→ c *(R8-5)*	3
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	

	23 b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	5
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	84
POD/TAF	28	Calculated value (µg/m³ and ppb)	……285.7 µg/m³ ……..61.13 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	300
Additional Comments	31		

Rationale Section	32		

ε-Caprolactam is a chemical with an unpleasant odor and moderately irritating properties at the port of entry, especially in form of particles. The available toxicological studies (which cover all toxicological endpoints) do not show a specific target organ of systemic toxicity and no indication of CMR properties or neurotoxicity.

Above air-borne concentrations of 10 mg/m^3 the major part of ε-caprolactam appears in the form of particles (dust, aerosols). Concentrations higher than 33 – 66 mg/m^3 were clearly irritating to the respiratory tract in occupationally exposed persons (Ferguson and Wheeler, 1973).

Ziegler et al. (2008) investigated chemosensory effects among volunteers. No adverse effects were recorded at the concentrations employed (50, 150 and 5000 µg/m^3; 6 hrs per day, 4 subsequent days). Unpleasant odour, however, was noted within a concentration-dependent relationship.

These two human studies are employed as supporting studies. The selected key study is a subchronic inhalation study in rats (Reinhold et al., 1998) which is considered of high validity. No systemic toxicity has been noted and local irritation of respiratory tissues was the only effect observed. The authors considered the top concentration (240 mg/m^3) as clearly adverse and the discrete effect observed at the medium dose (70 mg/m^3) as only adaptive in nature. The lowest concentration (24 mg/m^3) was a NOEC. For the EU-LCI derivation, however, the lowest concentration was taken as POD. The reason is that 70 mg/m^3 has been identified as irritating in humans. So, in order to employ a higher degree of conservatism which takes into account also observations in humans, the lowest concentration is taken as POD.

For the assessment factors it was assumed that the local effects observed were more concentration- related than dose- related, therefore the extrapolation factor for length of study was confined to 3. Furthermore, a time adjustment factor of 5.6 was employed in order to adjust from the exposure intervals in the experimental study to continuous exposure and an intra-species variability factor of 5 proposed. This amounts to an overall factor of 84 (rounded to 80) which is taken as a divisor for the POD and results in an LCI value of 300 µg/m^3.

It is pointed out that perception of an unpleasant odour may occur at concentrations below this value.

References

Ferguson and Wheeler. 1973. Am. Ind. Hyg. Assoc. J. 34, 384 – 389.

Ziegler et al., 2008. Int. Arch. Occup. Environm. Health 81 743 – 753.

A.10 α-Pinene

Compound	α-PINENE	*Data collection sheet (1/2)*
N°CAS 80-56-8	**Classification GHS:** H332: Harmful if inhaled (cat. 4), H319: Causes serious eye irritation (cat. 2) **CLP:** not included	
1 ppm (in air, 23 °C) = 5.61 mg/m³ 1 ppm (in air, 20 °C) = 5.66 mg/m³ MW=136.23		

Organization Name	ACGIH	BAuA	German IAQ	AgBB	ANSES	AFS
Risk Value Name	8-h TWA	Occup. target value	RWI (target value) RWII (adverse effects possible) for bicyclic monoterpenes, model substance = α-pinene	NIK (=LCI)	CLI (=LCI)	OEL
Risk Value (mg/m³)	112.12 (calculated for 23°C)	56.06 (calculated for 23°C)	RWI=0.2 RWII=2.0	1.5	0.45	150
Risk Value (ppm)	20	10	RWI=0.036 RWII=0.357 (calculated for 23°C)	0.267 (calculated for 23°C)	0.0803 (calculated for 23°C)	25
Reference period		Subacute	Subacute			
Year	2008	2005	2003			1990
Key Study	No information available	Järvisalo J, Vainio H: Acta Pharmacologica et Toxicologica 1980;46(1):32–36	Johard U, Larsson K, Löf A, Eklund A: Controlled short-time terpene exposure induces an increase of the macrophages and the mastcells in bronchoalveolar lavage	Value derived from AFS-OEL: × 0.01	Value taken from the EU-INDEX Project	No information available

			fluids. Am J Ind Med 1993;23:793–799			
Study type		Inhalation study	8 volunteers inhalating 450 mg/m^3 mixture of α-pinene, beta-pinene, delta-3-carene (10:1:5). 4×3hrs. in 2 weeks. Elevated cell-concentrations in BAL after exposition, interpreted as acute alveolar cellular reaction / inflammation marker.			
Species		Rat	Man			
Duration of exposure in key study		6h/d, 5d/w for 8 weeks	4 × 3 hrs. in 2 weeks			
Critical effect		Study with turpentine (95% α-pinene). Enhanced activities of drug biotransformation enzymes of liver microsomes: NADPH cytochrome c reductase and 7-ethoxycoumarin deethylase, and microsomal content of cytochrome P-450 (increased 35–60% only during first weeks). Increase in liver microsomal epoxide hydratase and UDPglucuronosyltransferase tended to adapt less. Result describes not an adverse effect per se, but influence of biotransformation of	20 hrs after exposure significant higher concentrations of alveolar cell concentrations (median pre-exposure 76 × l0^6 cells/L -> 126 × l0^6 cells/L), predominantly due to macrophages (72 × l0^6 cells/L -> 121 × l0^6 cells/L). Also mast cells increased: 1/10 -> 5/10 visual fields.			

		drugs is possible.				
Critical dose value	-	1,710 mg/m³ (300 ppm)	LOAEL: 450 mg/m³			
Adjusted critical dose		$ENAEL_{inhal}$: 128 mg/m³ (23 ppm)				
		Derived Exposure Target Value 56 mg/m³ (10 ppm)				
Single assessment factors (see table R.8.6)		No information given	UF_S 12 x UF_H 10 x $UF_{Children}$ 2 = 1.875 mg/m³ -> RWII = 2 mg/m³			
Other effects			Odour thresholds, different values published: α-pinene 3.9 mg/m³ (+)α-pinene 23 mg/m³ (−)α-pinene 107 mg/m³			
Confidence						
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies						

Compound	α-PINENE	*Data collection sheet (2/2)*
N°CAS 80-56-8	**Classification GHS:** H332: Harmful if inhaled (cat. 4), H319: Causes serious eye irritation (cat. 2) **CLP:** not included	
1 ppm (in air, 23 °C) = 5.61 mg/m³ 1 ppm (in air, 20 °C) = 5.66 mg/m³ MW=136.23		

Organization Name	**EU-INDEX Project**	**Mersch-Sundermann review**	**Gminski et al.**	**Data from ECHA for not specified α-pinene, CAS 80-56-8**	**NTP study with not specified α-pinene, CAS 80-56-8**
Risk Value Name	IAQ	Proposed LCI	Not appointed	Long-term exposure systemic effects general population inhalation DNEL	NOAEL
Risk Value (mg/m³)	0.45	4	Not appointed	1.06	
Risk Value (ppm)	0.0803 (calculated for 23°C)	0.714 (calculated for 23°C)	Not appointed	0.187 (calculated for 23°C)	50
Reference period				Subchronic	Subchronic
Year	2005	2007	2011	2012 (status ECHA-Homepage)	2006
Key Study	Falk Filipsson A: Short term inha-lation exposure to turpentine: toxicokinetics and acute effects in men. Occup Environ Med 1996;53:100–105 Falk A, Hagberg M, Löf A, Wigaeus-Hjelm E, Wang Z: Uptake, distribution and elimination of a-pinene	Animal study: Kasanen JP, Pasanen AL, Pasanen P, Liesivuori J, Kosma VM, Alarie Y: Stereospecifity of the sensory irritation receptor for nonreactive chemicals illustrated by pinene enantiomers. Arch Toxicol 1998; 72:514–523	Human inhalation study: Gminski R. Marutzky R. Keve-kordes S. Fuhrmann F. Burger W. Hauschke D. Ebner W. Mersch-Sundermann V: Chemosensory irritations and pulmonary effects of acute exposure to emissions from oriented strand board. Human & Experimental Toxicology 2011;30(9):1204–21	NTP-Study 2005	NTP-Study TDMS Number 2030203 =TOX-81 Study

	in man after exposure by inhalation. Scand J Work Environ Health 1990;16:372–8	Human exposure study: Falk Filipsson A: Short term inhalation exposure to turpentine: toxicokinetics and acute effects in men. Occup Environ Med 1996;53:100–105 Lowest OEL-value: Swedish OEL 150 mg/m^3 Odour threshold: lowest 4 mg/m^3			
Study type	8 volunteers inhalated 450 mg/m^3 turpentene: α-pinene, beta-pinene, delta-3-carene, 5:1:3 (1st study) or α-pinene alone (2nd study). Irritation by α-pinene was reported at 450 mg/m^3 but not at 225 mg/m^3. Dis-comfort against turpentene was reported, also airway resistance was increased. Both studies: 1 Exposition for 2 hrs	Animal study: Short-term (30') exposure (inhalation) and measurement of respiratory parameters. Concentrations of α-pinene 100–3,691 ppm.	24 volunteers were exposed for 2hrs to oriented strandboard (OSB) emissions in an emission chamber at 3 points of time (panels fresh, 2 and 8 weeks old). Chemosensory irritation, exhaled nitric oxide (NO) concentration, eye blink frequency, lung function and subjective perception of irritation (eyes, nose, throat) and olfactory perception were investigated.	Animal Study: Subchronic inhalation study exposition at 25 ppm / 50 ppm / 100 ppm / 200 ppm / 400 ppm. 10 Animals per sex and concentration used.	Animal Study: Subchronic inhalation study exposition at 25 ppm / 50 ppm / 100 ppm / 200 ppm / 400 ppm. 10 Animals per sex and concentration used.
Species	Man	Mouse / man		B6C3F1 Mice and F344 Rats	B6C3F1 Mice and F344 Rats
Duration of exposure in key study	1 Exposure for 2 hrs	Animal study: 30 min	3 × 2 hrs	(14 weeks according to ECHA) 90-day inhalation study	96 days for mice (14 weeks) =test-type "90 days"

Critical effect	Irritation / discomfort (self-reported) and airway resistance	Animal study: OF1 and NIH/S male mice, 4 of each used per experiment, exposure time 30', measurement of lung functions by body plethys-mograph. Endpoint RD50 = 50% depression of respiratory rate by sensory irritation of upper respiratory tract Human exposure study: 8 volunteers exposed to 450 mg/m^3 turpentene: α-pinene, beta-pinene, delta-3-carene, 5:1:3 (1st study) or α-pinene alone (2nd study). Irritation by α-pinene was reported at 450 mg/m^3 but not at 225 mg/m^3. Discomfort against turpentene was reported, also airway resistance was increased. Both studies: 1 Exposure for 2 hrs	No effects found except of odour perception.	From ECHA-Summary: Male and female mice at 100 ppm: minimal to moderate hyperplasia observed in the transitional epithelium of the urinary bladder The NOAEL in male and female rats is 50 ppm based on minimal to moderate hyperplasia observed in the transitional epithelium of the urinary bladder in animals treated at 100 to 400 ppm	Significant effects (p<=0.05) Male rats, moderate effects: granular casts in kidney: accumulation of hyaline droplets starting at 25 ppm. Note: 9/10 animals showed nephropaty in control group (other effects) Female rats, minimal effects: chronic lung inflammation. Note: 4/10 in control group, 5/9 at 400 ppm Mice in both sexes, minimal to moderate effects: hyperplasia of transitional epithelium of urinary bladder starting at 100 ppm (13/20 mice). The effect is concentration-dependent (200 ppm: 20/20 mice)
Critical dose value	LOAEL: 450 mg/m^3 NOAEL: 225 mg/m^3	Animal study: RD50 1080 ppm (9 g /m^3) Human exposure study: LOAEL: 450 mg/m^3 OEL: 150 mg/m^3 Odour threshold: 4 mg/m^3	Concentration of α-pinene in the chamber: 1.1–2.2 mg/m^3. α-pinene was a leading component of the OSB-emission, TVOC was 4.9–8.9 mg/m^3. The results represent a NOAEL for OSB-emissions, including an α-pinene TVOC-proportion of 16–25%.		

Adjusted critical dose	IAQ exposure limit: 0.45 mg × m^{-3}	Animal study: 4.5 mg/m^3 Human exposure study: 4.5 mg/m^3 OEL: 3.75 mg/m^3 Odour threshold: no adjustment, 4 mg/m^3			
Single assessment factors (see table R.8.6)	UF_L 10 x UF_S10 x UF_H 10 = 1000	Animal study: RD50 x 0.03 = reasonable OEL, then UF_S24/6 x UFH 10 = 40 Human exposure study: UFS10 x UFH 10 = 100 OEL: UFS24/6 x UFH 10 = 40			
Other effects	Odour thresholds: (+)α-pinene 12 mg/m^3 (2.1 ppm) (−)α-pinene 18 mg/m^3 (3.3 ppm) Reaction of (+)α-pinene with ozone amplifies irritative effect: Wolkoff P, Clausen PA, Wilkins CK, Nielsen GD: Formation of strong airway irritants in terpene/ozone mixtures. Indoor Air 2000;10:82–91	Odour thresholds, different values published: α-pinene range 4–25 mg/m^3			

	(ASTM mouse bioassay: 56 ppm at 21°C= 316 mg/m^3 -> 30% lower respiration rate for mixture)				
Confidence					
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies					

Compound	α-PINENE		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	2500
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	10 December 2012
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS - NLP	201-291-9
CAS-Nr.	6	Chemical Abstracts Service number	80-56-8
Harmonised CLP classification	7	Human health risk related classification	Not harmonised
Molar mass	8	[g/mol]	136.23
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	NTP 2006
Read across compound	10	Where applicable	
Species	11	Rat,… human	Mouse
Route/type of study	12	Inhalation, oral feed, …	Inhalation
Study length	13	Days, subchronic, chronic	SC
Exposure duration	14	Hrs/day, days/week	6h on 5 days/week
Critical endpoint	15	Effect(s), site of	Bladder epithelial changes
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	NOAEC
POD Value	17	[mg/m^3] or [ppm]	50 ppm
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
AF Study Length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	

	23 b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	10
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	112
POD/TAF	28	Calculated value (µg/m³ and ppb)	…… 2502 µg/m³ …… 446.42 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	2500
Additional Comments	31		

Rationale Section	32		

α-pinene is a major component of turpentine and therefore typical for coniferous wood emissions, mainly scots pine and common spruce. To derive risk values (mainly occupational exposures like sawmills), often short-term human inhalation studies were used, sometimes only with turpentine.

Examples for short-term exposures are the study of Falk Filipsson (1996) and Falk et al. (1990). In both studies, 8 volunteers were exposed for 2 hrs. Effects were, increased airway resistance and self- reported irritation/discomfort. The study of Falk Filipsson used turpentine. Johard et al. (1993) describe the exposure of 8 volunteers to turpentine for 4x3 hrs in two weeks and found elevated cell concentrations in bronchoalveolar lavage, interpreted as a cellular reaction showing acute inflammation (this study also used turpentine). A short-term animal study was the study of Kasanen et al. (1998), which identified the RD50 value due to sensory irritation of the upper respiratory tract after exposure of mice against α-pinenes (D, L) for 30 minutes.

As described in the rationale for the establishment of EU-LCI values, these values represent a chronic exposure scenario, therefore short-term studies require additional factors and are not preferred. Only one chronic animal inhalation study was identified by the data compilation sheet: Järvisalo and Vainio (1980), but again turpentine was used (95% α-pinene) and the described enhanced activities of drug bio-transformation enzymes of liver microsomes are not *per se* adverse.

Therefore, the chosen POD was derived from the subchronic NTP-toxicity study (TOX-81) which used not enantiomer specified α-pinene (CAS-No 80-56-8). This study was also chosen by ECHA to derive a DNEL (without providing explanation about the calculation).

The NTP study is a subchronic inhalation animal study (B6C3F1 Mice and F344 Rats) with exposures at 25 ppm / 50 ppm / 100 ppm / 200 ppm / 400 ppm. 10 Animals per sex and per concentration were used. The duration was up to 96 days (14 weeks) and therefore represents a subchronic 90 day study. Mice of both sexes showed minimal to moderate effects, i.e. hyperplasia of transitional epithelium of urinary bladder starting at 100 ppm. So, a NOAEL of 50 ppm was found for mice. The effect was concentration-dependent: 0/20 at 50 ppm, 13/20 at 100 ppm, 20/20 at 200 ppm and 400 ppm. It was decided not to use an additional factor for interspecies kinetic and dynamic differences (line 23b), because it is reasonable to assume that mice are more sensitive than humans because of faster metabolism, leading to higher exposure of bladder epithelium cells (in the NTP-study the effect was only found in mice, not in rats).

Although NTP-data are not published in a scientific journal and some information is missing (e.g. methods, purity of chemicals) this study was chosen as the best basis for deriving the EU-LCI value.

It should be noted, that D and L isomers of α-pinene cannot be separated with the analytical method normally applied for the emission chamber test standard method. So, the factsheet is prepared for not specified α-pinene and the NTP complies with this. For the critical effect chosen (urinary bladder epithelium changes), the composition of inhaled isomers can presumably be neglected because bladder epithelium is mainly exposed to metabolites rather to α-pinene itself. Ishida et al. (1981) have shown, that in rabbits, metabolism of D and L isomers of α-pinene leads to the excretion of the same compounds. Levin et al. (1992) confirmed in a human inhalation experiment, that (+) and (–)α-pinene both are metabolised to and excreted as verbenol in the same cis:trans ratio of 1:10. However, beta pinene and other terpenes showed a different metabolic pattern and may differently affect bladder epithelium, so simple transfer or read-across to other bicyclic monoterpenes seem to be inadequate. It should also be noted, that for irritation (not used as endpoint in this data sheet), D and L isomers of α-pinene behave different, only the D isomer of α-pinene was found to be irritative by Kasanen et al. (1998).

References

Falk A, Hagberg M, Löf A, Wigaeus-Hjelm E, Wang Z. 1990. Uptake, distribution and elimination of a-pinene in man after exposure by inhalation. Scand J Work Environ Health 1990; 16:372–8.

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Ishida T, Asakawa Y, Takemoto T, Aratani T. 1981. Terpenoids biotransformation in mammals III: Biotransformation of alpha-pinene, beta-pinene, pinane, 3-carene, carane, myrcene, and p-cymene in rabbits. J Pharm Sci 1981; 70:406–15.

Järvisalo J, Vainio H. 1980. Acta Pharmacologica et Toxicologica 1980; 46(1):32–36.

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Kasanen JP, Pasanen AL, Pasanen P, Liesivuori J, Kosma VM, Alarie Y.1998. Stereospecifity of the sensory irritation receptor for nonreactive chemicals illustrated by pinene enantiomers. Arch Toxicol 1998;72:514–523.

Levin J-O, Eriksson K, Falk A, Löf A1992. Renal elimination of verbenols in man following experimental a-pinene inhalation exposure. Int Arch Occup Environ Health (1992) 63:571–573.

NTP-study 2006: Identification: TDMS Number 2030203, TOX-81 Study.

A.11 n-Butanal

Compound	n-Butanal, n-Butyraldehyde		Data collection sheet
N°CAS 123-72-8 **EC** 204-646-6	**EU- Classification:** Not classified **CLP:** Acute Tox. Skin Irrit. Eye Irrit. Asp. Tox.		
	n-Butanal	n-Butanal	n-Butanal
Organization Name			
Risk Value Name	LOAEC	NOAEC	LOAEC
Risk Value (mg/m³)	363	145	360
Risk Value (ppm)	125	50	125
Reference period	Subchronic	Subchronic	Subchronic
Year	1979	1980	1979
Key Study	Union Carbide Corporation, 1979 OECS-SIDS 2005	Union Carbide Corporation, 1980 OECS-SIDS 2005	Union Carbide Corporation, 1979 OECS-SIDS 2005
Study type	Subchronic	Subchronic	Subchronic
Species	F 344 rats	Rats	
Duration of exposure in pivotal study	6h/day, 5 days/week, 13 weeks	6h/day, 5 days/12 weeks	6h/day, 5 days/week, 14 weeks
Critical effect	Squamous metaplasia of the nasal cavity		Goblet cell hyperplasia within the nasal mucosa
Critical dose value			
Adjusted critical dose			
Single assessment factors (see table R.8.6)			
Other effects			

Compound	n-Butanal (n-Butyraldehyde)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	650
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2013
General Information			
CLP-INDEX-Nr.	4	INDEX	605-006-00-2
EC-Nr.	5	EINECS – ELINCS - NLP	204-646-6
CAS-Nr.	6	Chemical Abstract Service number	123-72-8
Harmonised CLP classification	7	Human health risk related classification	Not harmonized
Molar mass	8	[g/mol]	72.11
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	Union Carbide 1980, OECD SIDS (2005)
Read across compound	10	Where applicable	
Species	11	Rat,… human	Rat
Route/type of study	12	Inhalation, oral feed, …	Inhalation
Study length	13	Days, subchronic, chronic	Sc
Exposure duration	14	Hrs/day, days/week	6/24;5/7d; 13 wks
Critical endpoint	15	Effect(s), site of	Irritation (squamous metaplasia of the nasal cavity)
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	NOAEC
POD Value	17	[mg/m^3] or [ppm]	145 mg/m^3 or 50 ppm
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
AF Study Length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	10

AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	2
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	224
POD/TAF	28	Calculated value (µg/m³ and ppb)	662.1 µg/m³ 223.2 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	650
Additional Comments	31		

Rationale Section (32)

In a non verifiable repeated-dose inhalation study male and female F344 rats were exposed by inhalation to n-butyraldehyde vapour at concentrations of 0, 125, 500, or 2000 ppm (0, 363, 1450, or 5800 mg/m³) for 6 hr/day, 5 days per week, for 13 weeks (Union Carbide Corporation, 1979). Animals in all treatment groups displayed a significant increase in the incidence of squamous metaplasia of the nasal cavity. This study resulted in a LOAEC of 125 ppm.

A subsequent 12-week inhalation study in male and female rats employing lower doses of 0, 1, 10, and 50 ppm (145 mg/m³) n-butyraldehyde did not result in any adverse effects on the nasal, olfactory, or respiratory epithelial tissues resulting in a NOAEC of 50 ppm (Union Carbide Corporation, 1980).

In another study, beagle dogs were exposed by inhalation to n-butyraldehyde vapor at concentrations of 0, 125, 500, and 2000 ppm for 6 hr/day, five days a week, for 14 weeks. Dogs exposed to 125 and 500 ppm displayed goblet cell hyperplasia within the nasal mucosa (Union Carbide Corporation, 1979).

The NOAEC of 50ppm (145 mg/m^3) from the rat-study is used for derivation of a EU-LCI. The subchronic NOAEC is divided by standard factors for study duration (2) and exposure duration (5.6). Rat and dogs - compared to humans –are considered equally sensitive. Thus no interspecies factor is used. For interspecies variation a factor of 10 is used. With the quality of the data base considered as insufficient a factor of 2 is selected.

The EU-LCI is above the odour detection threshold of ~2 µg/m^3 (Cometto-Muniz 2010).

References

OECS SIDS (2005). N-Valeraldehyde. UNEP Publications. Washington.

Ernstgard L, Iregren A, Sjögren B et al. (2006). Acute effects of exposure to hexanal vapors in humans. J Occup Environ Med 48: 573-580.

Cometto-Muniz JE, Abraham MH (2010). Odor detection by humans of lineal aliphatic aldehydes and helional as gauged by dose-response functions. Chem Senses 35:289-299.

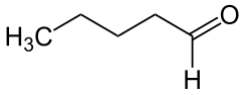
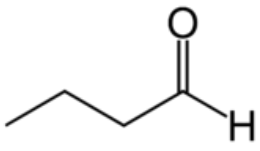
A.12 n-Pentanal (read-across from n-Butanal)

Compound	n-Pentanal (Valeraldehyde) (read-across from n-Butanal)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	800
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2013
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS - NLP	203-784-4
CAS-Nr.	6	Chemical Abstract Service number	110-62-3
Harmonised CLP classification	7	Human health risk related classification	Not harmonized
Molar mass	8	[g/mol]	86.13
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	n-Butanal
Species	11	Rat,… human	
Route/type of study	12	Inhalation, oral feed, …	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	
POD Value	17	[mg/m^3] or [ppm]	
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	

Intraspecies differences	24	Kinetic + dynamic Worker - General population	
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	
Molar adjustment factor	29	Used in read-across (86.13/72.11)	1.194
Rounded value	30	[µg/m³] (662.1 µg/m³ x 1.194 = 790.5 µg/m³)	800
Additional Comments	31		
Rationale Section	32		

Rationale for read-across

- Data poor compound: no adequate toxicological data for pentanal exist from which an EU-LCI value could be derived directly using the *de novo* procedure.
- Read-across from EU-LCI value of butanal: within the chemical class 'saturated aldehydes', butanal is the closest homologue compound with an EU-LCI value: one additional CH2 group in the aliphatic side chain of pentanal.
- Toxicological critical endpoint for butanal: irritation (squamous metaplasia of the nasal cavity).
- The key assumption underlying the read-across of the EU-LCI value from butanal to pentanal is that both compounds have the same critical endpoint (irritation) and this is caused by the common functional group (and not by the additional CH2 group).

Compound	Structure	MW [g/mol]	EU-LCI value
Pentanal		86.13	? (read-across to be used) *800 µg/m³*
Butanal		72.11	650 µg/m³ (*de novo* protocol) Unrounded value: 662.1 µg/m³ or 223.2 ppb

- Unrounded EU-LCI value butanal: 662.1 µg/m³ → to be used for read-across EU-LCI of pentanal.

No cut-off rule in place: difference in change length between the two homologue compounds is smaller

than two CH2 groups per aliphatic chain.

- Thus, EU-LCI value for pentanal is 662.1 µg/m^3. After MW conversion at 23 °C and 1.013 atm: EU-LCI propanal = 662.1 µg/m^3 x 1.194 = 790.5 µg/m^3 → rounded to 800 µg/m^3.

The EU-LCI is above the odour detection threshold of ~ 2 µg/m^3.

References

Nagata Y. (2003). Measurement of odor threshold by triangle odor bag method. Odor Measurement Rev 118-127.

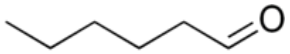
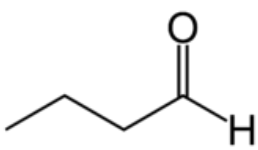
A.13 n-Hexanal (read-across from n-Butanal)

Compound	n-Hexanal (read-across from n-Butanal)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	900
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2013
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS - NLP	200-624-5
CAS-Nr.	6	Chemical Abstract Service number	66-25-1
Harmonised CLP classification	7	Human health risk related classification	Not harmonized
Molar mass	8	[g/mol]	100.16
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	n-Butanal
Species	11	Rat,… human	
Route/type of study	12	Inhalation, oral feed,…	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	
POD Value	17	[mg/m^3] or [ppm]	
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	

Intraspecies differences	24	Kinetic + dynamic Worker - General population	
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	
Molar adjustment factor	29	Used in read-across (100.16/72)	1.39
Rounded value	30	[µg/m³] (662.1 µg/m³ x 1.39 = 920.3 µg/m³)	900
Additional Comments	31		
Rationale Section	32		

Rationale for read-across

- Data poor compound: no adequate toxicological data for hexanal exist from which an EU-LCI value could be derived directly using the *de novo* procedure.
- Read-across from EU-LCI value of butanal: within the chemical class 'saturated aldehydes', butanal is the closest homologue compound with an EU-LCI value: two additional CH2 group in the aliphatic side chain of hexanal.
- Toxicological critical endpoint for butanal: irritation (squamous metaplasia of the nasal cavity).
- The key assumption underlying the read-across of the EU-LCI value from butanal to hexanal is that both compounds have the same critical endpoint (irritation) and this is caused by the common functional group (and not by the additional CH2 group).

Compound	Structure	MW [g/mol]	EU-LCI value
Hexanal		100.16	? (read-across to be used) *900 µg/m³*
Butanal		72.11	650 µg/m³ (*de novo* protocol) Unrounded value: 662.1 µg/m³ or 223.2 ppb

- Unrounded EU-LCI value butanal: 662.1 µg/m^3 → to be used for read-across EU-LCI of hexanal.

  No cut-off rule in place: difference in change length between the two homologue compounds is smaller than two CH2 groups per aliphatic chain.

- Thus, EU-LCI value for hexanal is 662.1 µg/m^3. After MW conversion at 23 °C and 1.013 atm: EU-LCI hexanal = 662.1 µg/m^3 x 1.39 = 920.3 µg/m^3 → rounded to 900 µg/m^3.
- The EU-LCI is consistent with the results of the acute exposure study in human volunteers and protects from acute sensory irritation: In an acute exposure study (Ernstgard et al., 2006) twelve healthy volunteers were exposed to 0, 2, and 10 ppm n-hexanal for 2 hours at rest in a balanced order. Two hours of exposure to n-hexanal resulted in mild irritation at 10 ppm, with no apparent adversity at 2 ppm (6 mg/m^3).

The EU-LCI is above the odour detection threshold of ~ 2 µg/m^3 (Cometto-Muniz 2010).

References

OECS SIDS (2005). N-Valeraldehyde. UNEP Publications. Washington.

Ernstgard L, Iregren A, Sjögren B et al. (2006). Acute effects of exposure to hexanal vapors in humans. J Occup Environ Med 48: 573-580.

Cometto-Muniz JE, Abraham MH (2010). Odor detection by humans of lineal aliphatic aldehydes and helional as gauged by dose-response functions. Chem Senses 35:289-299.

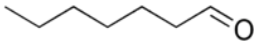
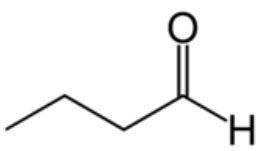
A.14 n-Heptanal (read-across from n-Butanal)

Compound	n-Heptanal (read-across from n-Butanal)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	900
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2013
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS – NLP	203-898-4
CAS-Nr.	6	Chemical Abstract Service number	111-71-7
Harmonised CLP classification	7	Human health risk related classification	Not harmonized
Molar mass	8	[g/mol]	114.18
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	n-Butanal
Species	11	Rat,… human	
Route/type of study	12	Inhalation, oral feed, …	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	
POD Value	17	[mg/m^3] or [ppm]	
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	

Intraspecies differences	24	Kinetic + dynamic Worker - General population	
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	
Molar adjustment factor	29	Used in read-across (100.16/72)	1.39
Rounded value	30	[µg/m³] (662.1 µg/m³ x 1.39 = 920.3 µg/m³)	900
Additional Comments	31		
Rationale Section	32		

Rationale for read-across

- Data poor compound: no adequate toxicological data for heptanal exist from which an EU-LCI value could be derived directly using the *de novo* procedure.
- Read-across from EU-LCI value of butanal: within the chemical class 'saturated aldehydes', butanal is the closest homologue compound with an EU-LCI value: three additional CH2 group in the aliphatic side chain of heptanal.
- Toxicological critical endpoint for butanal: irritation (squamous metaplasia of the nasal cavity).
- The key assumption underlying the read across of the EU-LCI value from butanal to heptanal is that both compounds have the same critical endpoint (irritation) and this is caused by the common functional group (and not by the additional CH2 group).

Compound	Structure	MW [g/mol]	EU-LCI value
Heptanal		114.18	? (read-across to be used) *900 µg/m³*
Butanal		72.11	650 µg/m³ (*de novo* protocol) Unrounded value: 662.1 µg/m³ or 223.2 ppb

- Unrounded EU-LCI value butanal: 662.1 µg/m^3 → to be used for read-across EU-LCI of heptanal.

  Cut-off rule in place: difference in change length between the two homologue compounds is larger than two CH2 groups per aliphatic chain. → cut-off to hexanal.

- Thus, EU-LCI value for heptanal is 662.1 µg/m^3. After MW conversion at 23 °C and 1.013 atm (+ cut-off rule at 2C): EU-LCI heptanal = 662.1 µg/m3 x 1.39 = 920.3 µg/m^3 → rounded to 900 µg/m^3.

The EU-LCI is above the odour detection threshold of ~ 2 µg/m^3.

References

Nagata Y. (2003). Measurement of odor threshold by triangle odor bag method. Odor Measurement Rev 118-127.

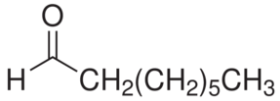
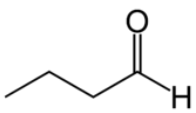
A.15 n-Octanal (read-across from n-Butanal)

Compound	n-Octanal (read-across from n-Butanal)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	900
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2013
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS – NLP	
CAS-Nr.	6	Chemical Abstract Service number	124-13-0
Harmonised CLP classification	7	Human health risk related classification	Not harmonized
Molar mass	8	[g/mol]	128.21
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	n-Butanal
Species	11	Rat,… human	
Route/type of study	12	Inhalation, oral feed, …	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	
POD Value	17	[mg/m^3] or [ppm]	
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	

Intraspecies differences	24	Kinetic + dynamic Worker - General population	
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	
Molar adjustment factor	29	Used in read-across (100.16/72)	1.39
Rounded value	30	[µg/m³] (662.1 µg/m³ x 1.39 = 920.3 µg/m³)	900
Additional Comments	31		
Rationale Section	32		

Rationale for read-across

- Data poor compound: no adequate toxicological data for octanal exist from which an EU-LCI value could be derived directly using the *de novo* procedure.
- Read-across from EU-LCI value of butanal: within the chemical class 'saturated aldehydes', butanal is the closest homologue compound with an EU-LCI value: four additional CH2 group in the aliphatic side chain of octanal.
- Toxicological critical endpoint for butanal: irritation (squamous metaplasia of the nasal cavity).
- The key assumption underlying the read-across of the EU-LCI value from butanal to octanal is that both compounds have the same critical endpoint (irritation) and this is caused by the common functional group (and not by the additional CH2 group).

Compound	Structure	MW [g/mol]	EU-LCI value
Octanal		128.21	? (read-across to be used) *900 µg/m³*
Butanal		72.11	650 µg/m³ (*de novo* protocol) Unrounded value: 662.1 µg/m³ or 223.2 ppb

- Unrounded EU-LCI value for butanal: 662.1 µg/m^3 → to be used for read-across EU-LCI of octanal.

  Cut-off rule in place: difference in change length between the two homologue compounds is larger than two CH2 groups per aliphatic chain. → cut-off to hexanal.

- Thus, EU-LCI value for octanal is 662.1 µg/m^3. After MW conversion at 23 °C and 1.013 atm (+ cut-off rule at 2C): EU-LCI octanal = 662.1 µg/m^3 x 1.39 = 920.3 µg/m^3 → rounded to 900 µg/m^3.

The EU-LCI is above the odour detection threshold of ~ 2 µg/m^3 (Cometto-Muniz 2010).

References

Cometto-Muniz JE, Abraham MH (2010). Odor detection by humans of lineal aliphatic aldehydes and helional as gauged by dose-response functions. Chem Senses 35:289-299.

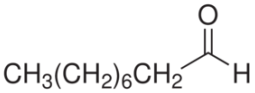
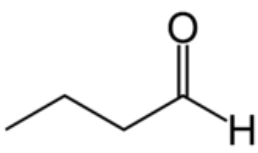
A.16 n-Nonanal (read-across from n-Butanal)

Compound	n-Nonanal (read-across from n-Butanal)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	900
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2013
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS – NLP	204-688-5
CAS-Nr.	6	Chemical Abstract Service number	124-19-6
Harmonised CLP classification	7	Human health risk related classification	Not harmonized
Molar mass	8	[g/mol]	142.23
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	n-Butanal
Species	11	Rat,… human	
Route/type of study	12	Inhalation, oral feed, …	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	
POD Value	17	[mg/m^3] or [ppm]	
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	

Intraspecies differences	24	Kinetic + dynamic Worker - General population	
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	
Molar adjustment factor	29	Used in read-across (100.16/72)	1.39
Rounded value	30	[µg/m³] (662.1 µg/m³ x 1.39 = 920.3 µg/m³)	900
Additional Comments	31		
Rationale Section	32		

Rationale for read-across

- Data poor compound: no adequate toxicological data for nonanal exist from which an EU-LCI value could be derived directly using the *de novo* procedure.
- Read-across from EU-LCI value of butanal: within the chemical class 'saturated aldehydes', butanal is the closest homologue compound with an EU-LCI value: five additional CH2 group in the aliphatic side chain of nonanal.
- Toxicological critical endpoint for butanal: irritation (squamous metaplasia of the nasal cavity).
- The key assumption underlying the read-across of the EU-LCI value from butanal to nonanal is that both compounds have the same critical endpoint (irritation) and this is caused by the common functional group (and not by the additional CH2 group).

Compound	Structure	MW [g/mol]	EU-LCI value
Nonanal		142.23	? (read-across to be used) *900 µg/m³*
Butanal		72.11	650 µg/m³ (*de novo* protocol) Unrounded value: 662.1 µg/m³ or 223.2 ppb

- Unrounded EU-LCI value for butanal: 662.1 µg/m^3 → to be used for read-across EU-LCI of nonanal.

  Cut-off rule in place: difference in change length between the two homologue compounds is larger than two CH2 groups per aliphatic chain. → cut-off to hexanal.

- Thus, EU-LCI value for nonanal is 662.1 µg/m^3. After MW conversion at 23 °C and 1.013 atm (+ cut-off rule at 2C): EU-LCI nonanal = 662.1 µg/m^3 x 1.39 = 920.3 µg/m^3 → rounded to 900 µg/m^3.

The EU-LCI is above the odour detection threshold of ~ 3 µg/m^3 (Cometto-Muniz 2010).

References

Cometto-Muniz JE, Abraham MH (2010). Odor detection by humans of lineal aliphatic aldehydes and helional as gauged by dose-response functions. Chem Senses 35:289-299.

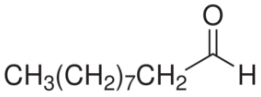
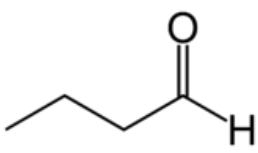
A.17 n-Decanal (read-across from n-Butanal)

Compound	n-Decanal (read-across from n-Butanal)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	900
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2013
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS – NLP	203-957-4
CAS-Nr.	6	Chemical Abstract Service number	112-31-2
Harmonised CLP classification	7	Human health risk related classification	not harmonized
Molar mass	8	[g/mol]	156.2
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	n-Butanal
Species	11	Rat,… human	
Route/type of study	12	Inhalation, oral feed, …	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	
POD Value	17	[mg/m^3] or [ppm]	
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	

Intraspecies differences	24	Kinetic + dynamic Worker - General population	
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	
Molar adjustment factor	29	Used in read-across (100.16/72)	1.39
Rounded value	30	[µg/m³] (662.1 µg/m³ x 1.39 = 920.3 µg/m³)	900
Additional Comments	31		
Rationale Section	32		

Rationale for read across

- Data poor compound: no adequate toxicological data for decanal exist from which an EU-LCI value could be derived directly using the de novo procedure.
- Read-across from EU-LCI value of butanal: within the chemical class 'saturated aldehydes', butanal is the closest homologue compound with an EU-LCI value: six additional CH2 group in the aliphatic side chain of decanal.
- Toxicological critical endpoint for butanal: irritation (squamous metaplasia of the nasal cavity).
- The key assumption underlying the read-across of the EU-LCI value from butanal to decanal is that both compounds have the same critical endpoint (irritation) and this is caused by the common functional group (and not by the additional CH2 group).

Compound	Structure	MW [g/mol]	EU-LCI value
Decanal		156.2	? (read-across to be used) *900 µg/m³*
Butanal		72.11	650 µg/m³ (*de novo* protocol) Unrounded value: 662.1 µg/m³ or 223.2 ppb

- Unrounded EU-LCI value for butanal: 662.1 µg/m^3 → to be used for read-across EU-LCI of decanal.

  Cut-off rule in place: difference in change length between the two homologue compounds is larger than two CH2 groups per aliphatic chain. → cut-off to hexanal.

- Thus, EU-LCI value for decanal is 662.1 µg/m^3. After MW conversion at 23 °C and 1.013 atm (+ cut-off rule at 2C): EU-LCI decanal = 662.1 µg/m^3 x 1.39 = 920.3 µg/m^3 → rounded to 900 µg/m^3.

The EU-LCI is above the odour detection threshold of ~3 µg/m^3 (Nagata 2003).

References

Nagata Y (2003). Measurement of odor threshold by triangle odor bag method. Odor Measurement Rev 118-127.

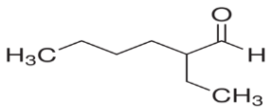
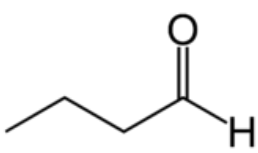
A.18 2-Ethyl hexanal (read-across from n-Butanal)

Compound	2-Ethyl hexanal (read-across from n-Butanal)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	900
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2013
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS – NLP	204-596-5
CAS-Nr.	6	Chemical Abstract Service number	123-05-07
Harmonised CLP classification	7	Human health risk related classification	Not harmonized
Molar mass	8	[g/mol]	128.21
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	n-Butanal
Species	11	Rat,… human	
Route/type of study	12	Inhalation, oral feed, …	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	
POD Value	17	[mg/m^3] or [ppm]	
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	

Intraspecies differences	24	Kinetic + dynamic Worker - General population	
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	
Molar adjustment factor	29	Used in read-across (100.16/72.11)	1.39
Rounded value	30	[µg/m³] (6.1 µg/m³ x 1.39 = 920.3 µg/m³)	900
Additional Comments	31		
Rationale Section	32		

Rationale for read-across

- Data poor compound: no adequate toxicological data for 2-ethyl hexanal exist from which an EU-LCI value could be derived directly using the *de novo* procedure.
- Read-across from EU-LCI value of butanal: within the chemical class 'saturated aldehydes', butanal is the closest homologue compound with an EU-LCI value: two additional CH2 group in the aliphatic main side chain of 2-ethyl hexanal, and one in the second minor side chain.
- Toxicological critical endpoint for butanal: irritation (squamous metaplasia of the nasal cavity).
- The key assumption underlying the read-across of the EU-LCI value from butanal to 2-ethyl hexanal is that both compounds have the same critical endpoint (irritation) and this is caused by the common functional group (and not by the additional CH2 groups).

Compound	Structure	MW [g/mol]	EU-LCI value
2-ethyl hexanal		128.21	? (read-across to be used) *900 µg/m³*
Butanal		72.11	650 µg/m³ (*de novo* protocol) Unrounded value: 662.1 µg/m³ or 223.2 ppb

- Unrounded EU-LCI value of butanal: 662.1 µg/m^3 → to be used for read-across EU-LCI of 2-ethyl hexanal.

  Cut-off rule in place: difference in change length between the two homologue compounds is larger than two CH2 groups per aliphatic chain. → cut-off to hexanal.

- Thus, EU-LCI value for 2-ethyl hexanal is 662.1 µg/m^3. After MW conversion at 23 °C and 1.013 atm (+ cut-off rule at 2C): EU-LCI 2-ethyl hexanal = 662.1 µg/m^3 x 1.39 = 920.3 µg/m^3 → rounded to 900 µg/m^3.

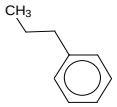
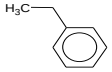
A.19 n-Propylbenzene (read-across from Ethylbenzene)

Compound	**n-Propylbenzene (read-across from Ethylbenzene)**		**Factsheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	950
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2013
General Information			
CLP-INDEX-Nr.	4	INDEX	601-024-00-X
EC-Nr.	5	EINECS – ELINCS - NLP	203-132-9
CAS-Nr.	6	Chemical Abstract Service number	103-65-1
Harmonised CLP classification	7	Human health risk related classification	Asp. Tox. 1 STOT SE 3
Molar mass	8	[g/mol]	120.19
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Ethylbenzene
Species	11	Rat,… human	
Route/type of study	12	Inhalation, oral feed, …	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	
POD Value	17	[mg/m^3] or [ppm]	0.860 mg/m^3 or 0.197 ppm
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	

Intraspecies differences	24	Kinetic + dynamic Worker - General population	
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	860 µg/m³ 197 ppb
Molar adjustment factor	29	Used in read-across	1.13 (=120.19/106.17)
Rounded value	30	[µg/m³] (860 µg/m³ x 1.13 = 971.8 µg/m³)	950
Additional Comments	31		
Rationale Section	32		

Rationale for read-across

- Data poor compound: no adequate toxicological data for n-propylbenzene; *de novo* derivation of EU-LCI for n-propylbenzene is not possible.
- Read-across from EU-LCI value of ethylbenzene: within the chemical class 'saturated aromatic hydrocarbons', ethylbenzene is the closest homologue compound with an EU-LCI value: one additional CH_2 group in the aliphatic side chain of n-propylbenzene.
- Toxicological critical endpoint for ethylbenzene: ototoxicity.
- The key assumption underlying the read-across of the EU-LCI value from ethylbenzene to propylbenzene is that both compounds have the same critical endpoint (ototoxicity) and this is caused by the common functional group (and not by the additional CH_2 group).

Compound	Structure	MW [g/mol]	EU-LCI value
n-Propylbenzene		120.19	? (read-across to be used) *950 µg/m³*
Ethylbenzene		106.17	850 µg/m³ (*de novo* protocol) Unrounded value: 860.6 µg/m³ or 197 ppb

- Unrounded EU-LCI value for ethylbenzene: 860 µg/m^3 → to be used for read-across EU-LCI of n-propylbenzene.

  No cut-off rule in place: difference in change length between the two homologue compounds is smaller than two CH_2 groups per aliphatic chain.

- Thus, EU-LCI value for ethylbenzene is 860 µg/m^3. After MW conversion (at 23 °C and 1.013 atm) : EU-LCI n-propylbenzene = 860 µg/m^3 x 1.13 = 971.8 µg/m^3 → rounded to 950 µg/m^3.

A.20 Phenyloctane and Isomers (read-across from Ethylbenzene)

Compound	Phenyloctane and Isomers (read-across from Ethylbenzene)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	1100
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2013
General Information			
CLP-INDEX-Nr.	4	INDEX	(Not in Annex IV of CLP Regulation 1272/2008)
EC-Nr.	5	EINECS – ELINCS - NLP	218-582-1
CAS-Nr.	6	Chemical Abstract Service number	2189-60-8
Harmonised CLP classification	7	Human health risk related classification	Not harmonized
Molar mass	8	[g/mol]	190.32
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Ethylbenzene
Species	11	Rat,… human	
Route/type of study	12	Inhalation, oral feed, …	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	
POD Value	17	[mg/m^3] or [ppm]	0.860 mg/m^3 or 0.197 ppm
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	

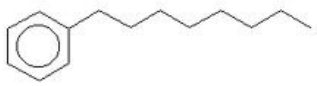
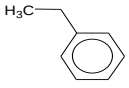
Intraspecies differences	24	Kinetic + dynamic Worker - General population	
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	860 µg/m3 197 ppb
Molar adjustment factor	29	Used in read-across	1.264
Rounded value	30	[µg/m³] (860 µg/m³ x 1.264 = 1087 µg/m³)	1100
Additional Comments	31		

Rationale Section	32		

Rationale for read-across

- Data poor compound: no adequate toxicological data for phenyl octane (and isomers); *de novo* derivation of EU-LCI for phenyl octane is not possible; therefore, read-across from other compounds was applied, and is justified below.
- Read-across candidate compounds for starting value: within the chemical class of 'saturated aromatic hydrocarbons' ethylbenzene is the closest homologue with an EU-LCI value; phenyl octane having additional $(CH_2)_6$ groups in the aliphatic chain compared to ethylbenzene. EU-LCI value for ethylbenzene: 197 ppb.

  Chemical structure, molecular weight of phenyl octane and ethylbenzene are listed in the following table:

Compound	Structure	MW [g/mol]	EU-LCI value
Phenyl octane and isomers		190.32	
Ethylbenzene		106.17	850 µg/m² (*de novo* protocol)- Unrounded value: 860.6 µg/m³ or 197 ppb

- Toxicological critical endpoints for homologue compounds:
  Ethylbenzene: ototoxicity, assuming the critical endpoint for phenyl octane is ototoxicity.
- The key assumption underlying the read-across of the EU-LCI value from ethylbenzene to phenyl octane is that both compounds have the same critical endpoint (ototoxicity) and that this endpoint is caused by the common functional group (and not by the additional CH2 groups).

- The cut-off rule on the molar adjustment factor is applicable: difference in change length between the two homologue compounds is larger than two CH2 groups per aliphatic chain.

- Thus after applying the MW conversion molar weight conversion (at 23°C and 1.013 atm) and applying the cut-off rule to butylbenzene: EU LCI phenyl octane= 1087.0 µg/m^3 → to be rounded to 1100 µg/m^3).

A.21 Diisopropylbenzene (1,3-, 1,4-) (read-across from Xylenes)

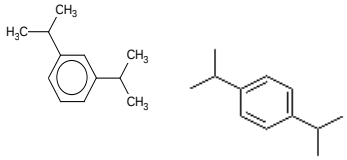
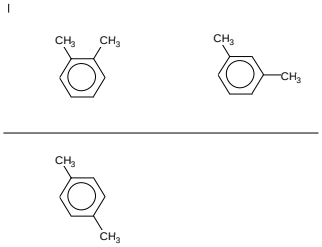
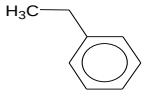
Compound	Diisopropylbenzene (1,3-, 1,4-) (read-across from Xylenes)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	750
EU-LCI status	2	Interim / Confirmed	Interim
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2013
General Information			
CLP-INDEX-Nr.	4	INDEX	(Not in Annex VI of CLP Regulation 1272/2008)
EC-Nr.	5	EINECS – ELINCS - NLP	202-773-1 for (1,3-) 202-826-9 for (1,4-)
CAS-Nr.	6	Chemical Abstract Service number	99-62-7 for (1,3-) 100-18-5 for (1,4-)
Harmonised CLP classification	7	Human health risk related classification	Not harmonized
Molar mass	8	[g/mol]	162.27
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Xylene
Species	11	Rat,… human	
Route/type of study	12	Inhalation, oral feed,…	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose,….	
POD Value	17	[mg/m^3] or [ppm]	0.492 mg/m^3 or 0.1126 ppm
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	
AF Study Length	20	sa→ sc→ c *(R8-5)*	
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	

Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	
AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	492 µg/m3 112.6 ppb
Molar adjustment factor	29	Used in read-across	1.526 (=162.27/106.17)
Rounded value	30	[µg/m³]	750
Additional Comments	31		

Rationale Section	32

Rationale for read-across

- Data poor compound: no adequate toxicological data for diisopropylbenzene (1,3-, 1,4-); *de novo* derivation of EU-LCI for diisopropylbenzene is not possible.
- Read-across candidate compounds for starting value: within the chemical class of 'saturated aromatic hydrocarbons' xylene and ethylbenzene are two compounds with EU-LCI values and having similar 'closest homologue' to diisopropylbenzene (1,3-, 1,4). Cumene (=isopropylbenzene) is another possible homologue, but it has no EU-LCI value.
- Toxicological critical endpoints for homologue compounds:
  - xylene: effects on central nervous system (CNS) (and irritation);
  - ethylbenzene: ototoxicity.
- Of these compounds, xylene has the lowest EU-LCI value (112.6 ppb). Thus, as a conservative approach, xylene is used as the most appropriate homologue compound to start the read-across.
- The key assumption underlying the read-across of the EU-LCI value from xylene to diisopropylbenzene (1,3-, 1,4-) is that both compounds have the same critical endpoint (CNS effects) and this endpoint is caused by the common functional group (and not by the additional CH_2 groups).

Compounds	Structure	MW [g/mol]	EU-LCI value
Diisopropylbenzene (1,3-, 1,4-)		162.27	? (read-across to be used) *750 µg/m³*
Xylene		106.17	500 µg/m³ (*de novo* protocol) Unrounded value: 491.9 µg/m³ or 112.6 ppb
Ethylbenzene		106.17	850 µg/m³ (*de novo* protocol) Unrounded value: 860.6 µg/m³ or 197 ppb

- No cut-off rule in place: difference in change length between the two homologue compounds is smaller than two CH_2 groups per aliphatic chain.
- Thus, the unrounded EU-LCI value for diisopropylbenzene (1,3-, 1,4-) is 492 µg/m³. After MW conversion (at 23 °C and 1.013 atm): EU-LCI diisopropylbenzene (1,3-, 1,4-) = 492 µg/m³ x 1.526 = 750.8 µg/m³ →to be rounded to 750 µg/m³.

APPENDIX B: Members of the ECA "*Urban Air, Indoor Environment & Human Exposure*" Steering Committee

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EUROPEAN COMMISSION

Stylianos **KEPHALOPOULOS** (*Scientific Co-ordinator*), Joint Research Centre, Institute for Health and Consumer Protection, Chemical Assessment and Testing Unit, Ispra

European Commission

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Author(s): *Stylianos Kephalopoulos, Otmar Geiss, Erwin Annys, Reto Coutalides, Derrick Crump, Christine Däumling, Katleen de Brouwere, Dieter de Lathauwer, Nicole Dommaschk, Martin Glöckner, P. Harrison, B. Heinzow, Rudolf Jäckh, Gunnar Johanson, Sandrine Le Guern, Christophe Rousselle, Jorma Säteri, Armin Schuster, Ana Maria Scutaru, Peter Tappler, Maria Uhl,Thomas Witterseh, Peder Wolkoff.*

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Abstract

The health based evaluation of chemical emissions from construction products is an integral part of the harmonisation framework for indoor products labelling schemes in the EU. The harmonisation process for the health based evaluation of gas-phase chemical emissions from construction products in Europe, is based on the LCI ('Lowest Concentration of Interest') approach and is described fully in this report.

The work was co-ordinated by the European Commission' Directorate General Joint Research Centre (DG JRC) and performed in the context of the PILOT INDOOR AIR MONIT administrative arrangement with the Directorate General for Health and Consumers (SANCO) in liaison with experts from the EU Member States and the Directorate General for Enterprise and Industry (DG ENTR).

This EU-LCI development work outlined in the present report builds on firm foundations of the exisiting national labelling schemes established by AgBB in Germany and ANSES in France that currently apply the LCI concept, as well as those in Finland, Denmark and Belgium. Ultimately, the harmonisation process and procedures described here will allow voluntary and mandatory labelling schemes to evaluate product emissions in the same way by using a robust health-based procedure. This work also supports the establishment of future emission classes for CE marking under the European Construction Products Regulation ((EU) No 305/2011) with a harmonised list of LCI values (EU-LCIs).

In the EU-LCI work performed to date, only volatile organic compounds (VOCs) have been considered. Very volatile (VVOCs) with the exception of acetaldehyde and formaldehyde, semi-volatile organic compounds (SVOCs) and carcinogens were not considered at this stage of the process.

This phase of the EU-LCI harmonisation process has established:

1. A robust protocol for establishing a harmonised list of compounds and their associated EU-LCI values which takes into account existing procedures used in some EU Member States. This procedure, based on sound toxicological and risk assessment principles, represents an appropriate health-protective, science-based and transparent yet pragmatic approach for the evaluation of chemical emissions from construction products.
2. A list of interim EU-LCI values for 82 compounds, which includes some of the compounds most relevant to DG ENTR's ad hoc group on emission classes (i.e., acetaldehyde, toluene, xylene, 1,2,4-trimethylbenzene, 1,4-dichlorobenzene, ethylbenzene, 2-butoxyethanol and styrene) and two compounds shaded of recent concern in Germany (ε-caprolactam) and Belgium (α-Pinene).
3. A flexible framework that enables future revision of the content of the EU-LCI list in terms of both the type and number of compounds included and their associated EU-LCI values. The framework provides the possibility of taking into account new knowledge (e.g. data resulting from the REACH implementation process or compounds identified and suggested by EU national authorities).

The protocol also provides guidance on applying a harmonised application of read-across and assessment factors in EU-LCI derivation.

Through application of the principles and rationale developed for the establishment of EU-LCI values, EU-LCI values have been established for a number of priority compounds. The EU-LCI WG compiled an EU-LCI master list containing a total of 177 compounds and subdivided into two groups, the first containing 82 compounds with agreed interim EU-LCI values and the second containing 95 compounds for which EU-LCI values are still to be derived.

The practical application of the EU-LCI values and the necessary consideration of multiple sources that are normally present in real building scenarios are discussed and potential harmonisation issues related to the overall evaluation of emissions from construction products (for example, common criteria and threshold values for TVOC, SVOC, sensory evaluation and the sum of "not-yet-assessable" compounds) are identified.

Finally, developments concerning policies at both EU and national levels that have explicitly or implicitly considered and/or referred to the work of the EU-LCI WG are reported.

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