SUBSTANCE EVALUATION REPORT

Public Name: **buta-1,3-diene**

EC Number(s): **203-450-8**

CAS Number(s): **106-99-0**

Submitting Member State Competent Authority:

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Conclusions of the most recent evaluation step	
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	X
Concern clarified; Need for risk management measures; RMO analysis to be performed	

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Executive summary

Grounds for concern

Buta-1,3-diene (thereafter referred to also as butadiene or 1,3-butadiene) is classified as carcinogen 1A and mutagen 1B. Therefore it may qualify for identification as SVHC under Art 57(a and b).

Buta-1,3-diene is a high production volume chemical. The substance is produced with very high tonnage (> 1,000,000 t/a).

Buta-1,3-diene was chosen for substance evaluation in 2014 under article 44 (1) REACH Regulation because of the potential high exposure to workers.

Although by far most of the uses of butadiene are handled in closed systems with little potential for exposure, there are some uses mentioned in the registration dossier indicating that there are also uses in (partly) open systems, or exposure may happen during interruption of processes and handling of crude products. The details of these uses and the potential exposure risk needed to be clarified in order to decide which risk management is appropriate.

Some uses (PROCs) mentioned in the registration dossier indicated that potential worker exposure might occur. Exposure scenarios to these uses needed to be evaluated for the quality of data and plausibility. The levels of exposure should be compared with available DMEL/DNEL and exposure risk relationships.
Present data indicate that the DMELs calculated may give rise to exposures well above a risk ratio of 4: 1,000.

Procedure

A manual screening for buta-1,3-diene was performed by the eMSCA in May 2012. As a result of this screening a justification document for buta-1,3-diene was written in September 2012 to put the substance on the CoRAP for substance evaluation under article 44 (1) REACH Regulation in 2014.

On 2014-03-27 ECHA published the CoRAP and initiated a substance evaluation of buta-1,3-diene. A meeting with representatives of the lead registrant was held on 2014-06-24.

On 2014-5-15 a request concerning the occupational diseases generated from buta-1,3-diene was performed.

A questionnaire regarding occupational diseases caused by buta-1,3-diene was created and send to the other MS on 2014-6-14.

Neither in Germany nor in other countries who answered the questionnaire any cases could be found which could be traced back specific to buta-1,3-diene.

The lead registrant submitted an update of the registration dossier in June 2014. A content of this update was the revision of the professional and the consumer uses. They also used ECETOC TRA v.3 instead of ECETOC TRA v.2 for the worker exposure assessment.

During the process of substance evaluation all data available until October 2014 were taken into account.

This substance evaluation includes all human health endpoints. The evaluation as well as the documentation in the SEV report focuses on certain aspects with relation to the initial concerns. Moreover, the available information in the registration dossiers were checked for plausibility and indications of additional concerns for buta-1,3-diene.

Conclusions

Worker

The eMSCA has assessed at first the concern initiating the substance evaluation, the potential exposure risk for workers. It has been concluded that the initial concern was clarified. The available data suggest that the occupational exposure risk is in an acceptable range and that there is no need for further activities.

Nevertheless, the eMSCA identified an aspect of risk assessment which had to be studied more in detail.

Considering the physicochemical properties of buta-1,3-diene and its industrial uses, workplace exposure occurs via inhalation. The registrants have provided an estimated $DMEL_{long\text{-}term,\ inhalation,\ systemic}$ of 1 ppm (2.21 mg/m^3) for occupational exposure. According to the registrants, this results in a mortality rate from leukemia of 0.39×10^{-4} which corresponds to approximately 4:100 000. This has also been proposed as the future acceptable limit for occupational risk in Germany (AGS, 2008).

However, in Germany, the Committee on Hazardous Substances (Ausschuss für Gefahrstoffe - AGS) currently determined values for tolerable (4:1,000) and acceptable (4:10,000) risk for buta-1,3-diene with 2 ppm and 0.2 ppm, respectively (see Table 1). This is a range where further measures of risk management are needed to minimise the occupational risk for the worker.

Table 1: Exposure-risk relationship for buta-1,3-diene according to the derivation by Working Group "Limit Values and Classification of Carcinogenic and Mutagenic Substances" (AK CM) in view of the justification for an occupational exposure limit (OEL).

Buta-1,3-diene concentration, long-termin mean, 35-40 years of occupational exposure		Exposure-related lifetime leukaemia risk
ppm	µg/m^3	
15	33,660	3%
5	11,220	1%
2	4,488	4 to 1,000
1	2,244	2 to 1,000
0.5	1,122	1 to 1,000
0.05	112	1 to 10,000
0.005	11	1 to 100,000

The eMSCA carried out an evaluation of both approaches, from registrants and AGS. The risk calculation of the registrants is not supported. Nevertheless, the proposed DMEL of 1ppm (2.21 mg/m^3) has been taken for risk assessment. Based on the registrants' DMEL of 1 ppm the reported exposure values do not exceed this DMEL in general. Within the AGS concept the reported exposure values are between the tolerance level of 2 ppm and the acceptance level of 0.2 ppm. Due to the fact that the exposure values are closer to the acceptance level both approaches lead to the conclusion that there is no need for further activities like the initiation of a restriction or an authorisation procedure.

Consumer

Based on epidemiological studies in workers exposed to butadiene an inhalative DMEL for consumers was derived with 1.50 µg/m^3 (0.0007 ppm).

During the substance evaluation an additional concern was identified due to a potential use of the substance by consumers as given in registration dossiers. In the dialogue with representatives of the lead registrant the representatives clarified the indicated consumer use to be an erroneous indication of a consumer related article service life in the registration dossiers.

The Lower Olefins and Aromatic REACH Consortium has informed the eMSCA that the erroneous indication shall be corrected. Prior to completion of this substance evaluation process, several registration dossiers have been updated. In view of the information given by the Lower Olefins and Aromatic REACH Consortium the additional concern is considered to be clarified. However, at the time of writing the conclusion the latest version of the disseminated dossier(s) on ECHA web-site still included the entry in question.

Buta-1,3-diene monomers remaining in polymers and co-polymers like synthetic rubbers, thermoplastic resins and styrene-butadiene latex lead to a consumer exposure.
The exposure from these sources has already been assessed in the European Risk assessment published in 2002.

The exposure assessment was based on the old data from EU RAR (2002). The two main sources are from indoor air and from butadiene-based food packing materials. Using a Derived Minimal Effect Level for consumers of 0.43 µg/kg bw/day for adults and 0.72 µg/kg bw/day for toddlers (age ≤ 3 years) the RCR for the oral route amounted to the value of 1.67 for toddlers. However, the EU RAR was based on the assumption that the maximum concentration of butadiene in foodstuffs in butadiene-based polymers is < 0.02 mg/kg. Recent regulations (EU 10/2011) lowered concentration limits to a detection limit of < 0.01 mg/kg food. This is supported by the fact that an inquiry of the data from the German food and commodity safety surveillance retrieved no data on buta-1,3-diene contents in food or commodities.

Using the exposure data from EU RAR (2002) and a DMEL for consumers (inhalative) of 1.50 µg/m^3 the risk characterisation ratio was 1.20 for adults and 0.95 for toddlers. Given that butadiene concentrations in indoor air used for the EU RAR exposure estimates are influenced by further sources besides tobacco smoke, than regarded in the EU RAR and that the calculations in the EU RAR are based on a rough estimation with a simple equation it is concluded that the RCR values for inhalation exposure are overestimations and will not lead to an unacceptable risk of the consumer.

The available information on the substance and the evaluation conducted has led the evaluating Member State to the conclusion that there is no need for regulatory follow-up action.

CONTENTS

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES 10

1.1 Name and other identifiers of the substance 10

1.2 Composition of the substance 11

1.3 Physico-chemical properties 12

2 MANUFACTURE AND USES 15

2.1 Quantities 15
2.1.1 Manufacturing processes 15

2.2 Identified uses 15
2.2.1 Uses by workers in industrial settings 15
2.2.2 Use by professional workers 16
2.2.3 Uses by consumers 16

2.3 Uses advised against 16
2.3.1 Uses by workers in industrial settings advised against 16
2.3.2 Use by professional workers advised against 16
2.3.3 Uses by consumers advised against 16

3 CLASSIFICATION AND LABELLING 17

3.1 Harmonised Classification in Annex VI of the CLP Regulation 17

3.2 Self-classification 17

4 ENVIRONMENTAL FATE PROPERTIES 20

5 HUMAN HEALTH HAZARD ASSESSMENT 20

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination) 20
5.1.1 Non-human information 20
5.1.2 Human information 20
5.1.3 Summary and discussion on toxicokinetics 20

5.2 Acute toxicity 23
5.2.1 Non-human information 23
5.2.1.1 Acute toxicity: oral 23
5.2.1.2 Acute toxicity: inhalation 24
5.2.1.3 Acute toxicity: dermal 24
5.2.1.4 Acute toxicity: other routes 24
5.2.2 Human information 24
5.2.3 Summary and discussion of acute toxicity 25

5.3 Irritation 26
5.3.1 Skin 26
5.3.2 Eye 26
5.3.3 Respiratory tract 26
5.3.4 Summary and discussion of irritation 26

5.4 Corrosivity 26

5.5 Sensitisation 26
5.5.1 Skin 26
5.5.2 Respiratory system 26
5.5.3 Summary and discussion on sensitisation 27

5.6 Repeated dose toxicity 27
5.6.1 Non-human information 27
5.6.1.1 Repeated dose toxicity: oral 27
5.6.1.2 Repeated dose toxicity: inhalation 28
5.6.1.3 Repeated dose toxicity: dermal 33
5.6.1.4 Repeated dose toxicity: other routes 33
5.6.2 Human information 34
5.6.3 Summary and discussion of repeated dose toxicity 37

5.7 Mutagenicity 38
5.7.1 Non-human information 38
5.7.1.1 In vitro data 38
5.7.1.2 In vivo data 40
5.7.2 Human information 44
5.7.3 Summary and discussion of mutagenicity 46

5.8 Carcinogenicity 46
5.8.1 Non-human information 46
5.8.1.1 Carcinogenicity: oral 46
5.8.1.2 Carcinogenicity: inhalation 47
5.8.1.3 Carcinogenicity: dermal 49
5.8.2 Human information 49
5.8.3 Summary and discussion of carcinogenicity 56

5.9 Toxicity for reproduction 58
5.9.1 Effects on fertility 58
5.9.1.1 Non-human information 58
5.9.1.2 Human information 61
5.9.2 Developmental toxicity 62
5.9.2.1 Non-human information 62
5.9.2.2 Human information 64
5.9.3 Summary and discussion of reproductive toxicity 64

5.10 Endocrine disrupting properties 65

5.11 Other effects 65
5.11.1 Non-human information 65
5.11.1.1 Neurotoxicity 65
5.11.1.2 Immunotoxicity 65
5.11.2 Human information 66
5.11.3 Summary and discussion of specific investigations 66

5.12 Combined effects 66

5.13 Derivation of DNEL(s) / DMEL(s) 66
5.13.1 Overview of typical dose descriptors for all endpoints 66
5.13.2 Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptor for critical health effects 68

5.14 Conclusions of the human health hazard assessment and related classification and labelling 70

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES 70

7 ENVIRONMENTAL HAZARD ASSESSMENT 70

8 PBT AND VPVB ASSESSMENT 70

9 EXPOSURE ASSESSMENT 71

9.1 Human Health 71
9.1.1 Exposure assessment for worker 71
9.1.1.1 Overview of uses and exposure scenarios 71
9.1.1.2 Scope and type of exposure 71
9.1.2 Exposure assessment for consumer 79
9.1.2.1 Overview of uses and exposure scenarios 79
9.1.2.2 Scope and type of exposure 80

9.2 Environmental exposure assessment 80

10 RISK CHARACTERISATION 81

10.1 Human Health 81
10.1.1 Workers 81
10.1.2 Consumers 82

10.2 Environment 84

11 OTHER INFORMATION 84

12 REFERENCES 85

13 ABBREVIATIONS 91

TABLES

Table 1: Exposure-risk relationship for buta-1,3-diene according to the derivation by Working Group "Limit Values and Classification of Carcinogenic and Mutagenic Substances" (AK CM) in view of the justification for an occupational exposure limit (OEL). 4
Table 2: Substance identity 10
Table 3: Constituents 11
Table 4: Impurities 11
Table 5: Additives 11
Table 6: Overview of physicochemical properties 12
Table 7: Aggregated tonnage (per year) 15
Table 8: Classification and labelling of buta-1,3-diene according to Annex VI, Part 3, and Table 3.1 (list of harmonised classification and labelling of hazardous substances) of CLP regulation. 17
Table 9: Notified classification and labelling of buta-1,3-diene according to CLP criteria. 18
Table 10: Compilation of experimental studies on acute toxicity after inhalative exposure according to the registration dossier. 24
Table 11: Compilation of human data on acute toxicity after inhalative exposure according to the registration dossier. 24
Table 12: Presentation of experimental studies on repeated dose toxicity after inhalative administration according to the registration dossier 28
Table 13: Presentation of exposure-related observations in humans according to the registration dossier 34
Table 14: Presentation of in-vitro genotoxicity studies according to the registration dossier 38
Table 15: Presentation of in-vivo genotoxicity studies according to the registration dossier 40
Table 16: Human information is compiled according to the registration dossier. Additionally, new publications have been considered. 44
Table 17: Presentation of carcinogenicity studies according to the registration dossier 47
Table 18: Human information is compiled according to the registration dossier. 49
Table 19: Presentation of fertility studies according to the registration dossier 58
Table 20: Presentation of developmental toxicity studies according to the registration dossier 62
Table 21: Presentation of immunotoxicity studies according to the registration dossier 65
Table 22: Dose descriptor(s) per endpoint for derivation of DNEL and DMEL 67

Table 23: Hazard conclusion for workers 69
Table 24: Summary of 8-hour TWA exposure data used in EU RAR (Commission 2002, table 4.13, p74). 72
Table 25: Summary of short-term exposure data used in EU RAR (Commission 2002, table 4.14, p75). 73
Table 26: Descriptive statistics for individual measurements of workplace exposure to buta-1,3-diene (mg/m³) by group (Albertini, Sram et al. 2003). 73
Table 27: Descriptive statistics for workplace area measurements of buta-1,3-diene (mg/m³) (Albertini, Sram et al. 2003). 74
Table 28: Overview of the measured values collected in the MGU, data period 1984-2013 (IFA 2014). 74
Table 29: Statistical evaluation differentiated by data periods (IFA 2014). 76
Table 30: Statistical evaluation for branches of industry and work area groups: sampling representative for exposure time ≥ 6 h (IFA 2014). 76
Table 31: Statistical evaluation for work area groups: sampling representative for exposure time ≥ 6 h (IFA 2014). 76
Table 32: Overview of exposure scenarios according to the registration (LOA, 2014). 77
Table 33: Overview of highest estimates of inhalation exposure in exposure scenarios 1-10 (according to the registration dossier). 78
Table 34: Exposure-risk relationship for buta-1,3-diene according to the derivation by Working Group "Limit Values and Classification of Carcinogenic and Mutagenic Substances" (AK CM) in view of the justification for an occupational exposure limit (OEL). 82
Table 35: Risk characterisation for oral exposure of consumers. 82
Table 36: Risk characterisation for inhalative exposure of consumers. 83
Table 37: Risk characterisation for combined exposure from indoor air and leaching from packing into foodstuffs (reasonable worst case). 83

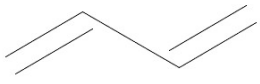
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 2: Substance identity

Public Name:	Buta-1,3diene
EC number:	203-450-8
EC name:	buta-1,3-diene
CAS number (in the EC inventory):	106-99-0
CAS number:	106-99-0
CAS name:	1,3-butadiene
IUPAC name:	buta-1,3-diene
Index number in Annex VI of the CLP Regulation	601-013-00-X
Molecular formula:	C_4H_6
Molecular weight range:	54.09
Synonyms:	Biethylene; Bivinyl; Butadiene; Butadiene-1,3; Divinyl; Erythrene; Vinylethylene; α,γ-Butadiene

Structural formula:



1.2 Composition of the substance

Name: Buta-1,3-diene

Description: Mono-constituent substance

Degree of purity: Further information is provided in the confidential Annex or rather IUCLID File.

Table 3: Constituents

Constituents	Typical concentration	Concentration range	Remarks
Buta-1,3-diene *EC number: 203-450-8*			see confidential annex

Table 4: Impurities

Impurities	Typical concentration	Concentration range	Remarks
see confidential annex			

Table 5: Additives

Additives	Typical concentration	Concentration range	Remarks
Name and EC number			

1.3 Physico-chemical properties

Table 6: Overview of physicochemical properties

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	*colourless gas with mild aromatic odour*	*Handbook data*
Melting/freezing point	*-108.9°C (1013 hPa)*	*Handbook data*
Boiling point	*-4.4°C (1013 hPa)*	*Handbook data*
Vapour pressure	*217 kPa (290 K)* *255 kPa (295 K)*	*Handbook data*
	274 kPa (25°C)	*Calculated value: (Q)SAR;* *US EPA, MPBPVP v.1.43 programme*
Surface tension	*12.49 mN/m (25°C, for the pure liquefied gas)*	*Publication: European Union Risk Assessment Report 1,3-BUTADIENE, CAS No: 106-99-0 EINECS No: 203-450-8*
Water solubility	*735 mg/L (20°C)*	*Publication/Handbook data*
	792.3 mg/L (25°C)	*Calculated value: (Q)SAR;* *US EPA, WSKOW v. 1.41 programme*
Partition coefficient n-octanol/water (log value)	*1.99 (25°C)*	*Handbook data*
	2.03	*Calculated value: (Q)SAR;* *US EPA, KOWWIN v. 1.67 programme*
Flash point	*idem*	*idem*
Flammability	*idem*	*idem*
Explosive properties	*idem*	*idem*
Self ignition temperature	*idem*	*idem*
Oxidising properties	*idem*	*idem*
Granulometry	-	*In accordance with column 2 of REACH Annex VII section 7.14., the study does not need to be conducted if the substance is marketed or used in a non- solid or granular form. Buta-1,3-diene is a gaseous substance. Therefore, granulometry is not applicable to buta-1,3-diene.*
Stability in organic solvents and identity of relevant degradation products	-	*In accordance with column 1 of REACH Annex IX section 7.15., a study is only required if stability of the substance is considered to be critical.* *Buta-1,3-diene is a highly volatile gaseous substance that is used as an intermediate in production of polymers and other chemicals. The ECHA Guidance on Chemical Safety Assessment (part R7a) notes that information on the stability of a compound in an organic solvent may be important in rare occasions, mostly to ensure confidence in*

		the test results. The Guidance also gives examples of when stability in organic solvents could be important, such as: - *for certain solubility measurements (e.g. octanol-water partition coefficient);* - *to check on the stability of reagent solutions, fortification standards or calibration standards;* - *when a test substance is dosed as a solution in an organic solvent (e.g. ecotoxicity studies);* - *when a test substance is extracted from an environmental sample, plant or animal tissue or diet matrix (arising from a variety of physico-chemical property, ecotoxicity and animal toxicity studies) into an organic solvent and stored pending analytical measurement.* *Based on the data summarized above, this property is not considered as critical and, therefore, testing results are omitted for buta-1,3-diene.*
Dissociation constant	-	*In accordance with column 2 of REACH Annex IX section 7.16.:* *The study does not need to be conducted if:* - *the substance is hydrolytically unstable (half-life less than 12 hours) or is readily oxidisable in water, or* - *it is scientifically not possible to perform the test for instance if the analytical method is not sensitive enough..* *Buta-1,3-diene is a gaseous substance with high volatility. Therefore, it would be difficult to test buta-1,3-diene for this property.* *The ECHA Guidance on Chemical Safety Assessment (part 7Ra) specifies that this property is important for ionisable organic substances, since it indicates which chemical species will be present at a particular pH (e.g. in fresh or marine waters, or in the gut). Evaluation of buta-1,3-diene structure shows that buta-1,3-diene is a neutral organic compound. Therefore, this property is not considered to be important for buta-1,3-diene.*
Viscosity	-	*The ECHA Guidance on Chemical Safety Assessment (part 7Ra) specifies viscosity is relevant only to liquids, and therefore for many substances this determination is not required.* *Buta-1,3-diene is a gaseous substance. Therefore, a study on the viscosity is not*

		required for buta-1,3-diene.
Auto flammability	*idem*	*idem*
Reactivity towards container material	*idem*	*idem*
Thermal stability	*idem*	*idem*

2 MANUFACTURE AND USES

2.1 Quantities

Table 7: Aggregated tonnage (per year)

1 – 10 t	10 – 100 t	100 – 1000 t	1000- 10,000 t	10,000-50,000 t
50,000 – 100,000 t	100,000 – 500,000 t	500,000 – 1000,000 t	**> 1000,000 t**	Confidential

2.1.1 Manufacturing processes

The principal industrial method for producing buta-1,3-diene is steam cracking within the petrochemical process, or related feed stocks. During the steam cracking process the raw material is mixed with steam and briefly heated in a furnace (up to 900°C) causing saturated hydrocarbons to break down into smaller, often unsaturated, hydrocarbons (olefins). Steam cracking of light gasoline (naphtha) yields, among other products, ethylene, propene, benzene and 1,3-butadiene (Schmidt et al. 2014). The composition of the starting material has a major influence on the cracking yields (products of the reaction). The composition of the product is also affected by the cracking severity (temperature and duration). In Western Europe, naphtha is the primarily used feed for the production of 1,3-butadiene by stream cracking (Grub, Löser 2011).

2.2 Identified uses

2.2.1 Uses by workers in industrial settings

- Manufacture
- Process regulator
- Importation and storage
- Formulation
- Use as a fuel
- Use in laboratories
- Use as laboratory reagents
- Monomer in production of other chemicals
- Use as an intermediate
- Distribution
- Uses in Rubber production and processing
- Polymer Production
- Polymer Processing

2.2.2 Use by professional workers

- Polymer Processing (it should be mentioned that according to the ECHA definition polymer processing, as described by the registrant, wouldn´t belong under professional but under industrial use).

2.2.3 Uses by consumers

Based on the data published in international assessment documents for 1,3-butadiene the consumer exposure situation can be described as follows: While consumers do not use the substance as such, they use articles or products (mixtures) which contain 1,3-butadiene or release it under specific conditions.

ECHA dissemination site (ECHA, March 2015) lists a consumer use for 1,3-butadiene described as "*Monomer in polymer*
Chemical product category PC 32: *Polymer preparations and compounds*
Environmental release category ERC 0: *Other: No expected release, monomer within polymer*
Subsequent service life relevant for that use? Yes"

According to the information given to the eMSCA during a meeting with the LOA REACH Consortium in June 2014, there is no consumer use of 1,3-butadiene. The listed consumer use on ECHA dissemination site is a wrong indication of an article service life, which shall be corrected.

The explanation fits to the result of an inquiry in a national Safety Data Sheet Register, which produced no SDS for products available to consumers and the data published in international assessment documents for 1,3-butadiene.

The explanation fits to the result of an inquiry in a national Safety Data Sheet Register, which produced no SDS for products available to consumers

2.3 Uses advised against

2.3.1 Uses by workers in industrial settings advised against

Buta-1,3-diene as such or in preparations should not be used outside industrial settings and/or be placed on the market for professional or consumer use.

2.3.2 Use by professional workers advised against

Buta-1,3-diene as such or in preparations should not be used outside industrial settings and/or be placed on the market for professional or consumer use.

2.3.3 Uses by consumers advised against

ECHA dissemination site (ECHA, February 2015) lists two entries in this section: „*consumer use*" and „*no identified uses advised against*".

3 CLASSIFICATION AND LABELLING

3.1 Harmonised Classification in Annex VI of the CLP Regulation

Buta-1,3-diene is listed by Index number 601-013-00-X in Annex VI of CLP Regulation. The following Table 8 shows the CLP classification in Annex VI, Table 3.1 of butadiene.

Table 8: Classification and labelling of buta-1,3-diene according to Annex VI, Part 3, and Table 3.1 (list of harmonised classification and labelling of hazardous substances) of CLP regulation.

Classification		Labelling			Specific Concentration Limits, M-Factors	Notes
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)		
Press. Gas				GHS02 GHS08 GHS04 Dgr		Note U Note D
Flam. Gas 1	H220	H220				
Muta. 1B	H340	H340				
Carc. 1A	H350	H350				

Signal Words	Pictograms		
Danger			
	Flammable	Health Hazard	Gas cylinder

The most important health effect of buta-1,3-diene is its carcinogenicity. Various experimental data from different species, including humans, demonstrate a dose-response relationship between buta-1,3-diene exposure and the incidence of lymphohaematopoietic cancer (leukaemia). Buta-1,3-diene is a genotoxic human carcinogen and therefore it is classified and labelled for Carcinogenicity Category 1A, H350.

As second, buta-1,3-diene is legally classified in Mutagenicity Category 1B, H340. This classification is confirmed by non-human studies. The substance shows genotoxic characteristics, both in vitro and in vivo in somatic and germ mouse cells. A mutagenic effect in humans was not demonstrated. Therefore a legal classification of buta-1,3-diene as Germ Cell Mutagenicity Category 1B; H340 is appropriate.

During the SEv of buta-1,3-diene the other toxicological endpoints were verified too. It was concluded that there is no need for additional classifications.

3.2 Self-classification

Self-classification notifications for buta-1,3-diene by industry are available in the C&L Inventory (http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database). An overview of

self-classification notifications for buta-1,3-diene is shown in Table 9. The number of aggregated notifications is 24 (February 2015).

Table 9: Notified classification and labelling of buta-1,3-diene according to CLP criteria.

Classification		Labelling			Specific Concentration limits, M-Factors	Notes	Number of Notifiers
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supple-mentary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)			
Flam. Gas 1 Muta. 1B Carc. 1A	H220 H340 H350	H220 H340 H350		GHS02 GHS08 GHS04 Dgr		Note U Note D	372
Flam. Gas 1 Muta. 1B Carc. 1A Repr. 2 Aquatic Chronic 3	H220 H340 H350 H361 H421	H220 H340 H350 H361 H421		GHS02 GHS08 Dgr		Note U Note D	355
Flam. Gas 1 Liq. Gas Muta. 1B Carc. 1A	H220 H280 H340 (inhalation) H350 (inhalation)	H220 H280 H340 H350		GHS02 GHS08 GHS04 Dgr			195
Flam. Gas 1 Liq. Gas Muta. 1B Carc. 1A	H220 H280 H340 H350	H220 H280 H340 H350		GHS02 GHS08 GHS04 Dgr			93
Flam. Gas 1 Liq. Gas Muta. 1B Carc. 1A	H220 H280 H340 H350	H220 H280 H340 H350		GHS02 GHS08 GHS04 Dgr		Note U	81
Flam. Gas 1 Press. Gas Muta. 1B Carc. 1A	H220 H280 H340 H350	H220 H280 H340 H350		GHS02 GHS08 GHS04 Dgr			56
Flam. Gas 1 Muta. 1B Carc. 1A	H220 H340 H350	H220 H340 H350		GHS02 GHS08 Dgr		Note U	43
Flam. Gas 1 Muta. 1B Carc. 1A	H220 H340 H350	H220 H340 (May cause genetic defects) H350 (May cause cancer)		GHS02 GHS08 Dgr		Note U Note D	29
Muta. 1B Carc. 1A	H340 H350	H340 H350		GHS02 GHS08 Dgr			18
Flam. Gas 1 Press. Gas Muta. 1B	H220 H280 H340	H220 H340		GHS02 GHS08 GHS04			16

Carc. 1A	H350			Dgr			
Flam. Gas 1	H220	H220 (H220)		GHS02 GHS08 GHS04 Dgr		Note U Note D	4
Press. Gas	H280	H280					
Muta. 1B	H340	H340 (H340)					
Carc. 1A	H350	H350 (H350)					
Flam. Gas 1	H220	H220		GHS02 GHS08 GHS04 Dgr		Note D	4
Press. Gas	H280	H280					
Muta. 1B	H340	H340					
Carc. 1A	H350	H350					
Flam. Gas 1	H220	H220		GHS02 GHS08 GHS04 Dgr			3
Muta. 1B	H340	H340					
Carc. 1A	H350	H350					
Flam. Gas 1	H220	H220		GHS02 GHS08 GHS04 Dgr		Note U Note D	2
Press. Gas	H280	H280					
Muta. 1B	H340	H340					
Carc. 1A	H350	H350					
Flam. Gas 1	H220	H220		GHS02 GHS08 GHS04 Dgr		Note U Note D	2
Liq. Gas	H280	H280					
Muta. 1B	H340	H340					
Carc. 1A	H350	H350					
Not classified							2
Flam. Gas 1	H220	H220		GHS02 GHS08 Dgr			2
Muta. 1B	H340	H340					
Carc. 1A	H350	H350					
Flam. Gas 1	H220	H220		GHS02 GHS08 Dgr			1
Press. Gas	H280	H280					
Muta. 1B	H340	H340					
Carc. 1A	H350	H350					
Flam. Gas 1	H220	H220		GHS02 GHS08 Dgr		Note D	1
Press. Gas	H280	H280					
Muta. 1B	H340	H340					
Carc. 1A	H350	H350					
Flam. Gas 1	H220			GHS02 GHS08 GHS04 Dgr		Note U Note D	1
Muta. 1B	H340	H340					
Carc. 1A	H350	H350					
		H280					
Flam. Gas 1	H220	H220		GHS02 GHS08 GHS04 Dgr		Note U Note D	1
Press. Gas	H280						
Muta. 1B	H340	H340					
Carc. 1A	H350	H350					
Flam. Gas 1	H220	H220		GHS02 GHS08 GHS04 Dgr		Note U Note D	1
Muta. 1B	H340	H340					
Carc. 1A	H350	H350					
Flam. Gas 1	H220	H220		GHS02 GHS08 GHS04 Dgr		Note U Note D	1
Liq. Gas	H280	H280					
Muta. 1B	H340 (inhalation)	H340					
Carc. 1A	H350 (inhalation)	H350					

4 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this evaluation.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

5.1.1 Non-human information

5.1.2 Human information

5.1.3 Summary and discussion on toxicokinetics

The toxicokinetic properties of butadiene have been thoroughly investigated and reviewed in recent years (EU-RAR, 2002, IARC, 2008, Kirman et al., 2010). Since metabolism of butadiene is an important prerequisite for the toxicity, the present knowledge is compiled in Figure 1.

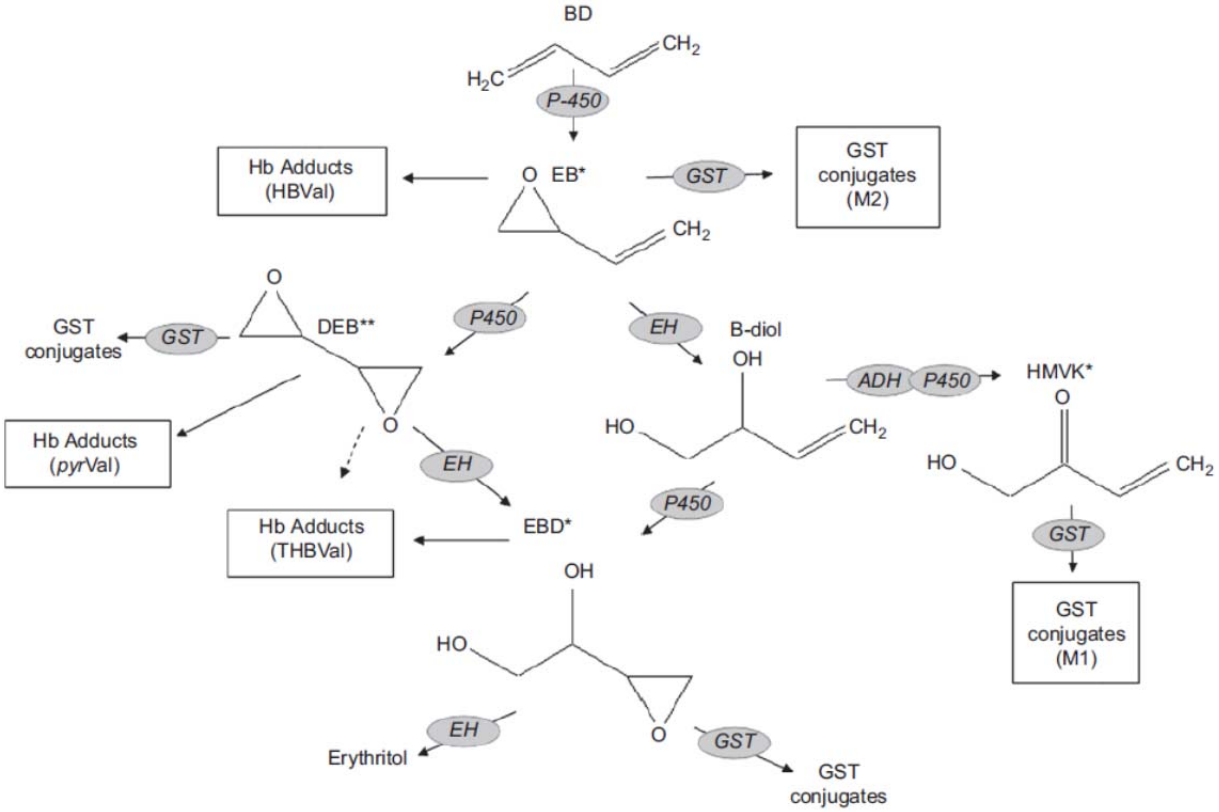


Figure 1: Metabolism of 1,3 butadiene (from Kirman et al., 2010)

*BD = 1,3-butadiene; EB = epoxybutene; DEB = diepoxybutane; B-diol = butenediol; HMVK = hydroxymethylvinyl ketone; EBD = epoxybutane diol; * = monofunctional alkylating agent; ** = bifunctional alkylating agent; P450 = cytochrome P450; GST = glutathione S-transferase; EH = epoxide hydrolase; ADH = alcohol dehydrogenase; HBVal = (N-(2-hydroxy-3-butenyl)-valine; M1 = 1,2-dihydroxy-4-(N-acetiycysteinyl)-butane; M2 = 1-(N-acetylcysteinyl)-2-hydroxy-3-butene;*

pyrVal = (N,N-(2,3-dihydroxy-1,4-butadiyl)-valine; THBVal = N-(2,3,4-trihydroxybutyl)-valine. BBBoxes indicate biomarkers of exposure that have been measured in exposed workers.

In vivo studies – Non-human information

"Studies in rodents and non-human primates have shown that 1,3-butadiene is absorbed via the lungs. In rodents, uptake and metabolism of 1,3-butadiene obeys simple first order kinetics at concentrations up to about 1,500 ppm, above which saturation of the process appears to occur. 1,3-Butadiene is widely distributed throughout the body. The first step in the metabolic pathway is the formation of epoxybutene, catalysed by mixed function oxygenases. The further metabolism of epoxybutene can proceed by a number of different pathways. There is some conjugation with glutathione. A second possible pathway is hydrolysis to butenediol, catalysed by epoxide hydrolase. Another possibility is further epoxidation to diepoxybutane. Further epoxidation and/or hydrolysis reactions can then occur, which ultimately lead to erythritol formation. It is not clear at which stage or stages in the pathway, CO_2 is formed. The main route of elimination of 1,3-butadiene and its metabolites in rodents and primates is urinary excretion or exhalation in the breath. Minor faecal excretion also occurs. In rodents, urinary excretion takes place in two phases with 77-99% of the inhaled dose excreted with a half-life of a few hours in rodents, while the remainder is excreted with a half-life of several days. There is no evidence for bioaccumulation of 1,3-butadiene. There are no data on the toxicokinetics of 1,3-butadiene following oral or dermal exposure, and although the possibility of uptake via these routes cannot be entirely discounted, their contribution to uptake and metabolism of 1,3-butadiene is anticipated to be negligible. In addition, there is no evidence of any significant potential for dermal uptake from a comparison of the results of whole-body inhalation exposure studies compared with those in which exposure was nose-only." (EU RAR, 2002)

"There are quantitative species differences in the toxicokinetics of 1,3-butadiene. In comparison with the rat, the mouse absorbs and retains approximately 4-7 fold higher concentrations of 1,3-butadiene per kg bodyweight. The mouse also produces approximately 2-20 fold higher concentrations of the metabolite, epoxybutene, than does the rat, for equivalent exposures. Very low concentrations of the diepoxide metabolite have been detected in the blood and various tissues of rats and mice at relatively high 1,3-butadiene exposures; this metabolite has been tentatively identified in the blood of monkeys, in vivo. Again, where measurements are available, tissue levels of diepoxybutane are generally higher in mice compared with rats, by up to 163-fold." (EU RAR, 2002)

More recent studies have confirmed that mice form greater quantities of the diepoxide metabolite than rats. Studies using 1,3-butadiene exposures at 1 ppm 1,3-butadiene for 4 weeks (which are more occupationally relevant) showed that the concentration of the haemoglobin adduct of the diepoxide metabolite (pyr-Val) was greater than 30-fold in the blood of mice compared to that in rats (Swenberg et al. 2007). Georgieva et al (2010) also exposed rats and mice to 1,3-butadiene at 0.1 to 625 ppm for 10 or 20 days and showed that mice formed 10- to 60-fold more of the haemoglobin adduct compared to rats at similar exposures. Csanady et al (2011) determined DEB concentrations in the blood of mice and rats immediately after 6 h exposures to various constant concentrations of butadiene of between about 1 and 1200 ppm. DEB concentrations in blood versus butadiene exposure concentrations in air could be described by one-phase exponential association functions. Herewith calculated (±)-DEB concentrations in blood increased in mice from 5.4 nmol/l at 1 ppm BD to 1860 nmol/l at 1250 ppm butadiene and in rats from 1.2 nmol/l at 1 ppm BD to 92 nmol/l at 200 ppm butadiene, at which exposure concentration 91% of the calculated DEB plateau concentration in rat blood was reached.

In vitro studies – Non-human information

"In vitro studies indicate that in the mouse, lung and liver tissue have similar capacity for 1,3-butadiene metabolism while in rats and humans, liver tissue has a greater capacity for metabolism than does lung tissue, although some metabolism does take place in lung tissue. Detoxification pathways are kinetically favoured over activation pathways in rodent and human tissue, although the ratio of activation: detoxification is highest in mouse tissue compared with rat or human tissue. In mouse liver and lung tissue, detoxification of epoxybutene appears to be mainly by conjugation with glutathione, with hydrolysis to butenediol a relatively minor pathway. In comparison, in human liver and lung, detoxification of epoxybutene is primarily by hydrolysis, with only some glutathione conjugation; this finding from in vitro studies supports the in vivo human metabolism data. Formation of the diepoxide has been demonstrated in mouse liver tissue exposed to butadiene in vitro, but not in rat or human tissue, although formation of diepoxybutane has been demonstrated in cDNA-expressed human liver microsomes exposed to epoxybutene. " (EU RAR, 2002)
A recent study (Filser et al, 2010) showed a qualitative species difference in the metabolism of 1,3-butadiene in isolated perfused livers from rats and mice. In 1,3-butadiene perfusions, predominantly epoxybutene and butenediol were found in both species but diepoxybutane was only detected in mouse livers.
"From the limited comparative information available from in vitro and in vivo studies, it appears that in relation to the formation of epoxide metabolites, the metabolism of 1,3-butadiene in humans is quantitatively more similar to that in the rat, rather than the mouse. However, in vitro studies have demonstrated considerable inter-individual variability in the oxidative metabolism of butadiene. " (EU RAR, 2002)

In vivo studies – Human information

"There is very limited information on the toxicokinetics of 1,3-butadiene in humans. In workers exposed by inhalation to 3-4 ppm 1,3-butadiene, metabolism to epoxybutene with subsequent hydrolysis to butenediol occurs. In one study, the mercapturic acid (glutathione) conjugate of butenediol has been identified as a urinary metabolite although no detectable levels of the epoxybutene mercapturate were found in the same study. This suggests that detoxification of epoxybutene proceeds by hydrolysis to butenediol, with subsequent conjugation. " (EU RAR, 2002)
Haemoglobin adducts from various metabolites of 1,3-butadiene have been identified and measured in humans (Albertini., 2004). Elevated levels of the haemoglobin adducts of epoxybutene have been reported in the blood of occupationally exposed workers (EU RAR, 2002; Bergemann et al., 2001). No difference has been seen between genders in the pattern of 1,3-butadiene detoxification, as evidenced by urinary metabolite levels [1,2-dihydroxy-4-acetyl) butane and 1-dihydroxy-2-(N-acetylcysteinyl) -3-butene]. Females, however, appear to absorb less 1,3-butadiene per unit of exposure, as reflected by urine metabolite concentrations (Albertini et al, 2007). Analytical techniques have recently been developed to measure the haemoglobin adduct of the diepoxide metabolite of 1,3-butadiene N, N-(2,3-dihydroxy-1,4-butadiyl) valine (pyr-Val). In one study, the pyr-Val adduct was not quantifiable in human blood samples from workers with cumulative occupational exposures of up to 6.3 ppm-weeks (Swenberg et al., 2007). In a subsequent study in which improvements were made to the technique to improve the sensitivity, quantifiable amounts of pyr-Val were found in the blood of occupationally exposed workers. At exposures between 0.1 and 1.0 ppm, humans form ~10% of the quantities of the pyr-Val adduct formed by rats (Georgieva et al., 2010). This indicates that the diepoxide metabolite is produced in humans, albeit in very low amounts.

In vitro studies – Human information

"The only other information in relation to toxicokinetics in humans comes from in vitro studies using human tissue, which indicate that metabolism of 1,3-butadiene to epoxybutene occurs in human liver, lung and bone marrow. In the one study that has investigated further metabolism of the monoepoxide to diepoxybutane, in liver and lung tissue, no detectable levels of the diepoxide were measured. Human liver tissue has greater capacity for metabolism to epoxybutene compared with lung tissue. However, the results for lung tissue must be treated with some caution as diseased tissue was used. There is evidence for considerable inter-individual variation in the capacity of human liver tissue to metabolise 1,3-butadiene to epoxybutane, with some human liver tissue samples showing capacity for metabolism comparable to, or exceeding, that in the mouse. The involvement of specific P450 isozymes in metabolism of butadiene to the monoepoxide has been demonstrated, and raises the possibility that differences in expression of P450 isozymes may explain some of the intra-individual variability that has been seen in vitro. " (EU RAR, 2002)

Summary and discussion

There are quantitative differences in the formation of the diepoxide metabolite in mice and rats, mice form greater quantities than rats. In humans only limited information exists on the toxicokinetics of butadiene. However, haemoglobin adducts from various metabolites of butadiene have been identified and measured in humans, even the diepoxide metabolite is produced in humans.

5.2 Acute toxicity

5.2.1 Non-human information

5.2.1.1 Acute toxicity: oral

No information presented by the registrant. The eMSCA does not see the need to request further information.

5.2.1.2 Acute toxicity: inhalation

Table 10: Compilation of experimental studies on acute toxicity after inhalative exposure according to the registration dossier.

Method/ Guideline	Species, Strain, Sex, No/group	Dose levels (mg/m^3)	LC50 (mg/m^3)	Remarks	Reference
No information given	Rat and mouse. Rats were exposed for 4 hours, mice were exposed for 2 hours. No more information is available.	No information given	Rat: 285.000 Mouse: 270.000	Key study	Shugaev (1969)

5.2.1.3 Acute toxicity: dermal

No information presented by the registrant. The eMSCA does not see the need to request further information.

5.2.1.4 Acute toxicity: other routes

No relevant information available.

5.2.2 Human information

Table 11: Compilation of human data on acute toxicity after inhalative exposure according to the registration dossier.

Method	Results	Remarks	Reference
Study design: Evaluation of the effect on the psycho-motor response Two male subjects inhaled 2000, 4000 or 8000 ppm 1,3-butadiene and their pulse rate, blood pressure and subjective symptoms were recorded. To evaluate the effect on the psycho-motor	Subjective symptoms: At 2000 (4425 mg/m^3) and 4000 ppm (8851 mgm^3) 1,3-butadiene resulted in slight smarting of the eyes and difficulty in focusing on instrument scales. The odour was described as objectionable. At 8000 ppm (17702 mg/m^3) butadiene there were no	Key study	Carpenter, Shaffer, Weir, Smyth (1944)

response, tapping rate and steadiness tests were performed before and during exposures.	subjective symptoms reported. It was proposed that this was due to slight anxiety/preoccupation with the control of this concentration (explosion risk). Following the first single exposure to butadiene, the subjects became much less aware of subjective symptoms when exposed subsequently to the same or a higher concentration. Steadiness test: Although unsteadiness was seen in both subjects at 4000 ppm, there was little or no effect noted at 8000 ppm or 2000 ppm. The maximum time in contact (as % of day's normal) was 266 and 136 for 4000 and 8000 ppm. At 2000 ppm the test was considered too brief to be reliable.		

5.2.3 Summary and discussion of acute toxicity

Data for evaluating acute inhalative toxicity of butadiene are obtained from animal testing in rats and mice. Two human volunteers were investigated in an acute inhalative toxicity test. No immediate adverse effects were apparent at concentrations of 2000 and 4000 ppm (4425 and 8851 mg/m^3). None of the studies were performed according to test guidelines for acute toxicity testing. However, the overall available information is sufficient to conclude that the acute toxicity of butadiene is low. An inhalative LC50 (4 h) of 285.000 mg/m^3 was determined in rats and an inhalative LC50 (4 h) of 270.000 mg/m^3 was determined in mice (Shugaev, 1969).

Based on the available data, it is concluded that butadiene does not require classification for acute toxicity according to Regulation (EC) No 1272/2008 and Directive 67/548/EEC.

5.3 Irritation

5.3.1 Skin

The registrant justifies the data waiving with the fact, that butadiene is flammable in air at room temperature. The eMSCA does not see the need for further information.

5.3.2 Eye

The registrant justifies the data waiving with the fact, that butadiene is flammable in air at room temperature. The eMSCA does not see the need for further information.

5.3.3 Respiratory tract

No relevant information available.

5.3.4 Summary and discussion of irritation

According to REACH Annexes VII and VIII, column 2, studies on skin and eye irritation do not need to be conducted as the substance is flammable in air at room temperature.

Two human volunteers inhaled butadiene at concentrations up to 8000 ppm (17701 mg/m^3). No immediate adverse effects were apparent at concentrations of 2000 and 4000 ppm (4425 and 8851 mg/m^3) although the subjects stated that the odour was objectionable and smarting of the eyes was recorded (Carpenter et al., 1944).

The EU RAR (2002) reports that eye irritation has been noted in humans exposed to very high concentrations of butadiene although in these cases there were mixed exposure to other chemicals too. No eye irritation was reported in chronic inhalation bioassay studies in mice and rats exposed to 1250 and 8000 ppm (2765 and 17701 mg/m^3) respectively.

The available data indicate that butadiene does not require classification for skin or eye irritation according to Regulation (EC) No 1272/2008.

5.4 Corrosivity

5.5 Sensitisation

5.5.1 Skin

The registrant justifies the data waiving with the fact, that butadiene is flammable in air at room temperature. The eMSCA does not see the need for further information.

5.5.2 Respiratory system

There are no studies available on respiratory sensitisation by butadiene.

5.5.3 Summary and discussion on sensitisation

According to REACH Annexes VII and VIII, column 2, studies on skin sensitisation do not need to be conducted as the substance is flammable in air at room temperature. There are no studies available on skin sensitisation with butadiene.

There are no studies available on respiratory sensitisation by butadiene and there are no indications that butadiene is a respiratory sensitizer.

There is no indication that butadiene does require classification for skin or respiratory sensitisation according to Regulation (EC) No 1272/2008.

5.6 Repeated dose toxicity

5.6.1 Non-human information

5.6.1.1 Repeated dose toxicity: oral

The registrant justifies the data waiving with the fact, that butadiene is flammable in air at room temperature. The eMSCA does not see the need for further information.

5.6.1.2 Repeated dose toxicity: inhalation

Table 12: Presentation of experimental studies on repeated dose toxicity after inhalative administration according to the registration dossier

Method/ Guideline	Species, Strain, Sex, No/group	concentration levels (mg/m^3)	NOAEC/ LOAEC ($mg/m^3/d$)	Remarks	Reference
Equivalent or similar to OECD 453 (Combined Chronic Toxicity / Carcinogenicity Studies) Vehicle: air Exposure: 6h/d, 5 d/week 105 weeks (females) 111 weeks (males) Whole body inhalation	Rat, Sprague-Dawley Male/female No: 110 per sex per dose 10 rats/sex were sacrificed after 52 weeks for interim assessment	0 2212 (1000 ppm) 17701 (8000 ppm)	NOAEC: 1000 ppm (2212 mg/m^3) (male/female), some toxic effects such as increased heart weight and kidney nephrosis were observed at 8000 ppm (17701 mg/m^3).	Key study	Owen, Glaister, Gaunt, Pullinger (1987)
Equivalent or similar to OECD 453 (Combined Chronic Toxicity / Carcinogenicity Studies) Vehicle: air Exposure: 6h/d, 5 d/week 9 month; 15 month and 2 years Whole body inhalation	Mouse, B6C3F1 Male/female No: 70 per sex per dose, except for the 625 ppm group that had 90 per sex	0 13,8 (6,25 ppm) 44,2 (20 ppm) 138 (62,5 ppm) 442 (200 ppm) 1383 (625 ppm)	No NOAEC identified (female) ovarian atrophy was observed at all dose levels (14, 44, 138, 442 or 1383 mg/m^3) in the presence of severe generalised toxicity NOAEC: 13,8 mg/m^3 (male) Survival was reduced at 44,2 mg/m^3 and above due to malignant neoplasms, increased	Key study	NTP, 1993

			incidences of non-neoplastic lesions in exposed mice including bone marrow atrophy; testicular atrophy, ovarian atrophy, anglectasis, germinal epithelial hyperplasia, and granulosa cell hyperplasia; uterine atrophy; cardiac endothelial hyperplasia and mineralization; alveolar epithelial hyperplasia; forestomach epithelial hyperplasia; and harderian gland hyperplasia		
The purpose of this study was to determine the effects of butadiene on the bone marrow after inhalation exposure of B6C3F1 mice for up to 24 weeks. Vehicle: air Exposure: 6h/d, 6 d/week Exposure for: 3, 6, 12, 18 or 24 weeks. Whole body inhalation	Mouse, B6C3F1 Male No: 40 mice/group. Control: sham-exposed	0 2765 (1250 ppm)	No NOAEC identified (male) Treatment related changes, indicative for macrocytic-megaloblastic anaemia, were present after 6 weeks of exposure at the one and only level of 2765 mg/m^3	Supporting study	Irons, Smith, Stillman, Shah, Steinhagen, Leiderman (1986a)

EPA OTS 798.2450 (90-Day Inhalation Toxicity) Vehicle: air Exposure: 6h/day, 5d/week for 13 weeks	Mouse, B6C3F1 Male/female No: 10 per sex and group	0 2212 (1000 ppm)	No NOAEC identified (male/female) only one concentration was tested, ovarian atrophy, mild macrocystic anaemia and slight testicular degeneration was observed	Supporting study	Bevan, Stadler, Elliot, Frame, Baldwin, Leung, Moran, Panepinto, 1996
Equivalent of similar to OECD 413 (Subchronic inhalation Toxicity: 90-Day) Vehicle: air Exposure: 6h/day, 5 d/week for 2 weeks and 14 weeks.	Mouse, B6C3F1 Male/female No: 10 per sex and group	0 1383 (625 ppm) 2765 (1250 ppm) 5532 (2500 ppm) 11063 (5000 ppm) 17701 (8000 ppm)	NOAEC: 2766 mg/m^3 (male/female) 14 week study: Increased mortality was observed at 11063 mg/m^3 and 17701 mg/m^3. Body weight gain was reduced at 5531 mg/m^3 and above. NOAEC: 5521 mg/m^3 (male/female). 2 week study: Body weight gain was reduced at 11063 mg/m^3 and 17701 mg/m^3.	Supporting study	NTP, 1984
Equivalent of similar to OECD 413 (Subchronic inhalation Toxicity: 90-Day) Vehicle: air Exposure: 6h/day, 5 d/week for 61 weeks.	Mouse, B6C3F1 Male/female No: 10 per sex and group	0 1383 (625 ppm) 2765 (1250 ppm)	No NOAEC identified (male/female) Severe non-neoplastic effects were observed at all dose levels. Ovarian and testicular atrophy, congestion, haemorrhage and hyperplasia of the lungs,	Supporting study	NTP, 1984

			haemorrhage and necrosis of the liver, thymus and bone marrow atrophy, epithelial hyperplasia and mineralisation of the heart. Chronic inflammation and fibrosis developed in the nasal cavities of males.		
The purpose of this study was to dermine the effects of butadiene on the bone marrow after inhalation exposure of NIH mice for up to 24 weeks. NIH mice do not express endogenous ectotropic type C murine leukaemia retroviruses (MuLV). The bone marrow is known to be a target for B6C3F1 mice but this straim may possess MuLV which could play a role in this toxicity. Vehicle: air Exposure: 6h/day, 6 d/week for 6 weeks	Mouse (NIH Swiss) Male No: 8 per group	0 2765 (1250 ppm)	No NOAEC identified (male) Treatment-related changes, indicative of macrocytic-megaloblastic anaemia and independent of MuLV background, were present after 6 weeks of exposure at the level tested	Supporting study	Irons, Smith, Stillman, Shah, Steinhagen, Leiderman (1986b)

EPA OTS 798.2450 (90-Day Inhalation Toxicity) Vehicle: air Exposure: 6h/day, 5d/week for 13 weeks	Rat (Crl:CD BR (Sprague-Dawley)) Male/female No: 10 per sex per group	0 2212 (1000 ppm)	NOAEC: 2212 mg/m^3 (male/female) No effects other than minor increase in liver and kidney weight in males were seen.	Supporting study	Bevan, Stadler, Elliot, Frame, Baldwin, Leung, Moran, Panepinto, 1996
The effects of the inhalation of butadiene were studied. Vehicle: air Exposure: 7.5h/day, 6 d/week) for 8 months.	Rat, Guinea pig, rabbit, dog Male/female for rat, Guinea pig and rabbit. Female for dog No: 12 rats/sex/group 6 Guinea pigs/sex/group 2 rabbits/sex/group 1 dog/group	0 1328 (600 ppm) 5089 (2300 ppm) 14825 (6700 ppm)	NOAEC: 5089 mg/m^3 (male/female) in rats, Guinea pigs, rabbits. Reduction of body weight gain and histopathological changes in liver at 14825 mg/m^3. NOAEC: 5089 mg/m^3 (female dogs). Reduction of body weight gain and histopathological changes (not further specified) in liver at 14825 mg/m^3.	Supporting study	Carpenter, Shaffer, Weir, Smyth, 1944
Subchronic inhalation study Vehicle: air Exposure: 6h/day. 5 d/week for up to 3 month	Rat (Sprague-Dawley, CD) Male/female No: 40/sex/group Investigations at 2, 6 and 13 weeks	0 2213 (1000 ppm) 4425 (2000 ppm) 8851 (4000 ppm) 17701 (8000 ppm)	NOAEC: 17701 mg/m^3 (male/female). No effects were observed at the highest concentration	Supporting study	Crouch, Pullinger, Gaunt, 1979

5.6.1.3 Repeated dose toxicity: dermal

The registrant justifies the data waiving with the fact, that butadiene is flammable in air at room temperature. The eMSCA does not see the need for further information.

5.6.1.4 Repeated dose toxicity: other routes

No relevant information available.

5.6.2 Human information

Table 13: Presentation of exposure-related observations in humans according to the registration dossier

Method/ Guideline	Sex, No/group	exposure levels	Results	Remarks	Reference
The objective of the study was to evaluate haematological parameters in workers at two butadiene plants who had participated in the Shell Butadiene Medical Surveillance Program throughout their working career. The haematology parameters were compared between the two facilities and with a group of employees who had not participated in the program.	404 employees were identified from Butadiene Medical Surveillance Program participants across both sites (394 males and 10 females). The comparison group contained a total of 773 employees across both sites (750 males and 23 females).	Entrance criteria to the Butadiene Medical Sur-veillance Program was open to employees at both plants who were already hired in 1997 or were hired after 1997. There were 3 over-lapping groups: 1. Employees who were potentially exposed to butadiene at or above 0.5 ppm TWA-8 (8h time weighted average) for 30 or more days/year. 2. Employees who were potentially exposed to butadiene at or above 1.0 ppm TWA-8 during 10 or more days/year. 3. Employees who were	The percentage of abnormal values for the six haematological parameters between the butadiene group and the comparison group did not differ significantly for the total population. Overall, 96-99% of the values for both exposed and comparison groups were within normal ranges. Considered separately, 95-99% of both exposed and comparison groups from Deer Park and Norco were within normal ranges. Overall, the percentage of WBC abnormalities was higher among employees in the butadiene surveillance	Key study	Tsai, Ahmed, Ransdell, Wendt, Donnelly (2005)

		potentially exposed to butadiene at or above 5.0 ppm over 15 min during 10 or more days/ year. Additionally, active employees hired prior to 1997 were eligible if they were exposed to 10 ppm of butadiene 30 or more times a year and were still employed by Shell in 1997. Any employee with documented butadiene-related disease was also eligible for the program. The comparison group consisted of male and female Shell employees who were not eligible for either the Butadiene Medical Surveillance Program or the Benzene Medical Surveillance Program and were identified	group than those in the comparison group, although the difference was not statistically significant. WBC abnormalities were lower in the surveillance group than those in the comparison group for Deer Park alone but the difference was not statistically significant. Analysis of the 2 sites separately showed no statistically significant differences between the butadiene surveillance group and the comparison group for any of the haematological parameters. In the total combined population the only effect was a statistically significant decrease in mean haemoglobin (Hgb) in the butadiene surveillance		

		from other Shell surveillance programs eg asbestos, lead etc.	group compared with the comparison group although the difference was very small (14.31 g/100ml vs. 14.44g/100ml) and is probably of no clinical significance. The difference was not statistically significant, however, after adjustment for multiple comparisons using Bonferroni's method. The exposure data showed that the butadiene surveillance group for 1979-1996 had a mean overall exposure of 4.55 ppm (10.07 mg/m^3) (8h, 10h and 12h-TWA), from 1997; this figure was 0.25 ppm (0.55 mg/m^3). Both facilities gave similar results.		

5.6.3 Summary and discussion of repeated dose toxicity

Several reports evaluated the repeat dose toxicity of butadiene (ECETOC, 1997, EU RAR, 2002, US EPA, 2002 and TCEQ, 2008). There have been no new reports on the chronic toxicity of butadiene since 2002. No studies using the dermal or oral route are available for butadiene. The requirement for data on repeat dose oral and dermal toxicity is waived in accordance with REACH Annex XI, as butadiene is a flammable gas at room temperature.

There are great differences in the toxicity of butadiene in mice and rats. The key study in rats investigated animals exposed to butadiene at 0, 2212 or 17701 mg/m^3 (1000 and 8000 ppm), 6 h/day, 5 days/week, for up to two years (Owen et al., 1987). In this carcinogenicity study no effects on haematology, blood chemistry, urine analysis and neuromuscular function were associated with treatment. The non-neoplastic findings were observed as changes in clinical condition, suppression of body weight gain, reduced survival, increased weights of liver, kidney, heart, lung and spleen, nephrosis of the kidney and focal metaplasia in lung. A NOAEC of 2212 of mg/m^3 was established for systemic toxicity on some toxic effects (increased heart weight and kidney nephrosis) observed at 17701 mg/m^3 (8000 ppm).

The key study in mice investigated animals exposed to butadiene at 13, 44, 138, 442 or 1382 mg/m^3 (6.25, 20, 62.5, 200 or 600 ppm), 6 h/day, 5 days/week, for up to two years (NTP, 1993). Survival was reduced at 44 mg/m^3 (20 ppm) and above, due to malignant neoplasms (see section 5.8.1.2). Increased incidences of non-neoplastic lesions in exposed mice included bone marrow atrophy, testicular atrophy, ovarian atrophy, cardiac endothelial hyperplasia and mineralization, alveolar epithelial hyperplasia, forestomach epithelial hyperplasia, and Harderian gland hyperplasia. Ovarian atrophy was observed at all concentration levels after two years. No NOAEC could be deduced from this study.

An epidemiological study compared workers from two plants with a non-butadiene exposed group (Tsai et al., 2005). Haematological parameters were investigated in workers at two butadiene plants who had participated in the Shell Butadiene Medical Surveillance Program from 1979 to 2003 with a group of employees who had not participated in the program and who had been considered as not exposed to butadiene (although they may have been exposed to other chemicals). From 1979 to 1996 the butadiene surveillance group had a mean daily exposure to 10.1 mg/m^3 (4.55 ppm) (mean of 8h, 10h and 12h-time weighted average); from 1997, this figure was 0.55 mg/m^3 (0.25 ppm). In 1996 the OSHA exposure limit was decreased from 1000 ppm to 1 ppm. No significant differences were observed in six blood count parameters (white blood cell count, lymphocyte count, red blood cell count, haemoglobin concentration, mean corpuscular volume and platelet count) between butadiene surveillance group and comparison group. For the carcinogenicity of butadiene see section 5.8.2.

Conclusion

Based on the available data, it is concluded that butadiene does not require classification for repeated dose toxicity (STOT RE) according to Regulation (EC) No 1272/2008 and Directive 67/548/EEC.

5.7 Mutagenicity

5.7.1 Non-human information

5.7.1.1 In vitro data

Table 14: Presentation of in-vitro genotoxicity studies according to the registration dossier

Method/ Guideline	Test organism, Strain Dose levels	Results	Remarks	Reference
Bacterial reverse mutation assay (e.g. Ames test) (gene mutation) Mutagenicity test on S. typhimurium and E. coli using the developed gas exposure method (using a gas sampling bag as an exposure vessel and a preparation vessel of diluted gas)	S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 (met. act.: with and without) E. coli WP2 uvrA (met. act.: with and without) Tests were performed at toxic concentration levels or about 50% of the maximum exposure concentration	Negative without metabolic activation Positive with metabolic activation Test Results: Negative for S. typhimurium TA 1535, TA 1537, TA 98, TA 100 and E. coli WP2 uvr A; met. act.: without; cytotoxicity: no, but tested up to limit concentrations. Positive for S. typhimurium TA 1535; met. act.: with; cytotoxicity: no, but tested up to limit concentrations. Negative for S. typhimurium TA 1537, TA 98, TA 100 and E. coli WP2 uvr A; met. act.: with; cytotoxicity: no, but tested up to limit concentrations.	Key study	Araki, Noguchi, Kato and Matsushima (1994)
Bacterial reverse mutation assay (e.g. Ames test) (gene mutation)	S. typhimurium TA 1535, TA 98 and TA 100 (met. act.: with and without) E. coli WP2	Positive with metabolic activation (TA 1535) Test results: Positive for S. typhimurium TA 1535;	Key study	Madhusree, Goto, Ohkubo, Tian, Ando, Fukuhara, Tohkin (2002)

Positive control substances: AF2 (2-(2-furyl)-3-(f-nitro-2-furyl)acrylamide) for TA 98, TA 100 and WP2uvrA/ pKM101; ENNG (N-ethyl-N'-nitro-N-nitrosoguanine) for TA 1535 BaP (benzo(a)pyrene) for TA 100, TA 98 and WP2uvrA/ pKM101; 2AA (2-Aminoanthracene) for TA 1535. Mutagenicity test on S. typhimurium and E. coli using the developed gas exposure method (using a gas sampling bag as an exposure vessel and a preparation vessel of diluted gas (Araki et al., 1994))	uvrA/ pKM101 (met. act.: with and without) Test concentrations: 0 (air only), 10, 25 and 50%	met. act.: with and without; cytotoxicity: yes (revertant colonies increased at 25% and decreased with 50% butadiene); positive controls valid: yes		
In vitro mammalian chromosome aberration test (chromosome aberration) Equivalent or similar to OECD 473 (In vitro mammalian chromosome	Mammalian cell line: A clonal sub-line derived from the lung of a newborn female Chinese hamster (CHL/IU) (met. act.: with and without) Test concentration:	Positive with and without metabolic activation Positive for mammalian cell line: A clonal sub-line derived from the lung of a newborn female Chinese hamster (CHL/IU) met. act.: with and without;	Key study	Asakura, Sasaki, Sugiyama, Arito, Fukushima, Matsushima (2008)

aberration test) Positive control substances: vinyl chloride and methyl chloride	0 – 20% atmosphere of butadiene for 6 h.	cytotoxicity: Reduction in growth index was measured; negative controls valid: yes; positive controls valid: yes.		

5.7.1.2 In vivo data

Table 15: Presentation of in-vivo genotoxicity studies according to the registration dossier

Method/ Guideline	Test organism, Strain Dose levels	Results	Remarks	Reference
Gene mutation Inhalation The mutagenic potential and mutational spectra of 1,3 butadiene, 1,2-epoxybutane and diepoxybutane were determined in splenic T cells from exposed B6C3F1 mice.	Mouse, B6C3F1, male No: 8 animals/ sex/ dose 625 ppm for two weeks (6h/day; 5 d/week)	Genotoxicity: positive Vehicle control valid: yes In cells from animals exposed to 625 ppm, there was a statistically significant increase in mutation frequency.	Key study	Cochrane, Skopek (1994)
Hrpt assay in splenic T cells (gene mutation) Inhalation The objective of this study was to investigate age and gender dependent differences in butadiene-induced mutagenicity at	Mouse, B6C3F1, male/female Rat, F344, male/female No: 5 animals/ sex/ dose 62.5 ppm (female rats for 4 weeks) 1250 ppm (male and female mice	Genotoxicity: Positive (mouse, male) Vehicle controls valid: yes Weak positive in rat (male/female)	Supporting study	Meng, Walker, McDonald, Henderson, Carter, Cook, McCash, Torres, Bauer, Seilkop, Upton, Georgieva, Boysen, Swenberg, Walker(2007)

the hrtp locus in splenic T cells in rats and mice.	for 2 weeks; male rats for 2 weeks) (6h/day, 5 d/week)			
Equivalent or similar to OECD 474 (Mammalian erythrocyte micronucleus test) Inhalation	Mouse, (102/E1 x C3H/E1)F1, male/female No: Bone marrow micronucleus test: 5 per sex per dose Peripheral blood micronucleus test: 2 per sex per dose 0, 50, 200, 500 or 1300 ppm 6h per day for 5 consecutive days	Genotoxicity: positive Butadiene at concentrations of 50, 200, 500 or 1300 ppm for 6 h per day for 5 days induced micronuclei in bone marrow and peripheral blood. Male mice were more sensitive than females at the higher exposure concentrations.	Key study	Adler, Cao, Filser, Gassner, Kessler, Lkiesch, Neuhäuser-Klau (1994)
Equivalent or similar to OECD 474 (Mammalian erythrocyte micronucleus test) Inhalation	Rat, Crl:CD BR, male No: 5 per dose 10-10000 ppm 6h/day for 2 days	Genotoxicity: negative Toxicity: yes (PCE suppression in bone marrow)	Key study	Cunningham, Choy, Arce, Rickard, Vlachos, Kinney, Sarrif (1986)
Equivalent or similar to OECD 474 (Mammalian erythrocyte micronucleus test) Inhalation	Mouse, B6C3F1, male No: 5 per dose 10-10000 ppm 6h/day for 2 days	Genotoxicity: Positive Toxicity: yes (PCE suppression in bone marrow) There was a dose related increase in the frequency of micronuclei.	Key study	Cunningham, Choy, Arce, Rickard, Vlachos, Kinney, Sarrif (1986)

Equivalent or similar to OECD 478 (Genetic toxicology: Rodent dominant lethal test) Inhalation	Rat, Sprague-Dawley, male/female No: Males: 25 for 0 (air controls), 65, 400 and 1250 ppm groups, 50 for 0 (room controls) ppm. Females: 50, 48, 50, 50, 100 for 0 (air controls), 65, 400, 1250 and 0 (room controls) ppm, respectively. 0, 65, 400, 1250 ppm 6h/day, 5d/week for 10 weeks	Genotoxicity: negative One male, treated with 65 ppm butadiene died (cause unknown); no animals in any of the other treatment groups died. Butadiene treatment did not cause a persistent decrease in body weight in any treatment group. Mating frequency and pregnancy rate were not significantly reduced as a result of treatment. The period to coition was also unaffected by treatment. There was no significant reduction in comparison with the appropriate controls in the number of *corpora lutea* in any treatment group indicating that there had been no effect on pre-implantation loss. The number of implantation sites was significantly reduced in the 65 ppm group but this was not considered to represent a genetic effect since it was not accompanied by a significant increase in post-implantation losses and it was not dose-related. There was no significant reduction of implantation sites in any other group. Neither post-implantation losses (early deaths, late deaths or late deaths	Key study	BIBRA (1996)

		including dead foetuses) nor abnormal foetuses were significantly increased in any treatment group.		
Equivalent or similar to OECD 478 (Genetic toxicology: Rodent dominant lethal test) Inhalation	Mouse, (102/E1 x C3H/E1)F1, male No: 20/ dose 0, 1300 ppm 6h/day for 5 consecutive days 4 hours after the final exposure each male was mated with 2 untreated females for 4 consecutive weeks.	Genotoxicity: positive A statistically significant increase in post-implantation losses was seen in the second week post-exposure, from 8.2% in week 2 controls to 15.4% at 1300 ppm. Increased incidence in weeks 1 and 3 did not reach statistical significance.	Key study	Adler, Cao, Filser, Gassner, Kessler, Lkiesch, Neuhäuser-Klau (1994)

5.7.2 Human information

Table 16: Human information is compiled according to the registration dossier. Additionally, new publications have been considered.

Method	Result	Remarks	Reference
Endpoint addressed: Genetic toxicity Study type: Cross sectional study Study population: Workers with occupational exposure Forty-nine workers at a styrene-butadiene-rubber plant in southeast Texas, USA were involved in this study. Some of the results from this study have been previously reported (Ward et al., 1996). Workers were pre-assigned into a low- and a high-exposure group based on historical butadiene exposure levels in different work areas. Workers were given a questionnaire to complete and asked to wear a passive badge dosimeter for one 8-hour work shift to measure both butadiene and styrene. At the end of the work shift, blood and urine samples were collected. From the blood sample, mononuclear cells were separated and cultured, and the HPRT mutant assay was conducted using the autoradiographic technique. The concentration of butadiene urinary metabolite 1,2-dihydroxy-4-(N-acetylcysteinyl-S-)-butane, was measured and used as a surrogate for internal exposure.	In the high-exposure group, the mean butadiene exposure was 3.18 ± 1.23 ppm (7.03 ± 2.72 mg/m^3); if two unusually high outliers are eliminated, then the mean butadiene exposures were 1.48 ± 0.37 ppm (3.27 ± 0.82 mg/m^3). There were mostly non-detects in the low-exposure group with a mean butadiene exposure of 0.15 ± 0.02 ppm (0.33 ± 0.04 mg/m^3). Urine 1,2-dihydroxy-4-(N-acetylcysteinyl-S-)-butane concentrations were significantly associated with measured butadiene exposure levels. HPRT variant frequencies were significantly higher in the high-exposure group compared to the low-exposure group. The overall worker cohort showed a significant association between individual 1,2-dihydroxy-4-(N-acetylcysteinyl-S-)-butane urine concentration and individual variant frequency value. However, due to the considerable overlap in urine 1,2-dihydroxy-4-(N-acetylcysteinyl-S-)-butane concentrations between individuals in the low- and high-exposure groups, the correlation was not significant when each exposure group was considered separately. The 1,2-dihydroxy-4-(N-acetylcysteinyl-S-)-butane concentration ranged from 200 to 1,200 ng/mg creatinine in the low-exposure group, and 500 to 8,000 ng/mg creatinine in the	Key study	Ammenheuser, Bechtold, Abdel-Rahman, Rosenblatt, Hastings-Smith, Ward, (2001)

	high-exposure group. The variant frequency values for workers in the high-exposure group were considerably higher than the variant frequency values in the low-exposure group in the region of 1,2-dihydroxy-4-(N-acetylcysteinyl-S-)-butane concentration overlap, in which half or more workers in each exposure group are found.		
Endpoint addressed: Genetic toxicity Study type: Case-control study Study population: Workers with occupational exposure 166 Han Chinese workers at a Polybutadiene Latex plant in Ningbo, China, were investigated. For comparison 20 Han Chinese men and 21 women, without butadiene exposure, were selected as control group. All participants were given a questionnaire to complete. Exposure was assessed by regular air sampling throughout the plant. Blood samples were investigated in the cytokinesis-blocked micronucleus test.	The mean cumulative butadiene exposure was 587 mg/year. Butadiene-exposed workers had a mean micronucleus frequency of 3.39 ± 2.42 per thousand which was significantly higher than the mean micronucleus frequency of the controls (1.48 ± 1.26) ($P < 0.01$). Within the workers themselves, Poisson regression demonstrated that high butadiene- exposed workers (>587 mg/year, where 587 mg/year was the median level of exposure) had a significantly increased micronucleus frequency compared with the low butadiene-exposed group (≤587 mg/year; FR = 1.30, 95% CI: 1.14-1.53; $P < 0.01$).	Key study	Wang, Wang, Tan, Feng, Ye, Feng, Liu, Zheng, Xia (2010)
Endpoint addressed: Genetic toxicity Study type: Case-control study Study population: Workers with occupational exposure Forty-five workers in a butadiene workshop in the Nanjing area, China, were matched to appropriate controls with no exposure to known genotoxic agents. Questionnaires and blood samples for all subjects were	After excluding an outlier measurement, the butadiene production plant hat a mean concentration of 2.27 ± 3.33 ppm or 5.02 ± 7.36 mg/m^3. In the control administration office, six measurements showed a mean concentration of 0.84 ± 0.20 ppm or 1.86 ± 0.44 mg/m^3, which was significantly lower ($P < 0.01$) than that for the butadiene production plant. Butadiene-exposed workers had	Supporting study	Xiang, Ao, Yang, Liu, Sun, Han, Li, Cui, Zhou, Liu and Cao (2012)

accompanied by a physical examination. Blood samples were investigated in the cytokinesis-blocked micronucleus test. Exposure was assessed in two ways, personal sampling and stationary sampling	a mean micronucleus frequency of 8.00 ± 3.78 per thousand which was significantly higher than the mean micronucleus frequency of the controls (5.62 ± 2.41) ($P < 0.01$).		

5.7.3 Summary and discussion of mutagenicity

The mutagenicity of butadiene has been reviewed previously (EU-RAR, 2002, IARC 2008, Albertini et al., 2010). Butadiene has been yielded in positive results for mutagenicity in both bacterial and mammalian cell systems. In-vivo investigations demonstrated species differences of the genotoxicity in mice and rats: In mice butadiene acted genotoxicaly in both in somatic cells as well as in germ cells. In rats, the evaluation yielded in negative or weak positive results of butadiene genotoxicity in somatic and germ cells. Since it is known, that butadiene requires metabolic activation to react with DNA, it is likely that differences in the metabolic capacity between mice and rats, as described in the section on toxicokinetics, metabolism and distribution, contribute to the difference in genotoxicity. Many studies investigated the genotoxic properties in butadiene-exposed workers. Several studies did not find an association between chromosome mutation and exposure towards butadiene. However, two recent studies in different industrial plants in China showed increased rates of micronuclei in workers exposed to butadiene (Wang et al., 2010; Xiang et al., 2012). It should be noted, that the studies with negative results were performed under exposure conditions with low exposure towards butadiene (<1 ppm) in contrast to the studies with positive results (butadiene exposure > 1 ppm).

Conclusion

Butadiene is genotoxic in vitro and in vivo in both somatic and germ cells. Therefore the classification of butadiene according to Regulation (EC) No. 1272/2008 in Muta 1B is appropriate.

5.8 Carcinogenicity

5.8.1 Non-human information

5.8.1.1 Carcinogenicity: oral

No relevant information available.

5.8.1.2 Carcinogenicity: inhalation

Table 17: Presentation of carcinogenicity studies according to the registration dossier

Method/ Guideline	Test organism, Strain Dose levels [mg/m^3]	Results	Remarks	Reference
Equivalent or similar to OECD 453 (Combined chronic toxicity / carcinogenicity studies) Up to 10 animals from each group were examined after 9 and 15 months of exposure.	Mouse, B6C3F1, male/female No.: 14 – 450 (70 per sex) 1406 (90 per sex) Inhalation: gas (whole body) Vehicle: air Exposure levels: 0, 14 (6.25 ppm) 45 (20 ppm) 141 (62.5 ppm) 450 (200 ppm) 1406 (625 ppm) 6h/day, 5d/week for 103 weeks	No NOAEC identified (carcinogenicity): Incidences of neoplasms were increased at all doses (14 mg/m^3 and higher in females and 45 mg/m^3 and higher in males). Statistically significant increases occurred in the incidences of malignant lymphoma; histiocytic sarcoma; cardiac haemangiosarcoma; harderian gland adenoma; hepatocellular adenoma and carcinoma; alveolar/bronchiolar adenoma and carcinoma; mammary gland carcinoma, adenoacanthoma, and malignant mixed tumour (females only); benign and malignant ovarian granulosa cell tumour; and forestomach squamous cell papilloma and carcinoma.	Key study	NTP (1993)
Equivalent or similar to OECD 453 (Combined chronic toxicity / carcinogenicity studies)	Rat, CD (Sprague-Dawley), male/female No.: 110 (per	No NOAEC identified (carcinogenicity): There was a significantly increased incidence of several tumours. (pancreatic	Key study	Owen, Glaister, Gaunt, Pullinger, 1987

10 animals from each group were examined after 12 months of exposure.	sex/dose) Inhalation: gas (whole body) Vehicle: air Exposure levels: 0, 2250 (1000 ppm) 18000 (8000 ppm) 6h/day, 5d/week for 105 weeks (females) or for 111 weeks (males)	exocrine adenom, uterine sarcoma, Zymbal gland carcinoma, mammary tumours (benign and malignant), thyroid follicular cell tumours and testis Leydig-cell tumours).		
Equivalent or similar to OECD 453 (Combined chronic toxicity / carcinogenicity studies) The study was planned as a 103-week exposure, but was terminated at week 60 for male mice and week 61 for female mice due to rapidly declining survival owing to neoplasias	Mouse, B6C3F1, male/female No.: 50 per sex, per dose) Inhalation: gas (whole body) Vehicle: air Exposure levels: 0, 1406 (625 ppm) 2813 (1250 ppm) 6h/day, 5d/week for 60 weeks (male) and 61 weeks (female)	No NOAEC identified: (carcinogenicity, males and females) Increased incidences of neoplasms were seen at both doses (625 ppm and 1250 ppm in males and females). Statistically significant increases occurred in the incidences of haemangiosarcomas of the heart, malignant lymphomas, alveolar/bronchiolar adenomas and carcinomas, and papillomas of the stomach in males and females; and acinar cell carcinomas of the mammary gland, granulosa cell tumours of the ovary, and hepatocellular adenomas and carcinomas in females.)	Supporting study	NTP, 1984

5.8.1.3 Carcinogenicity: dermal

No relevant information available.

5.8.2 Human information

Table 18: Human information is compiled according to the registration dossier.

Method	Result	Remarks	Reference
Retrospective cohort study Study population: Workers with occupational exposure 17964 men were originally included into this study, having worked, before 1 January 1992, for at least one year at any of eight synthetic rubber plants, seven in the United Staates and one in Cancada. Previous evaluations have been published in Delzell et al., 1996, Macaluso et al., 1996, Sathiakumar et al., 1998, Delzell et al., 2001 and Macaluso et al., 2004. The updated investigation included 17924 men. The decrease was due to the combination of work histories of 31 men in the original study who had worked at two different plant and had two separate sets of record. Furthermore, eight men were excluded, who had worked for slightly less than one year and one subject was a woman. For 16579 men sufficient information was available on work area and job group to prepare quantitative exposure estimations. The association was evaluated between exposure to butadiene, styrene and dimethyldithiocarbamate (DMDTC) and mortality from lympohaematopoetic cancer. Poisson regression analyses	Overall, 17924 workers were evaluated. Of the 6237 deaths among workers during 1944-1998, 4659 (75%) occurred in the original study period of 1944-91, and 1578 (25%) occurred in 1992-98, the time period covered by the update. The standardised mortality ratio (SMR) was 86 (6237 observed/7242 expected deaths) with 95% CI 84-88). For all cancer combined the SMR was 92, CI 88 - 97. There were fewer deaths than expected for each specific form of cancer, except for colorectal cancer (SMR=109, CI 94 - 125), prostate cancer (SMR=104, CI 88 – 121), Hodgkin´s disease (SMR=111, CI 58 – 195), and leukemia (SMR=116, CI 91 – 147). Lung cancer (SMR=91, CI 84 to 99) accounted for 35% of all cancer deaths. Ever hourly workers had more than expected leukaemia deaths (63/51, SMR=123, CI 94 to 157) and Non-Hodgkin lymphoma deaths (49/44, SMR=111, CI 82 to 147), whereas never hourly subjects had fewer than expected deaths of both diseases. The leukemia excess was highest in the subgroup of ever hourly men with 20-29 years since hire and	Key study	Graff, Sathiakumar, Macaluso, Maldonado, Delzell, 2005 Sathiakumar, Graff, Macaluso, Maldonado, Delzell, 2005 Delzell, Sathiakumar, Graff, Macaluso, Maldonad, Matthew, 2006

were applied to model lymphohaematopoetic cancer (LHC) rates and included all subjects with LHC as a underlying or contributing cause of death. The comparison was performed with data from the general population.	10+years worked (SMR=258, CI 156 to 403). Hourly workers hat an overall leukaemia SMR of 135 (CI 103 to 175) for the 1968-98 time period. The total group of leukemias consisted of the 68 subjects who had worked at one of the six plants and who had leukemia as the underlying cause of death, 12 with leukemia as a contributing cause of death and one who died of myelodysplasia but whose medical records indicated the he had acute leukemia. Single-agent Poisson regression analyses, adjusting for age and years since hire, indicated a positive association between butadiene ppm-years and leukemia (RRs 1.0, 1.4, 1.2, 2.9, and 3.7, respectively, for exposures of 0, >0 to <33.7, 33.7 to <184.7, 184.7 to <425, and 425+ ppm-years) and between styrene ppm-years and leukemia (RRs 1.0, 1.3, 1.6, 3.0, and 2.7, respectively, for exposures of 0, >0 to <8.3, 8.3 to <31.8, 31.8 to <61.1, and 61.1+ ppm-years). DMDTC mg-years/cm also was positively associated with leukemia, without dose-response (RRs 1.0, 2.5, 3.0, 4.9, and 2.7, respectively, for 0, >0 to <185.3, 185.3 to <739, 739 to <1610, and 1610+ mg-years/cm). Multiple agent analyses indicated that after adjusting for styrene ppm-years and DMDTC as well as for age and years since hire, the butadiene–leukemia association was weakened (RRs 1.0, 1.4, 0.9,		

	2.1, and 3.0 respectively, for 0, >0 to <33.7, 33.7 to <184.7, 184.7 to <425, and 425+ ppm-years; all CIs included 1.0). This study found a positive association between butadiene and leukemia that was not explained by exposure to other agents examined.		
Retrospective cohort study Study population: Workers with occupational exposure This study based on the data set used in the studies by Sathiakumar et al. (2005), Graff et al. (2005) and Delzell et al. (2006), which has been described above. Cox regression analyses for leukemia were based on 16091 workers and 485732 person-years of observation.	All three butadiene exposure indices (butadiene ppm-years, total number of exposure to butadiene concentrations >100 ppm and average intensity of butadiene) were associated positively with leukemia. Using continuous, untransformed butadiene ppm-years the regression coefficient (β) from an analysis that controlled only for age was 2.9×10^{-4} ($p < 0.01$); the regression coefficient adjusted for all covariates (age, year of birth, race, plant, years since hire and dimethyldithio-carbamate) was similar in magnitude ($\beta = 3.0\times10^{-4}$, $p = 0.04$). Lagging exposure (lag periods of 5, 10, 15, 20 years) had minimal impact on the results for leukemia for any of the three butadiene exposure indices. In models that controlled only for age, lymphoid neoplasms were associated with butadiene ppm-years and myeloid neoplasms, with butadiene peaks, but neither trend was statistically significant after adjusting for multiple covariates.		Cheng, Sathiakumar, Graff, Matthews, Delzell, 2007
Retrospective cohort study Study population: Female Workers with occupational exposure	Employees had a total of 181,831 and an average of 37 person-years of follow-up during the 1943-2002 study period. Employees' median duration of employment was	Key study	Sathiakumar and Delzell (2009), Sathiakumar, Brill, Delzell

The study included 4,863 women employed at eight North American plants that made styrene-butadiene rubber (SBR) and related products. The main objectives were to evaluate mortality patterns and to determine if certain employment factors and quantitative exposure to certain chemicals were associated with the cancers of *a priori* interest or with other diseases. Based on the epidemiologic studies of men and on toxicological data, cancers of *a priori* interest included leukemia, non-Hodgkin lymphoma (NHL), other forms of lymphohematopoietic cancer (LHC), breast cancer and ovarian cancer. The study included women who had worked at any one of the plants for at least one day during the period of 1943 through 2002. Identifying and work history information came from plant records. Poisson regression analyses examined site-specific cancer rates in relation to butadiene, styrene and DMDTC.	1.6 years, and 30% were ever hourly. In total, there were 1,198 observed compared to 1,383 expected deaths (SMR=87, 95% confidence interval (CI)=82-92). SMRs for all causes were 94 for ever-hourly women and 82 for never-hourly women. Employees with relatively long potential induction time (20+ years since hire) and relatively long duration of years of employment (5+ years) had SMRs for all causes of death combined and for all cancers that were somewhat lower than those of the total study group. Mortality was below or close to expectation for leukemia (total cohort: 10 observed/13 expected, SMR=79, CI=38-145; ever-hourly: 2/4.3; never-hourly: 8/8.4) and multiple myeloma (total cohort: 7/7.9, SMR=88, CI=35-182; ever-hourly: 3/3.3; never-hourly: 4/4.6). For NHL, the total cohort had 15 observed compared to 14 expected deaths (SMR=108, CI=61-178; ever-hourly: 7/4.4; never-hourly: 8/9.5). No increases in deaths from cancers of the breast were seen in the total cohort (72/74, SMR=97, CI=76-123) or in ever-hourly employees (18/23, SMR=77, CI=46-121); never-hourly employees had 54 observed and 51 expected breast cancer deaths (SMR=107, CI=80-139). For the total cohort and for the ever-hourly and never-hourly subgroups, ovarian cancer deaths were close to expectation (total cohort: 21/22, SMR=94, CI=58-143; ever-hourly, 7/7.2; never-hourly, 14/15).		(2009)

	Employees had an excess of lung (106/83, SMR=127, CI=104-154) and bladder cancer deaths (8/4.3, SMR=186, CI=80-366). Both excesses were concentrated among ever-hourly employees (lung cancer: 47/26, SMR=182, CI=133-242; bladder cancer: 6/1.7, SMR=353, CI=130-768) and among ever-hourly employees with 20+ years since hire, but neither cancer displayed a pattern of increasing SMRs with increasing duration of employment. The results do not provide any support for the hypothesis that employment in the synthetic rubber industry in general or exposure to butadiene or other chemicals cause leukemia or other LHCs. The absence of any association between employment factors and leukemia or other LHCs in this study may reflect the fact that the numbers of women and of person-years with relatively high exposure to butadiene and other chemicals were quite small. Employees had an excess of lung cancer and bladder cancer deaths. For these two cancers, the absence of any trend of increasing SMRs with increasing duration of employment, the lack of any exposure-response trend for cumulative exposure to butadiene, styrene or DMDTC and the absence of positive results in studies of male employees indicate that these occupational exposures may not have been responsible for the observed excesses of lung and bladder cancers among women in the industry.		

Retrospective cohort study Study population: Workers with occupational exposure This study based on the data set used in the studies by Sathiakumar et al. (2005), Graff et al. (2005) and Delzell et al. (2006), which has been described above. A Poisson regression analysis was used to assess the leukemia mortality data. Furthermore a model was developed to adjust for the number of tasks that involed butadiene concentrations of 100 ppm or more for any length of time. A more detailed analysis was performed for all leukemia subgroups in Sielken & Valdez-Flores (2011, 2013).	Sielken et al. (2007) came to the following evaluation: After age and the cumulative number of butadiene peaks are incorporated as categorical covariates in the Poisson regression model, the estimated concentration (EC0 0 1) corresponding to an excess risk of 0.001 as a result of continuous environmental exposure is 11.2 ppm; however, the estimated slope for butadiene cumulative ppm-years in the linear rate ratio for leukemia used to derive this EC $_{0\,0\,1}$ is not statistically significantly different from zero. Sensitivity analyses using alternative models indicate either essentially no risk or estimated EC $_{0\,0\,1}$ values of 9 and 77 ppm. Analyses suggesting the absence of a statistically significant low-dose risk versus cumulative butadiene ppm-years are presented. For total leukemia, six exposure covariates (cumulative butadiene high-intensity tasks (HITs), cumulative styrene HITs, cumulative styrene >50 ppm, cumulative styrene 650 ppm, cumulative DMDTC, and cumulative butadiene >100 ppm) significantly improve the maximum likelihood. Before any of the exposure covariates are added to the Cox model for leukemia, the slope per cumulative butadiene ppm-years is statistically significantly different than zero; however, the slope per cumulative butadiene ppm-years is not statistically significantly different than zero after any one of the exposure		Sielken, Valdez-Flores, Gargas, Kirman, Teta, Delzell (2007), Sielken, Valdez-Flores (2011), Sielken, Valdez-Flores (2013)

	covariates is added to the Cox model. For chronic lymphocytic leukemia, the slope per cumulative butadiene ppm-years is statistically significantly different than zero. No exposure or non-exposure covariate significantly improves the maximum likelihood. For chronic myelogenous leukemia, the slope per cumulative butadiene ppm-years is not statistically significantly different than zero. Cumulative butadiene HITs significantly improves the maximum likelihood for chronic myelogenous leukemia. When cumulative butadiene HITs is added to the Cox model, the maximum likelihood estimate of the slope per cumulative butadiene ppm-years is negative. For acute myelogenous leukemia, the slope per cumulative butadiene ppm-years is not statistically significantly different than zero. Three exposure covariates (cumulative styrene HITs, cumulative styrene >50 ppm, and cumulative DMDTC) significantly improve the maximum likelihood for acute myelogenous leukemia. The maximum likelihood estimate of the slope per cumulative butadiene ppm-years is negative in the Cox models either with or without one of these three exposure covariates.		

5.8.3 Summary and discussion of carcinogenicity

Inhalative exposure towards butadiene resulted in carcinogenicity in mice as well as in human workers. At higher concentrations compared to mice, increased rates of tumours were observed in rats (≥ 2250 mg/m^3). In rats there was an increased incidence of tumours such as pancreatic exocrine adenoma (increased in high-dose males), uterine sarcoma (treatment-related trend), Zymbal gland carcinoma (increased in high-dose females), mammary tumours (adenomas and carcinomas were increased in females to a similar extent in both dose groups), thyroid follicular cell tumours (significant trend in females) and testis Leydig-cell tumours (dose-related increase) (Owen et al., 1987). In B6C3F1-mice two carcinogenicity studies have been performed. The first study (NTP 1984) used two butadiene concentrations of 1406 and 2813 mg/m^3. The study was terminated in week 60 for male mice and week 61 for female mice due to rapidly declining survival owing to neoplasias. The second study (NTP 1993) used much lower concentrations (14, 45, 141, 450 and 1406 mg/m^3) for 103 weeks. Incidences of neoplasms were increased at all doses in female mice and at 45 mg/m^3 and higher in male mice. Statistically significant increases occurred in the incidences of malignant lymphoma, histiocytic sarcoma, cardiac haemangiosarcoma, harderian gland adenoma, hepatocellular adenoma and carcinoma, alveolar/bronchiolar adenoma and carcinoma, mammary gland carcinoma, adenoacanthoma, and malignant mixed tumour. A more recent carcinogenicity study testing lower doses than 2250 mg/m^3 in rats is not available. It seems that mice were more sensitive than rats which might be expected due to higher serum concentrations at comparable doses. However, a NOAEC for carcinogenicity in rats was not established.

The evaluation of the carcinogenicity in humans relies on a retrospective cohort study (Graff et al., 2005; Sathiakumar et al., 2005; Delzell et al., 2006). The study population consisted of workers with occupational exposure. 17964 men were originally included into this study, having worked, before 1 January 1992, for at least one year at any of eight synthetic rubber plants, seven in the United Staates and one in Canada. Previous evaluations have been published in Delzell et al., 1996, Macaluso et al., 1996 Sathiakumar et al., 1998, Delzell et al., 2001 and Macaluso et al., 2004. The updated investigation included 17924 men. The decrease was due to the combination of work histories of 31 men in the original study who had worked at two different plant and had two separate sets of record. Furthermore, eight men were excluded, who had worked for slightly less than one year and one subject was a woman. For 16579 men sufficient information was available on work area and job group to prepare quantitative exposure estimations. The association was evaluated between exposure to butadiene, styrene and dimethyldithiocarbamate (DMDTC) and mortality from lympohematopoetic cancer. Poisson regression analyses were applied to model lymphohaematopoetic cancer (LHC) rates and included all subjects with LHC as the underlying or contributing cause of death. The comparison was performed with data from the general population (Graff et al., 2005; Sathiakumar et al., 2005; Delzell et al., 2006).

Overall, 17924 workers were evaluated. Of the 6237 death among workers during 1944-1998, 4659 (75%) occurred in the original study period of 1944-91, and 1578 (25%) occurred in 1992-98, the time period covered by the update. The standardised mortality ratio (SMR) was 86 (6237 observed/7242 expected deaths) with 95% CI 84-88). For all cancer combined the SMR was 92, CI 88 - 97 (Graff et al., 2005; Sathiakumar et al., 2005).

There were fewer deaths than expected for each specific form of cancer, except for colorectal cancer (SMR=109, CI 94 - 125), prostate cancer (SMR=104, CI 88 – 121), Hodgkin´s disease (SMR=111, CI 58 – 195), and leukemia (SMR=116, CI 91 – 147). Lung cancer (SMR=91, CI 84 to 99) accounted for 35% of all cancer deaths (Graff et al., 2005; Sathiakumar et al., 2005).

Ever hourly workers had more than expected leukaemia deaths (63/51, SMR=123, CI 94 to 157) and non-Hodgkin´s lymphoma deaths (49/44, SMR=111, CI 82 to 147), whereas never hourly subjects had fewer than expected deaths from both diseases. The leukemia excess was highest in the subgroup of ever hourly men with 20-29 years since hire and 10+years worked (SMR=258, CI 156 to 403). Hourly workers had an overall leukaemia SMR of 135 (CI 103 to 175) for the 1968-98 time period (Graff et al., 2005; Sathiakumar et al., 2005).

The total group of leukemias consisted of the 68 subjects who had worked at one of the six plants and who had leukemia as the underlying cause of death, 12 with leukemia as a contributing cause of death and one who died of myelodysplasia but whose medical records indicated the he had acute leukemia (Graff et al., 2005; Sathiakumar et al., 2005).

Single-agent Poisson regression analyses, adjusting for age and years since hire, indicated a positive association between butadiene ppm-years and leukemia (RRs 1.0, 1.4, 1.2, 2.9, and 3.7, respectively, for exposures of 0, >0 to <33.7, 33.7 to <184.7, 184.7 to <425, and 425+ ppm-years) and between styrene ppm-years and leukemia (RRs 1.0, 1.3, 1.6, 3.0, and 2.7, respectively, for exposures of 0, >0 to <8.3, 8.3 to <31.8, 31.8 to <61.1, and 61.1+ ppm-years). DMDTC mg-years/cm also was positively associated with leukemia, without dose-response (RRs 1.0, 2.5, 3.0, 4.9, and 2.7, respectively, for 0, >0 to <185.3, 185.3 to <739, 739 to <1610, and 1610+ mg-years/cm) (Graff et al., 2005; Sathiakumar et al., 2005).

Multiple agent analyses indicated that after adjusting for styrene ppm-years and DMDTC as well as for age and years since hire, the butadiene–leukemia association was weakened (RRs 1.0, 1.4, 0.9, 2.1, and 3.0 respectively, for 0, >0 to <33.7, 33.7 to <184.7, 184.7 to <425, and 425+ ppm-years; all CIs included 1.0). This study found a positive association between butadiene and leukemia that was not explained by exposure to other agents examined (Graff et al., 2005; Sathiakumar et al., 2005).

The study population was analysed by Cox regression analyses for leukemia. Analyses were based on 16091 workers and 485732 person-years of observation. All three butadiene exposure indices (butadiene ppm-years, total number of exposure to butadiene concentrations >100 ppm and average intensity of butadiene) were associated positively with leukemia (Cheng et al., 2007).

Using continuous, untransformed butadiene ppm-years the regression coefficient (β) from an analysis that controlled only for age was 2.9×10^{-4} ($p < 0.01$); the regression coefficient adjusted for all covariates (age, year of birth, race, plant, years since hire and dimethyldithiocarbamate) was similar in magnitude ($\beta = 3.0\times10^{-4}$, $p = 0.04$). Lagging exposure had minimal impact on the results for leukemia for any of the three butadiene exposure indices. In models that controlled only for age, lymphoid neoplasms were associated with butadiene ppm-years and myeloid neoplasms, with butadiene peaks, but neither trend was statistically significant after adjusting for multiple covariates (Cheng et al., 2007).

The EU-RAR concluded in 2002, that butadiene should be regarded as carcinogenic in humans (EU-RAR, 2002). IARC concluded in 2008, there is sufficient evidence in humans for the carcinogenicity of butadiene and there is sufficient evidence in experimental animals for the carcinogenicity of butadiene. The overall evaluation was, butadiene is carcinogenic to humans (IARC, 2008).

Butadiene is a genotoxic human carcinogen. The appropriate classification is Carcinogenicity Carc 1A according to directive 1272/2008 (CLP).

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

5.9.1.1 Non-human information

Table 19: Presentation of fertility studies according to the registration dossier

Method/ Guideline	Test organism, Strain Dose levels [mg/m^3]	Results	Remarks	Reference
OECD Guideline 421 (Reproduction /Developmental Toxicity Screening Test) Other guideline: OPPTS 870.3550	Rat (Crl:CD (Sprague-Dawley)IGS BR) Male/female 12 animals per sex per dose Inhalation Exposure levels 0, 675 (300 ppm) 3375 (1500 ppm) 13500 (6000 ppm) Exposure: 6 h/day, 7 d /week F0 males were exposed for 83-84 consecutive days. F0 females were exposed 14 days prior to initiation of the breeding period, throughout gestation and from lactation day 5 through the day prior to euthanasia.	NOAEC Systemic toxicity: 675 mg/m^3 (300 ppm), in F0 males effects on body weight parameters. NOAEC Reproductive toxicity: 13500 mg/m^3 (6000 ppm), highest dose tested. Treatment-related decreases in body weights and body weight gains were observed in F0 males and 1500 and 6000 ppm and in F1 males and females at 1500 and 6000 ppm during the PND 21-27 period.	Key study	WIL (2003)
GLP, non-guideline study Mice were	Mouse (B6C3F1) male 20 animals per	NOAEC F0: 450 mg/m^3 (200 ppm). There was a concentration-related	Key study	Hackett (1988)

exposed for 5 consecutive days. During the 5th post-exposure week the mice were killed, examined for gross lesions of the reproductive tract, and the sperm examined	dose Inhalation Exposure levels 0, 450 (200 ppm) 2250 (1000 ppm) 11250 (5000 ppm) Exposure: 6 h/day Exposure period: 5 days	increase in the percentage of abnormal sperm in exposed mice: statistically significant increases occurred at 2250 mg/m^3 (1000 ppm) and 11250 mg/m^3 (5000 ppm) of 73% and 129% respectively.		
Non-GLP, non-guideline study. Mice were exposed to butadiene for 5 days. The objectives of this study were 1. To investigate chromosome aberrations in first cleavage embryos. 2. To identify the target of, and dose-response relationships for cytotoxic effects. 3. To analyse sperm for alterations in chromatin structure.	Mouse (102/E1 x C3H/E1)F1) male 28 animals per sex per dose (for 293 and 2925) 24 animals per sex per dose (for 0 and 1125) Inhalation Exposure levels 0, 293 (130 ppm) 1125 (500 ppm) 2925 (1300 ppm) Exposure: 6 h/day Exposure period: 5 days	LOAEC: 293 mg/m^3 (130 ppm). Effects on differentiating spermatogonia (decrease of round and elongated spermatids) were observed after exposure of males to butadiene	Supporting study	Pacchierotte, Tiveron, Ranaldi, Bassani, Cordelli, Leter (1998)
No guideline followed. Sexes housed together and allowed to mate. Number of	Rat (Albino rat), Guinea pig, rabbit (male/female) 12 rats per sex per dose 6 guinea pigs per	NOAEC 15075 mg/m^3 (6700 ppm). No deaths and no effects on fertility were recorded at the highest dose tested. However, the	Supporting study	Carpenter, Shaffer, Weir, Smyth (1944)

pups/litter counted. Two rat pups/sex/group from the 1st filial generation continued on study and were exposed with their parents The effects of the inhalation of 1,3-butadiene on fertility were studied. Male and female rats, guinea pigs and rabbits were exposed to butadiene for 8 months.	sex per dose 2 rabbits per sex per dose Inhalation Exposure levels 0, 1350 (600 ppm) 5175 (2300 ppm) 15075 (6700 ppm) Exposure: 7.5 h/day, 6 d /week	numbers of animals were small.		
Non-GLP, non-guideline study. Male rats and mice were exposed to test substance for 10 weeks and 4 weeks (respectively) followed by mating with untreated females. Females were killed prior to parturition and numbers of live foetuses, numbers of foetuses with gross malformations, numbers of post-implantation deaths, skeletal malformations and cytogenetic analyses determined.	Rat (Sprague Dawley) Mouse (CD-1) Inhalation Exposure levels Rats: 0, 146 (65 ppm) 900 (400 ppm) 2813 (1250 ppm) Mice: 0, 28 (12.5 ppm) 146 (65 ppm) 293 (130 ppm) 25 male animals per dose Exposure: 6 h/day, 5 d /week Rats were exposed for 10 weeks. Mice were	NOAEC (Mice) (F1): 28 mg/m^3 (12.5 ppm). Increase in early deaths at 146 mg/m^3 (65 ppm) and 293 mg/m^3 (130 ppm). NOAEC Rats (F1): 2813 mg/m^3 (1250 ppm), highest dose tested.	Supporting study	Anderson, Hughes, Edwards, Brinkworth (1998)

	exposed for 4 weeks			

5.9.1.2 Human information

No relevant information available.

5.9.2 Developmental toxicity

5.9.2.1 Non-human information

Table 20: Presentation of developmental toxicity studies according to the registration dossier

Method/ Guideline	Test organism, Strain Dose levels [mg/m^3]	Results	Remarks	Reference
GLP, equivalent or similar to OECD Guideline 414 (Prenatal Developmental Toxicity)	Rat (Sprague-Dawley CD) Inhalation Exposure levels 0, 450 (200 ppm) 2250 (1000 ppm) 18000 (8000 ppm) 24 mated females per dose. Exposure: 6 h/day, daily Pregnant animals were exposed from day 6 through day 15 of gestation.	NOAEC (maternal toxicity): 450 mg/m^3 (200 ppm). Dose-related decrease in maternal weight gain at all dose levels tested (significant at the two high concentrations). NOAEC (developmental toxicity): 2250 mg/m^3 (1000 ppm). Major fetal defects such as abnormalities of the skull, spine, sternum and long bones were observed at 18000 mg/m^3 (8000 ppm). Mean fetal weight and crown-rump-length was lower in butadiene exposed groups but it reached statistical significance only at the highest dose. A dose-related increase in wavy ribs in the butadiene groups was considered to be associated with the dose-related growth retardation.	Key study	HLE (1982)
GLP compliant, Guideline study. Equivalent or similar to EU method B.31 (Prenatal	Rat (Sprague-Dawley) Inhalation Exposure levels 0,	NOAEC (maternal toxicity): 450 mg/m^3 (200 ppm). Based on reduced body weight gain during the first 5 days of exposure in females exposed to		Hackett (1987a)

Developmental Toxicity Study)	90 (40 ppm) 450 (200 ppm) 2250 (1000 ppm) 30 sperm-positive females per dose. Exposure: 6 h/day, daily Pregnant animals were exposed from day 6 through day 15 of gestation.	2250 mg/m^3 (1000 ppm). NOAEC (developmental toxicity): 2250 (1000 ppm). No effects were observed at the highest concentration.		
GLP-compliant, Guideline study, equivalent or similar to EPA OPP 83-3 (Prenatal Developmental Toxicity Study) Females were mated with unexposed males. Three days prior to the initiation of exposure, the animals were housed in the exposure chambers in the exposure room. From day 16 until sacrifice at day 18, all animals were housed in exposure chambers with filtered-air atmospheres. The 5 days of mating resulted in staged starts and cessations of exposures.	Mouse (CD-1) Inhalation Exposure levels 0, 90 (40 ppm) 450 (200 ppm) 2250 (1000 ppm) Between 31 and 33 plug-positive females per group Exposure: 6 h/day, daily Pregnant animals were exposed from day 6 through day 15 of gestation.	NOAEC (dev. Tox.): 90 mg/m^3 (40 ppm). Reduced fetal weight and minor skeletal abnormalities indicative of growth retardation at 450 and 2250 mg/m^3 (200 and 1000 ppm). Body weight of males was significantly reduced at 90 mg/m^3 (40 ppm). NOAEC (matern. Tox.): 90 mg/m^3 (40 ppm). Reduced body weight gain, reduced weight of gravid uterus. Compared to control values, the weight gain of pregnant animals was decreased significantly at gestation 11 to 16 from 90 mg/m^3 (40 ppm). The reductions for 90, 450 and 2250 mg/m^3 (40, 200 and 1000 ppm) were 4.5, 14 and 20%. According to a new statistical analysis the orginal report by	Key study	Hackett (1987b)

Accordingly, "filler" animals (excess males and females) were used to maintain a constant animal load in the exposure chambers.		Hackett et al (1987b) showed some inconsistencies for the calculation of mean values for maternal and fetal body weight values.		

5.9.2.2 Human information

No relevant information available.

5.9.3 Summary and discussion of reproductive toxicity

In a reproduction/developmental screening study (OECD 421) in rats, butadiene did not show any influence on fertility, the NOAEC (reproductive toxicity) was 13500 mg/m^3 (TL2, 2003). In a non-guideline study the influence of butadiene was investigated on the fertility of male rats and male mice. The exposed males were mated with untreated females. There were no effects on male-mediated fertility in rats but a statistically significant increase in early deaths in mice treated with ≥146 mg/m^3 (Anderson et al., 1998).

Two studies investigated the developmental toxicity in rats (HLE, 1982; Hackett, 1987a). The first study showed significant maternal toxicity (reduced maternal weight gain) at two highest concentration levels (450, 2250 and 18000 mg/m^3). Major fetal defects such as abnormalities of the skull, spine, sternum and long bones were observed at the highest concentration only (HLE, 1982). The second study showed maternal toxicity in highest concentration group of 2250 mg/m^3 and no effects on the developmental toxicity (Hackett, 1987a).

In the mouse ovarian and testicular atrophy was observed in the NTP carcinogenicity studies (NTP 1984, NTP 1993). Testes atrophy occurred at 1382 mg/m^3 and above, whereas ovarian atrophy was observed at all dose levels (13 mg/m^3 and above). The appearance in the lowest dose group coincided with general senescence of the reproductive system (EU RAR 2002). Since survival was reduced in both NTP chronic studies due to tumour development, the EU RAR interpreted the gonadal effects as secondary to severe generalised toxicity (EU RAR 2002). It is unknown, if the butadiene-induced ovarian atrophy has an effect on the reproductive function in the mouse. Since butadiene is classified as a genotoxic carcinogen, no further investigations are required on fertility.

The influence of Butadiene-exposure on male mice was investigated in two studies. The study of Hackett (1988) on sperm-head morphology showed a concentration-related increase in the percentage of abnormal sperm in mice exposed to butadiene for five consecutive days. Statistically significant increases occurred at 2250 mg/m^3 and above. The study of Pacchierotti et al., (1998) showed effects on the sperm chromatin structure already at the lowest tested concentration of 293 mg/m^3. Chromosome-type structural aberrations were significantly elevated in first-cleavage embryos conceived by males mated during the first and second week after the end of exposure. The lowest effective tested concentration was 1125 mg/m^3, the same reported for dominant lethal induction under identical exposure conditions.

A developmental toxicity study was performed in mice using butadiene concentrations of 90, 450 and 2250 mg/m^3. Maternal toxicity was observed in the highest concentration groups with reduced body weight gain and reduced weight of gravid uterus. Developmental toxicity was also observed in the two highest concentration groups with fetal growth retardation and minor skeletal abnormalities (Hackett, 1987b).

There are no studies on the effect of butadiene on fertility and developmental toxicity in humans.

In conclusion, butadiene exposure towards pregnant rats and mice resulted in developmental toxicity at the same concentrations when maternal toxicity appeared. There is no evidence of developmental toxicity in the absence of maternal toxicity. The available evidence indicates that butadiene has a low potential for developmental toxicity in humans. Since butadiene is a classified genotoxic carcinogen no further studies are required. No classification is required for reproductive toxicity according to directive EU 1272/2008.

5.10 Endocrine disrupting properties

No relevant information available.

5.11 Other effects

5.11.1 Non-human information

5.11.1.1 Neurotoxicity

No relevant information available.

5.11.1.2 Immunotoxicity

Table 21: Presentation of immunotoxicity studies according to the registration dossier

Method/ Guideline	Test organism, Strain Dose levels [mg/m^3]	Results	Remarks	Reference
Non-GLP, non-guideline study To evaluate humoral and cell-mediated immune function in mice exposed to butadiene by inhalation. Immune function assays were selected to evaluate specific	Mouse (B6C3F1) Inhalation Exposure levels 0, 2813 (1250 ppm) 5-6 animals per sex per dose. Exposure: 6 h/day, 5 d/week 6, 12, 24 weeks	NOAEC: 2813 mg/m^3 (1250 ppm) (Only one concentration was tested). Some minor changes in immune function were observed such as depression of spleen cellularity at 6 weeks of treatment or increase in spontaneous lymphocyte proliferation in both the	supporting study	Thurmond, Lauer, House, Stillman, Irons, Steinhagen (1986)

humoral and cell-mediated immunity and spontaneous cytotoxicity; lymphoid organ histopathology was also evaluated.		mitogen assay and the mixed lymphocyte culture. However, there were no toxicologically significant persistent immunological effects.		

5.11.2 Human information

No relevant information available.

5.11.3 Summary and discussion of specific investigations

The effect of butadiene on immune function in mice was investigated at a concentration of 2813 mg/m^3 for exposure periods of 6, 12 and 24 weeks. Both specific humoral and cell-mediated immunity were investigated. Some minor changes in immune function were observed such as depression of spleen cellularity at 6 weeks or increase in spontaneous lymphocyte proliferation in both the mitogen assay and the mixed lymphocyte culture. Overall, there were no toxicologically significant persistent immunological effects.

There is no necessity to classify butadiene for immunotoxic properties according the directive EU1272/2008.

5.12 Combined effects

No relevant information available.

5.13 Derivation of DNEL(s) / DMEL(s)

According to Section R.8.4 of the REACH Guidance in Information Requirements and Chemical Safety Assessment (ECHA, 2012), a DNEL for the leading health effect needs to be derived for every relevant human population and every relevant route, duration and frequency of exposure, if feasible. The lead registrant has calculated DNELs and DMELs that are intended to protect both workers and general population from long-term systemic effects caused during inhalation exposure to buta-1,3-diene. The derivation of DMEL for workers and general population was based on data from human epidemiology studies.

5.13.1 Overview of typical dose descriptors for all endpoints

An overview of all dose-descriptors for the different toxicity endpoints of buta-1,3-diene is available from the registration dossier of the lead registrant. For calculation of DNEL/DMEL by the eMSCA the dose-descriptors are gathered from the available and relevant experimental animal studies. Out of this database together with information published in reviews of international bodies (listed above) suitable studies and typical dose descriptors for derivation of DNEL and DMEL are discussed. In the following Table 22 a summary of this evaluation is shown.

Table 22: Dose descriptor(s) per endpoint for derivation of DNEL and DMEL

Endpoint Route Species	Does descriptor/ Qualitative assessment	Reference Remarks on the study
Irritation/ Corrosivity Eye Dog and rabbit	Not irritating	***Carpenter et al., (1944).*** No adverse effect observed.
Repeated dose toxicity Inhalation Rat	NOAEC (systemic): 1000 ppm based on increased heart weight and kidney nephrosis occurring at 8000 ppm.	***Owen et al., (1987)***, equivalent or similar to OECD Guideline 453. Sprague-Dawley rats (male/female) were exposed to 1,000 or 8,000 ppm (2,212 and 17,701 mg/m^3) buta-1,3-diene by vapour inhalation for 105 weeks (females) and 111 weeks (males) (6 hr/day, 5 days/week). Exposure to buta-1,3-diene results in suppression of body weight gain, reduced survival, increased weights of liver, kidney, heart, lung and spleen, nephrosis of the kidney and focal metaplasia in lung.
Mutagenicity in vitro / in vivo	Positive results	***Araki et al., (1994); Madhusree et al., (2002); Cochrane et al., (1994); Adler et al., (1994a&b); Cunningham et al., (1986a&b); BIBRA (1996).*** The available data indicate that buta-1,3-diene is genotoxic in vitro and in vivo in both somatic and germ cells in mouse but is not genotoxic in vivo in both somatic and germ cells in rat. There is therefore evidence for species differences in regard to the genotoxicity of buta-1,3-diene.
Carcinogenicity Inhalation Rat, mouse, humans	No NOAEC identified. Tumor development in rats and mice and leukaemia in humans	***Owen et al., (1987); NTP (1984, 1993); Bucher et al., (1993).*** Buta-1,3-diene is a multiple organ carcinogen. It causes sarcomas, lymphomas, papillomas, adenomas and carcinomas in both rats and mice at all exposure levels. ***Sathiakumar et al., (2005, 2009); Graff et al., (2005); Delzell el al., (2006); Cheng et al., (2007); Sielken et al., (2007, 2013); TL1 (Unpublished reports;2006, 2008).*** Buta-1,3-diene is a genotoxic human carcinogen. Target organ is the cardiovascular/haematological system.
Reproductive toxicity: effects on fertility Inhalation Rat	NOAEL: 6000 ppm	***WIL (2003)***, OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test) Crl:CD® (Sprague-Dawley) IGS BR rats (male/female) were exposed to 300, 1,500 and 6,000 ppm buta-1,3-diene by vapour inhalation. The duration of exposure was 6 hours/day on 7 days of a week. There were no treatment-related effects on fertility.

Reproductive toxicity: developmental toxicity Inhalation Rat, mouse		***Hackett (1987a); HLE (1984); Hackett (1987b).*** Buta-1,3-diene caused developmental toxicity in rats and mice, in the presence of maternal toxicity, manifested as retardation in foetal development.
Rat	NOAEC (maternal toxicity): 200 ppm based on reduced body weights. NOAEL (developmental toxicity): 1,000 ppm. The NOAEC for teratogenicity was 1,000 ppm.	Buta-1,3-diene has been tested in two key rat developmental toxicity tests conducted by inhalation exposure. In Hackett 1987a rats were exposed to 40, 200 or 1,000 ppm (88, 442, 2,212 mg/m^3). In the second study (HLE, 1984) doses were 200, 1,000 and 8,000 ppm (442, 2,212 and 17,701 mg/m^3). Maternal toxicity occurred at all dose levels tested. At 8,000 ppm, increased incidences of major foetal defects occurred such as severe wavy ribs. These effects were considered to be indicative of delayed development associated with maternal toxicity.
Mouse	NOAEC (developmental toxicity): 40 ppm (88 mg/m^3) based on the key study of Hackett (1987b) in mice.	CD1 mice were 6h/day exposed to buta-1,3-diene at concentrations of 40, 200 or 1,000 ppm (88, 442 or 2,212 mg/m^3) (Hackett 1987b). Buta-1,3-diene produced significant signs of maternal toxicity (reduced body weight gain) at concentrations of 200 and 1,000 ppm. The NOAEC for maternal toxicity was 40 ppm (88 mg/m^3).

5.13.2 Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptor for critical health effects

The most critical endpoint of buta-1,3-diene is carcinogenicity, proved in a variety of studies in rat, mouse and human. Based on the results of the mutagenicity studies (see Table 22) a genotoxic mode-of-action is considered for buta-1,3-diene. It has been generally accepted that genotoxic carcinogens have no dose threshold for their carcinogenic potential. Therefore, as a genotoxic mutagen and carcinogenbuta-1,3-diene is a non-threshold substance. For these a derived no effect level (DNEL) cannot be calculated which is why the registrant should develop a derived minimum effect level (DMEL). This is a reference risk level considered to be of very low concern (Section R.8.4 of the REACh Guidance).

DMEL derivation for workers

Inhalation systemic effects - Long-term:

At the workplace exposure to buta-1,3-diene may occurs via inhalation. Consequently, DMEL has to be derived for inhalation route. For occupational exposure, the registrants have provided an estimated $DMEL_{long\text{-}term,\ inhalation,\ systemic}$ of 1 ppm (2.21 mg/m3) (see Table 23). Exposure of workers to this DMEL results in a risk estimate for excess leukaemia deaths (all cell types combined) of 0.39×10^{-4} which corresponds to approximately 4:100 000. This is close to the future acceptance level of 0.4 x 10-4 for occupational risk in Germany (AGS, 2008).

Table 23: Hazard conclusion for workers

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects – long-term	DMEL (derived minimum effect level): 2.21 mg/m^3	carcinogenicity (by inhalation)

Detailed information about the DMEL calculation like assessment factors or the point of departure is missing in the dossier provided by the registrants. A more comprehensive description of the derivation of this value would be desirable. The only information given by the registrant about the calculation of the DMEL is that a Cox regression model for leukaemia reported by Cheng et al. (2007) has been used. The registrant writes in the dossier that dose descriptors and assessment factors are already included in the model. But for the comprehensibility of the DMEL derivation a presentation of these used factors would be reasonable.

Consumers

A hazard was identified for workers and consumers. Butadiene is a genotoxic carcinogen. The relevant studies have been performed in workers exposed to butadiene. The REACH Guidance Chapter R.8, Appendix R.8-13 specifies that a community/national occupational exposure limit (OEL) may be used in place of developing a DNEL when such guidance value is available, provided exposure route and duration are the same, and there is no newer scientific information that would lead to a different result requiring the implementation of specific RMM: DMEL derivation followed the analysis of the German AGS (2008), who calculated an exposure based life-time leukemia risk of 1 to 100.000 for a butadiene exposure of 11 µg/ m^3 (according to 0.005 ppm) for a working period of 35 to 40 years.

DMEL(inh) (workers) = 11 µg/ m^3, (0.005) ppm

For consumers the assessment followed the above mentioned calculation and made corrections for the exposure times (8 h/day for workers vs 24 h/consumers and 40 years at work vs 70 years of life and 5 day/week at work for workers vs 7 days/week for consumers). Therefore the DMEL for consumers was calculated for an exposure related life-time leukemia risk of 1 to 100.000 for a lifelong butadiene exposure of 1,50 µg/ m^3 (according to 0.0007 ppm).

DMEL(inh) (consumers) = 1.50 µg/ m^3 (0.0007) ppm

This DMEL(inh) is converted into a DMEL(oral) applying the factors according to the REACH Guidance, Chapter R.8, Example R.8-1: A respiratory volume of 20 m^3/adult person/day and a body weight of 70 kg is applied.

DMEL(oral) (consumers) = 1.50 µg/ m^3 x 20 m^3/person/d / 70 kg/person = 0.43 µg/kg/d

For Children, age 3 years, a DMEL is calculated with the following assumptions according to the REACH Guidance, Chapter R.15, Table R.15-16: A respiration volume of 7 m^3/child/d and a body weight of 14.5 kg is applied.

DMEL(oral) (Child) = 1.50 µg/ m^3 x 7 m^3/person / 14.5 kg/person = 0.72 µg/kg/d

5.14 Conclusions of the human health hazard assessment and related classification and labelling

Butadiene is a genotoxic compound which is carcinogenic to humans. The compound is sufficiently classified according to CLP as Carc 1A and Muta 1B.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES

Not relevant for this evaluation.

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this evaluation.

8 PBT AND VPVB ASSESSMENT

Not relevant for this evaluation.

9 EXPOSURE ASSESSMENT

9.1 Human Health

9.1.1 Exposure assessment for worker

The vapour pressure at 270 K (17 °C) is 217 kPa, which is the value used for the CSA of the registration. Its boiling point is -4.4 °C. In its monomeric form buta-1,3-diene is a highly volatile gas and the main route of occupational exposure is by inhalation. Oral and dermal exposure can be assumed to be very minor routes of exposure, especially if a good standard of occupational hygiene is assumed.

The exposure assessment for workers included both modelled data from the registration dossier and real workplace measurement data as provided by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA 2014).

9.1.1.1 Overview of uses and exposure scenarios

According to the registration dossiers following uses were identified:

- Manufacture
- Importation and storage
- Formulation
- Use as a fuel
- Use as laboratory reagents
- Monomer in production of other chemicals
- Intermediate in production of other chemicals
- Intermediate use of the substance
- Distribution
- Uses in Rubber production and processing
- Polymer Production (industrial)
- Polymer Processing (professional)

9.1.1.2 Scope and type of exposure

Buta-1,3-diene is an important industrial chemical. In the Risk Assessment Report (Commission 2002) the total production capacity in the EU is estimated between 1,202,000 and 4,960,000 tonnes/year and a figure of 1,892,000 tonnes /year is assumed therein as a realistic estimate for the amount of buta-1,3-diene used in the EU. (The added quantities (estimated) for 2010 in IUCLID lead to a figure of 319,789 tonnes).

Buta-1,3-diene is mainly used as an intermediate (monomer) in the production of polymers and copolymers such as synthetic rubbers (PBR and SBR) and plastics (ABS, NBR, MBS). In its monomeric form buta-1,3-diene is used in closed systems with a non-dispersive pattern of use. The concentration of residual butadiene monomer in end-use products is low. - In the Risk Assessment Report (Commission 2002) figures of 0.04 to 0.2 ng/mg of residual butadiene monomers are given. Exposures from these products are thus expected to be minimal and therefore likely to be negligible.

Occupational exposure is mainly expected to occur during the production of buta-1,3-diene (steam cracking of petroleum and the extraction of the monomer) and the production of butadiene

polymers. The use of butadiene polymers is considered as a minor source of occupational exposures.

9.1.1.2.1 Monitoring data

Occupational exposure data published in the EU Risk Assessment Report 2002

In the EU RAR (EU RAR, 2002) occupational exposure data from HSE's National Exposure Database, from UK industry and data form literature (published review articles) until 2000 were evaluated. Occupational exposure to buta-1,3-diene was found to be likely at four tasks/scenarios:

1) production of buta-1,3-diene (monomer)
2) production of butadiene polymers
3) use of butadiene polymers
4) production and handling of motor fuels

The exposure data taken into account were summarised in two tables as in the following:

Table 24: Summary of 8-hour TWA exposure data used in EU RAR (Commission 2002, table 4.13, p74).

Industry	Source	No of Samples	Arithmetic Mean (ppm)	Range (ppm)	Percent less than		
					1 ppm	5 ppm	10 ppm
Monomer production							
cracker / extraction	HSE 1984	10	2	<0.3-17	90	90	100
petroleum cracker	CEFIC 1986 to 1993	1548	nk	nk	96.4	99.6	99.6
extraction plants		1035	nk	nk	81.4	92.5	97.1
extraction plants	CEFIC 1995	nk	<0.01-5*	0-18.1	nk	nk	nk
integrated extraction / SBR production plant		nk	0.07-3.4	0.02-60	nk	nk	nk
cracker / extraction plants	UK industry 1988-1994	268	0.39	max=3.9	nk	100	-
monomer	Sorsa et al. (1996)	70% < 0.2 ppm (2plants) & 0.2-2 ppm for 3rd plant, with 10% > 10 ppm.					
Polymer Production							
various butadiene polymers	HSE 1984	135	1.8	< 0.3-37.5	72.6	93.3	97
synthetic rubber / latex	IISRP 1994	661	nk	nk	71.1	93.3	99.5
SBR / ABS / SB latex	UK industry 1993/94	66	1.9	0-12	nk	nk	nk
various polymers	UK industry, no date.	two plants: first; 95% < 1 ppm; and second with most < 3 ppm					
not specified	Fajen et al. (1990)	4338	1.14	< 0.005-42.9	nk	nk	nk
not specified	Sorsa et al. (1996)	two plants: majority between 5 and 10 ppm, with 40% > 10 ppm					
During the use of butadiene polymers							
Rubber tyre plant	Fajen et al. (1990)	124	nk	nd*	100	-	-
During the production and handling of motor fuels							
various	CONCAWE 1987	nk	nk	nd – 14.37	Nk	nk	nk

* reported as representative 8-hour TWAs
nk. Not known
nd. Non detected. Limit of detection was 0.3 µg/sample

Table 25: Summary of short-term exposure data used in EU RAR (Commission 2002, table 4.14, p75).

Industry	Source	No of Samples	Arithmetic Mean (ppm)	Range (ppm)
Monomer production				
extraction plants	CEFIC 1995	nk	nk	0-100
integrated extraction / SBR production plant		nk	Nk	0-177
monomer	Sorsa et al. (1996)	nk	Nk	up to 100*
Polymer Production				
not specified	Fajen et al. (1990)	14	36.1	0.087-280
During the production and use of motor fuels				
self service station – filling tank	CONCAWE 1987	nk	0.71	nd-4.72
Modelled data for monomer / polymer industries				
monomer / polymer	EASE	33 ppm for sampling and 33 to 76 ppm for loading / unloading		

The occupational exposure data in the EU RAR were contextualised according to the four main scenarios stated above. Exposure as a result of residual monomer from use of butadiene polymers (scenario 3) was deemed to be negligible. Relevant exposure levels were identified during the production of buta-1,3-diene (scenario 1) and the production of butadiene polymers (scenario 2). In the risk characterisation the EU RAR used an exposure level of 1 ppm for the 8-hour TWA exposure for the production of the monomer (scenario 1) and an exposure level of 5 ppm for the polymer production (scenario 2). Since all of the data in this report were collected before 2000 they are considered to be out of date and most of the findings can be expected to be obsolete as more rigid occupational exposure limits were set since.

Occupational exposure data from Health Effects Institute (HEI)

The Health Effects Institute (HEI) conducted a comprehensive study at two butadiene facilities in the Czech Republic to evaluate whether biomarkers of exposure to buta-1,3-diene could be established in an industrial setting (Albertini, Sram et al. 2003). In in the course of this study N=536 individual workshift measurements of the exposure to buta-1,3-diene were carried in 1998 both in monomer production and in polymerisation facilities as well as on administrative workers as control subjects. The results of the descriptive statistics for the individual exposure measurements are presented in Table 26 and the descriptive statistics for workplace area measurements are presented in Table 27.

Table 26: Descriptive statistics for individual measurements of workplace exposure to buta-1,3-diene (mg/m³) by group (Albertini, Sram et al. 2003).

	Control	Monomer	Polymer
N measurements	28	217	319
Mean concentration	0.026	0.643	1.760
SD	0.030	2.056	4.692
Minimum	0.002	0.002	0.002
Maximum	0.125	19.909	39.030
50th percentile	0.013	0.074	0.293
90th percentile	0.071	1.886	4.344

Table 27: Descriptive statistics for workplace area measurements of buta-1,3-diene (mg/m³) (Albertini, Sram et al. 2003).

	Adminis-tration	Monomer Unit	Polymer Unit
N measurements	18	60	89
Mean concentration	0.043	0.316	0.892
SD	0.098	0.388	1.223
Minimum	0. 00025	0. 00025	0.00025
Maximum	0.391	1.824	6.241
50th percentile	0.005	0.153	0.414
90th percentile	0.183	0.989	2.400

Individual exposure levels from personal measurements were consistent with the workplace area measurements in the HEI study. According to this study the workers had "very little exposure" for "much of the time"; and "nearly all of the monomer production and polymerization workers had workshifts during which their exposure levels were "comparable to those for administrative control subjects." The authors concluded that exposure to buta-1,3-diene therefore tends to occur in peaks which is very difficult or even impossible to be estimated on a basis of one measurement per person accordingly.

Occupational exposure data from German Social Accident Insurance (IFA)

Measured workplace exposure data in Germany have been evaluated in a study by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA 2014). The data have been gathered over the period from 1984 to 2013 and were documented in accordance the measurement system of the German Social Accident Insurance Institutions for exposure assessment (MGU).

79.6 % of the measurements are representative for exposure times equal to or over 6 hours and the measurements were done in 85 branches of industry and 201 work areas. The data are therefore highly representative and highly valid for the situation in Germany and deemed to be equally representative for similar work areas in the EU.

Table 28 provides an overview of the measured values while tables 18 and 19 summarize the statistic evaluations for industry groups and for work area groups respectively.

Table 28: Overview of the measured values collected in the MGU, data period 1984-2013 (IFA 2014).

General description	Number of measured values (%)
Total	930
Type of sampling: Stationary Personal	 649 (70%) 280 (30%)
Number of data < quantification limit	885 (95%)
Sampling representative for: Exposure time ≥ 6 h Exposure time < 6 h	 740 (80%) 76 (8%)

Examples: Exposure conditions	
Measurement plan:	
Workplace measurements	923 (99%)
Interior measurements	7 (1%)
Reason for measurement: investigation in case of suspected occupational disease	83 (9%)
Without mechanical ventilation	328 (35%)
With mechanical ventilation	452 (49%)
No details	150 (16%)
Without local exhaust ventilation	464 (50%)
With local exhaust ventilation	360 (39%)
No details	106 (11%)

General description of measurements of buta-1,3-diene in: 85 branches of industry and 205 work areas

The criteria for inclusion of measured data in the evaluation are:

- Data period 1984 to 2013
- Standard method in the MGU (until 1992 measurement method in testing)
- Measured data relating to occupational exposure
- Sampling is representative for exposure duration.
- Exposure duration ≥ 6 hours or < 6 hours
- If any single values fell below the measurement method´s analytical quantification limit (a. q.), half of each value was adopted in the evaluation
- Data sets comprising fewer than ten measured data were disregarded.
- The evaluation is performed according to time periods, industry groups and work area groups

The following abbreviations and indices are used in the evaluation tables:

a. q. Analytical quantification limit (limit of quantification)

* If any single values fell below the measurement methods analytical quantification limit (a. q.), half of each value was adopted in the evaluation.

\+ The distribution value is below the largest analytical quantification limit (a. q.) in the data set. The quantification limit may deviate from the quantification limit quote in the introduction, e.g. depending on sampling duration or flow rate.

! The number of measured values below the analytical quantification limit (a. q.) is greater than the number of measured values represented by this cumulative frequency value. No concentration is therefore given for this cumulative frequency value.

** Less than five enterprises are included. Data derived out of less than enterprises may not be representative for the whole industry or a whole industrial sector.

Table 29 provides the statistical evaluation differentiated by data periods.

Table 29: Statistical evaluation differentiated by data periods (IFA 2014).

Data period	Exposure time in h	Number of measured data	Number of holdings	Number of values < limit of quantification*	Values < limit of quantification* (%)	Highest quantification limit a. q.* (mg/m³)	50-%-value (mg/m³)	90-%-value (mg/m³)	95-%-value (mg/m³)
1984-2013	≥ 6	733	376	691	94,3	8,3	a. q. !	a. q. !	2.77 +
	< 6	76	60	75	98,7	8	a. q. !	a. q. !	a. q. !
1984-1989	≥ 6	22	10	22	100	1.5	a. q. !	a. q. !	a. q. !
	< 6	0							
1990-1994	≥ 6	201	83	176	87,6	5.5	a. q. !	1 +	4.9 +
	< 6	17	16	16	94,1	4	a. q. !	a. q. !	3.95 +
1995-1999	≥ 6	196	108	181	92,3	8	a. q. !	a. q. !	3 +
	< 6	23	14	23	100	7	a. q. !	a. q. !	a. q. !
2000-2010	≥ 6	227	138	226	99,6	8	a. q. !	a. q. !	a. q. !
	< 6	24	19	24	100	8	a. q. !	a. q. !	a. q. !
2011-2013	≥ 6	87	56	86	98,9	8.3	a. q. !	a. q. !	a. q. !
	< 6	12	11	12	100	6	a. q. !	a. q. !	a. q. !

Table 30 provides the statistical evaluation for branches of industry and work area groups.

Table 30: Statistical evaluation for branches of industry and work area groups: sampling representative for exposure time ≥ 6 h (IFA 2014).

Branches of industry	Work area groups	Number of measured data	Number of holdings	Number of values < limit of quantification*	Values < limit of quantification* (%)	Highest quantification limit a. q.* (mg/m³)	50-%-value (mg/m³)	90-%-value (mg/m³)	95-%-value (mg/m³)
without limitation	without limitation	733	376	691	94.3	8.3	a. q. !	a. q. !	2.77 +
Chemical industry	Distillation,	21	2 **	8	38.1	1	1 +	5.9	8.85
	Reaction container								
	Storage, storage tanks	20	1 **	10	50	1	1 +	15	20
Maritime navigation, freight and tanker navigation (Shipping companies)	without limitation	25	1 **	11	44	1	3	5	6.75

Table 31 provides a statistical evaluation for the work area groups.

Table 31: Statistical evaluation for work area groups: sampling representative for exposure time ≥ 6 h (IFA 2014).

Branches of industry	Work area groups	Number of measured data	Number of values > limit of quantification*
Chemical industry	Distillation,	13	8
	Reaction equipment and facilities,		
	Reaction containers in general	2	

	Raw material storage, interim storage	6	5
	Storage tanks in general	3	3
	Storage tanks, filling and transfer	5	4
		12	3
Chemical industry Total		41	23
Maritime navigation, freight and tanker navigation (Shipping companies)	Superstructures	3	2
	Main deck	18	12
	Sampling, in general	2	
	repair and maintenance, in general	2	
Maritime navigation, freight and tanker navigation (Shipping companies) Total		25	14

All of the measured values above the detection limit are representative for exposure times below 6 hours indicating exposure situations that are not representative for full shift lengths.

For the respective periods of time (1990-1999) the IFA measurement data are similar to the exposure levels presented in the EU RAR and the HEI study. Taking into to account that buta-1,3-diene was classified as carcinogenic in the beginning 1990s and since then occupational exposure limit values have been raised these data are certainly outdated for most of the workplaces. The analysis of the IFA data over time in table AB show a clear trend towards lower exposures from the periods of 1990-1994, 1995-1999 and since 2000 until 2013 respectively. All of the data since 2000 were actually below the indicated limits of quantification and show a clear trend that the overall exposure levels have been reduced in average to below 1 mg/m³ in Germany. On the other hand the limit of quantification of 1 mg/m³ of the IFA data is quiet high and not suited to allow a risk assessment according to the German exposure risk relationship (ERR) for buta-1,3-diene, that became legally binding in Germany in 2012. According to this concept a tolerable workplace concentration of buta-1,3-diene is reached at levels equivalent to or below 5 mg/m³ while an acceptable workplace concentration is assumed at levels equivalent to or below 0.5 mg/m³. For most of the IFA data the analytical quantification limit of 1 mg/m³ does not allow a clear assessment whether the exposure levels are according to the German regulation in an acceptable region (< 0.5 mg/m³) or just well below the tolerable concentration limit of 5 mg/m³. (They clearly are well below the concentration limit defining unacceptable risks for workers).

9.1.1.2.2 Modelled data

Exposure assessments in the updated registration of the lead registrant (LOA 2014) include ten exposure scenarios (ES) as shown in Table 32. Only worker exposures are covered by these ES. Nine of the exposure scenarios cover industrial uses and one is linked to professional use of butadiene polymers (ES 10 - Use by professional worker – Polymer processing). As confirmed by the registrants the last ES is not intended to demonstrate safe use for polymers with residual monomer contents up to 1% but to demonstrate safe use even with conservative estimates. This information is in line with the EU RAR where residual monomer content in butadiene polymers was found to be negligible.

Table 32: Overview of exposure scenarios according to registration (LOA, 2014).

ES number	Exposure scenario name
1	Manufacture
2	Formulation
3	Use at industrial site – intermediate use of the substance

ES number	Exposure scenario name
4	Use at industrial site – Distribution
5	Use at industrial site – Uses in rubber production and processing
6	Use at industrial site – Use as laboratory reagents
7	Use at industrial site – Use as a fuel
8	Use at industrial site – Polymer production
9	Use at industrial site – Polymer processing
10	Use by professional worker – Polymer processing

The worker exposure estimates have been developed using ECETOC TRA version 3.

According to ECETOC gases are at the boundary of the domain of reliable application of the TRAv3. In the ECETOC Technical Report no. 114, it is written: "The TRA does not predict exposure to gases." … "However the TRA does allow exposures to very volatile liquids (with no upper bound set on vapour pressure) to be estimated. As these very volatile liquids might be assumed to be the equivalents of gases for many circumstances of use (PROCs), then provided users are able to assure themselves of such equivalencies, then it is reasonable to assume that the high volatility exposure prediction can also be used to predict exposures to gases in certain scenarios" (ECETOC 2012, table 3, p. 16). Indeed the assumptions made in the registration dossier for estimating the worker exposures seem to be reasonable and the choice of PROCs justifiable. Also, the registration dossier states: "In the ECETOC TRA any substance with a vapour pressure higher than 10 kPa is assigned a transfer to air factor of 1 (i.e. 100%), the substance is considered to be completely released into air instantly. This is exactly what would happen to butadiene if it was to leak or be release into the environment. Therefore, the model's basic underlying assumption is applicable to our substance" (LOA 2014, p. 120). For the reasons given the use of ECETOC TRA v3 appears to be correct and within the boundaries of the models applicability.

The following table gives an overview of the highest predicted inhalation exposure values within each exposure scenario according to the registration.

Table 33: Overview of highest estimates of inhalation exposure in exposure scenarios 1-10 (according to registration dossier).

ES number	Highest predicted inhalation exposure
1 - Manufacture (industrial)	1.183 mg/m³
2 - Formulation (industrial)	1.69 mg/m³
3 - intermediate use of the substance (industrial)	1.183 mg/m³
4 – Distribution (industrial)	1.578 mg/m³
5 - Uses in rubber production and processing (industrial)	1.623 mg/m³
6 - Use as laboratory reagents (industrial)	1.11 mg/m³
7 - Use as a fuel (industrial)	2.028 mg/m³
8 - Polymer production (industrial)	1.69 mg/m³
9 - Polymer processing (industrial)	1.893 mg/m³
10 - Polymer processing (professional worker)	1.578 mg/m³

9.1.1.2.3 Comparison of monitoring and modelled data

The modelled data of the lead registrant (LOA 2014) are in the same range as the measured values and compare well with actual exposure levels. As discussed above the measurement data from before 2000 are most likely outdated since the classification of buta-1,3-diene as carcinogenic and mutagenic (Carc. Cat. 1; Muta. Cat. 2) did lead to significant improvements in risk management and

reduction of exposure at workplaces. Most of the more recent measurement data in this SEv Report (since 2000) are taken from the IFA report on buta-1,3-diene (IFA 2014) and show a clear trend in lowering the exposure levels over time. Since the IFA data were taken for regulatory compliance issues and the then applicable German occupational exposure was at 11 mg/m³ they do have a relatively high limit of quantification (1 mg/m³). Therefore, the IFA data are unsuited to assess the workplaces in order to determine the risk according to the ERR which is now legally binding in Germany. But according to the IFA database almost all workplace measurements taken between 2000 and 2013 were below the limit of quantification (mostly taken at workplaces where butadiene polymers were thermally treated and therefore with a relative high probability of exposure). Although the IFA data are solely from workplaces in Germany they indicate that exposure levels of buta-1,3-diene in the region of the modelled exposure values or below are well achievable at industrial sites and are achieved in practice.

9.1.2 Exposure assessment for consumer

9.1.2.1 Overview of uses and exposure scenarios

As was pointed out in section 2.2 consumers do not use 1,3-butadiene as such, but become exposed when they use articles and potentially also products (mixtures) which contain the substance or release it under specific conditions.

The most recent available data in the SPIN Exposure Toolbox (SPIN 2014) indicates for Norway, Denmark and Sweden consistently a very probable use in article productions by one or several uses and a very probable consumer exposure by one or several uses.

The European Union Risk Assessment Report (EU 2002) identifies six sources for consumer exposure: release of residual free monomers from polymeric consumer products, up-take of such monomers via their leaching into food, thermal degradation of polymeric consumer products, liquid propane gas, motor fuel vapours and cigarette smoke.

This matches the information on consumer uses contained in the CICAD report on 1,3-butadiene (WHO 2001), which was prepared by the Environmental Health Directorate of Health Canada based on documentation prepared concurrently as part of the Priority Substances Program under the Canadian Environmental Protection Act.

Within the European Union the use of 1,3-butadiene for certain types of products is regulated. For plastic materials and articles intended to come into contact with food the specifications are that no monomer transfer into the food is detectable with a detection limit of 0.01 mg/kg or that remaining monomers in the end product must not exceed 1 mg/kg. While a generic ban prohibits utilisation of substances classified as CMR substances of the category 1A in toys or their components, such substances may be used if their individual concentration is equal to or smaller than 0.1 % (1 g/kg).

An inquiry of the data from the German food and commodity safety surveillance retrieved no data on 1,3-butadiene contents in food or commodities. Some studies on remaining 1,3-butadiene contents have been published for this kind of products available on the Japanese Market around 2010 (Abe 2014, Abe 2013, OHNO 2010). The detected 1,3-butadiene contents differed depending on the investigated (co)polymerised material. Highest levels were found for Acrylonitrile-Butadiene-Styrene Copolymers. In general the contents were in compliance with the European Regulations. All exemptions were restricted to food contact materials.

The European situation is reflected in the exposure scenarios within the European Union Risk Assessment Report (EU 2002). Information on the registrant's exposure scenarios is given in the confidential annex.

9.1.2.2 Scope and type of exposure

9.1.2.2.1 Monitoring data

9.1.2.2.2 Modelled data

The European Union Risk Assessment Report (EU 2002) investigated up-takes for different routes and sources of 1,3-butadiene. This included "leaching of free monomers from packaging into foodstuff" for adults and toddlers (oral, 0.015 and 0.017 mg/d, respectively) and "release of free monomer from polymeric consumer products (indoor air)" for adults and toddlers (inhalative, 0.036 and 0.01 mg/d, respectively). The combined worst-case exposure to 1,3-butadiene from these was assessed as 0.0007 mg/kg BW/d for adults. Based on the figures for toddlers would be exposed to 0.0019 mg/kg BW/d.

9.1.2.2.3 Comparison of monitoring and modelled data

9.2 Environmental exposure assessment

Not relevant for this evaluation.

10 RISK CHARACTERISATION

10.1 Human Health

10.1.1 Workers

Considering buta-1,3-diene as a genotoxic carcinogen has no threshold for its carcinogenic potential, a derivation of a derived no effect level (DNEL) is not possible. For this reason it was not possible to calculate risk characterisation ratios (RCRs). Instead of a DNEL a derived minimum effect level (DMEL) is calculated which allows the assessment of the carcinogenic potential of the substance. In Germany, a risk-oriented concept for carcinogenic substances is recommended by the Committee for Hazardous Substances (AGS). The lifetime cancer risk is assessed in judging tolerance and acceptance risk levels for workers to minimise the exposure to carcinogenic chemicals at workplaces. The derivation of the tolerance and acceptance concentration is carried out by means of the exposure-risk relationships (ERB). *Tolerable risk:* The tolerable risk defines the additional cancer risk of 4:1,000 that is tolerated, meaning that, statistically, 4 out of 1,000 persons exposed to the substance throughout their working life will develop cancer. Below this value or threshold the risk is temporarily tolerable if accompanied by further measures for risk reduction and control. *Acceptable risk:* The acceptable risk defines the additional cancer risk of 4:10,000 that is accepted, meaning that, statistically, 4 out of 10,000 persons exposed to the substance throughout their working life will develop cancer. Beginning in 2013 until 2018 at the latest, the acceptable risk according to the AGS will be lowered to 4 out of 100,000 cases.

Quantitative risk characterisation

Considering the physicochemical properties of buta-1,3-diene and its industrial uses, workplace exposure occurs via inhalation. The registrants have provided an estimated $DMEL_{long\text{-}term,\ inhalation,\ systemic}$ of 1 ppm (2.21 mg/m^3) for occupational exposure. The calculation of excess leukaemia deaths (all cell types combined) based on a simple Cox regression model including a variety of assessment factors. According to the registrant, this results in a mortality rate from leukaemia of 0.39×10^{-4} which corresponds to approximately 4:100,000. This has also been proposed as the future acceptable limit for occupational risk in Germany (AGS, 2008).

However, in Germany, the AGS currently determined values for tolerable (4:1,000) and acceptable (4:10,000) risk for buta-1,3-diene with 2 ppm and 0.2 ppm, respectively (see Table 34). In the range between the tolerable and acceptable risk further measures of risk management are needed to minimise the occupational risk for the worker.

The eMSCA carried out an evaluation of both approaches, from registrant and AGS. The risk calculation of the registrant is not supported. Nevertheless, the proposed DMEL of 1 ppm (2.21 mg/m3) has been taken for risk assessment. Based on the registrants DMEL of 1 ppm the reported exposure values do not exceed this DMEL in general. Within the AGS concept the reported exposure values are between the tolerance level of 2 ppm and the acceptance level of 0.2 ppm. Due to the fact that the exposure values are closer to the acceptance level, both approaches lead to the conclusion that there is no need for further activities like the initiation of a restriction or an authorisation procedure.

Table 34: Exposure-risk relationship for buta-1,3-diene according to the derivation by Working Group "Limit Values and Classification of Carcinogenic and Mutagenic Substances" (AK CM) in view of the justification for an occupational exposure limit (OEL).

Buta-1,3-diene concentration, long-termin mean, 35-40 years of occupational exposure		Exposure-related lifetime leukaemia risk
ppm	µg/m³	
15	33,660	3%
5	11,220	1%
2	4,488	4 to 1,000
1	2,244	2 to 1,000
0.5	1,122	1 to 1,000
0.05	112	1 to 10,000
0.005	11	1 to 100,000

10.1.2 Consumers

Table 35: Risk characterisation for oral exposure of consumers.

For toddlers, a body weight of 14.5 kg has been used and for adults a body weight of 70 kg has been used.

Operation	Group	oral Expo-sure (µg/day)	Oral exposure (µg/kg b.w./day)	DMEL oral (µg/kg b.w./day)	Risk characterisation Ratio for oral Exposure
"leaching of free monomer from packaging into foodstuff"	Adults	15	0.2	0.43	0.47
	toddler	17	1.2	0.72	1.67

Exposure assessment based on the old data from EU-RAR (2002). The two main sources are from indoor air and from butadiene-based food packing materials The RCR for the oral exposure of consumers amounted to the value of 1.67 for toddlers.

However, the EU RAR based on the assumption that the maximum concentration of butadiene in foodstuffs in butadiene-based polymers is < 0.02 mg/kg, recent regulations (EU 10/2011) lowered concentration limits to a detection limit of < 0.01 mg/kg food. This is supported by the fact, that an inquiry of the data from the German food and commodity safety surveillance retrieved no data on 1,3-butadiene contents in food or commodities.

Based on the above mentioned regulatory measures no concern will be raised.

Table 36: Risk characterisation for inhalative exposure of consumers.

For toddlers, a respiration volume of 7 m^3/d (Guidance Table R15-16) has been used. For adults a respiration volume of 20 m^3/d has been used (Guidance Example R.8-1)

Operation	Group	Inhalative Exposure (µg/day)	Inhalative Exposure ($\mu g/m^3$)	DMEL for Inhalative Exposure – ($\mu g/m^3$)	Risk characterisation Ratio for Inhalative Exposure
"release of free monomer from polymeric consumer products (indoor air)"	Adults	36	1.80	1.50	1.20
	toddler	10	1.43	1.50	0.95

Exposure assessment based on the old data from EU-RAR (2002). It states "*consumer exposure may occur as a result of release of free monomer from polymeric consumer products*." "*The two main sources are from indoor air (primarily due to release from carpet backings) and from food packing materials.*" However, the influence of carpet backings was put into perspective with the statement "*the most recent information indicates that the release of free monomer from carpet backings is not detectable.*" Excluding data confounded by tobacco-smoke and due to limited data availability the inhalative exposure calculation was performed with data taken from one reference. The EU RAR (2002) states "*the only available measured data for the presence of monomer in indoor air suggest that indoor levels are generally below 2.2 µg/ m^3*." The inhalative exposure was calculated from this maximum, a respiration rate and an exposure time of 24 hours. Iterative factors (e.g. time balances) were not taken into account. Given, that butadiene concentrations in indoor air are influenced by more sources besides tobacco-smoke than regarded in the EU RAR and that the calculations in the EU RAR are based on a rough estimation with a simple equation it is concluded that the RCR values for inhalative exposure are an overestimation and will not lead to an unacceptable risk of the consumer.

Table 37: Risk characterisation for combined exposure from indoor air and leaching from packing into foodstuffs (reasonable worst case).

Operation	Group	exposure (µg/kg b.w./day)	DMEL transformed for oral Exposure– (µg/kg b.w./day)	Risk characterisation Ratio for combined Exposure
Combined exposure	Adults	0.7	0.43	1.63
	Toddler	1.9	0.72	2.64

Exposure assessment based on the old data from EU-RAR (2002). In adults the inhalative exposure has a dominant influence on the RCR leading to a RCR for the combined exposure of 1.63. Driven by the oral exposure of butadiene leached from packing into foodstuff, the RCR for the combined exposure of consumers amounted to the value of 2.64 for toddlers.

The part of the inhalative risk has been judged as an overestimation of the exposure values in the EU RAR.

Furthermore, the EU RAR based on the assumption that the maximum concentration of butadiene in foodstuffs in butadiene-based polymers is < 0.02 mg/kg, recent regulations (EU 10/2011) lowered concentration limits to a detection limit of < 0.01 mg/kg food. This is supported by the fact, that an inquiry of the data from the German food and commodity safety surveillance retrieved no data on 1,3-butadiene contents in food or commodities.

Therefore it is concluded that the exposure has been lowered by regulatory measures taken and no concern will be raised.

10.2 Environment

Not relevant for this evaluation.

11 OTHER INFORMATION

no other information

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13 ABBREVIATIONS

AGS - Committee for Hazardous Substances
AK CM – Working Group “Limit Values and Classification of Carcinogenic and Mutagenic Substances”
DNEL - derived no effect level
DMEL - derived minimal effect level
ERB - exposure-risk relationship
RCRs - risk characterisation ratios