OELs 6

Study on collecting the most recent information on substances to analyse health, socio-economic and environmental impacts in connection with possible amendments of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work

Final report V3

Isoprene

November 2024

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EUROPEAN COMMISSION

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LIST OF ABBREVIATIONS AND ACRONYMS

ACSH	Advisory Committee of Safety and Health at Work
AM	Arithmetic mean
ARN	Assessment of Regulatory Needs
AUC	Area Under the Curve
BAT	Best Available Technique
BGV	Biological guidance value
BLV	Biological Limit Value
BMD	Benchmark Dose Modelling
BR	Better Regulation
BREF	Best available techniques reference document
C&L	Classification & Labelling (inventory)
CAGR	Compound Annual Growth Rate
CAREX	Carcinogen Exposure (inventory)
CAS	Chemicals Abstracts Service
CBA	Cost Benefit Analysis
CDC	US Centre for Disease Control and Prevention
CEA	Cost Effectiveness Analysis
CEN	European Committee of Standardization
CLP	Classification, Labelling and Packaging of substances Regulation
CMRD	Carcinogens, Mutagens and Reproductive substances Directive
CNS	Central Nervous System
CSR	Chemical Safety Report
CSR	Chemical Safety Report
DALY	Disability Adjusted Life Years
DG	Directorate General
DNA	Deoxyribonucleic Acid
DNEL	*Derived no-effect level*
DRR	Dose Response Relationship
ECHA	European Chemicals Agency
EEA	European Economic Area
ERR	Exposure Risk Relationship
ES	Exposure Scenario
EUDR	EU Deforestation-Free regulation
FDB	Future Disease Burden
FID	Flame Ionisation Detection
FoBiG	Forschungs und Beratungsinstitut Gefahrstoffe
GD	Gestation Day
GESTIS	Internationale Grenzwerte für chemische Substanzenm (International limits for chemical substances)
GM	Geometric mean
IA	Impact Assessment
IARC	International Agency for Research of Cancer
IHME	Institute for Health Metrics and Evaluation
ISO	The International Organization for Standardization
LEV	Local Exhaust Ventilation
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest observed adverse effect level
LOD	Limit of Detection
LOQ	Limit of quantification
MCA	Multi-Criteria Analysis
MCV	Mean Cell Volume

NACE	"Nomenclature statistique des activités économiques dans la Communauté européenne" or the Statistical Classification of Economic Activities in the European Community
NOAEL	No observed adverse effect level
NOES	National Occupational Exposure Survey
OEL	Occupational Exposure Limit
OSH	Occupational Safety and Health
PAH	Polycyclic aromatic hydrocarbons
PBMC	Peripheral Blood Mononuclear Cell
PBPK	Physiologically based pharmacokinetic
PBT	Persistent, bio-accumulative, and toxic
PNEC	Predicted No Effect Concentrations
PPE	Personal Protection Equipment
PROC	The process categories
PT	Physiological Toxicokinetic
PV	Present Value
QALY	Quality-Adjusted Life Year
R&D	Research & Development
RAC	Committee for Risk Assessment
RBC	Red bloodcells
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RMM	Risk Management Measure
RMOA	Risk Management Option Analysis
RoI	Registry of restriction intentions
RPA	Risk & Policy Analysts
RPE	Respiratory Protective Equipment
SBR	Styrene Butadiene Rubber
SCOEL	Scientific Committee on Occupational Exposure Limits
SDG	Sustainable Development Goal
SEAC	Committee for Socio-Economic Analysis
SIEF	Substance Information Exchange Forums
SIS	Styrene Isoprene Styrene
SME	Small and Medium-sized Enterprise
STEL	Short Term Exposure Limit
TWA	Time Weighted Average
WCS	Worker Contributing Scenario
WPC	Working Party on Chemicals
WTP	Willingness to Pay

ABSTRACT EN-FR-DE

EN: This study supports the European Commission's Impact Assessment of a potential Occupational Exposure Limit (OEL) value for isoprene under the scope of Carcinogens, Mutagens and Reprotoxic substances Directive (CMRD, Directive 2004/37/EC). This report estimates costs and benefits for a range of potential OELs for isoprene. The monetised impacts relate primarily to the compliance costs of achieving the OEL and the avoided costs of ill health for conditions including liver cancer and the two non-cancer endpoints (degradation of olfactory epithelium and degeneration of spinal cord white matter). Isoprene in its monomeric form is used to manufacture rubber materials and an estimated 10,500 workers are exposed to isoprene monomer in the EU. Four reference OELs are assessed against the baseline: 1.3, 8.5, 40 and 129.4 mg/m^3. The cost benefit ratios for all policy options indicate higher costs than benefits, with no benefits estimated for any policy options as current exposure levels are not high enough to result in a case of ill health. All estimated impacts are minimal for the Committee for Risk Assessment (RAC) recommended OEL of 8.5 mg/m^3: the costs are €1.5 million over 40 years at this OEL and all estimates have low levels of uncertainty.

FR: Cette étude soutient l'analyse d'impact de la Commission européenne concernant une éventuelle valeur limite d'exposition professionnelle (LEP) pour l'isoprène dans le cadre de la directive sur les agents cancérigènes, mutagènes et toxiques pour la reproduction (CMRD, directive 2004/37/CE). Ce rapport estime les coûts et les avantages d'une série de valeurs limites d'exposition potentielles pour l'isoprène. Les impacts monétisés concernent principalement les coûts de mise en conformité pour atteindre la LEP et les coûts évités des problèmes de santé, notamment le cancer du foie et les deux paramètres non cancérigènes (dégradation de l'épithélium olfactif et dégénérescence de la substance blanche de la moelle épinière). L'isoprène sous sa forme monomère est utilisé pour fabriquer des matériaux en caoutchouc et on estime à 10 500 le nombre de travailleurs exposés à l'isoprène monomère dans l'UE. Quatre LEP de référence sont évaluées par rapport à la ligne de base : 1,3, 8,5, 40 et 129,4 mg/m^3. Les ratios coûts-avantages de toutes les options stratégiques indiquent des coûts plus élevés que les avantages, aucun avantage n'étant estimé pour aucune option stratégique étant donné que les niveaux d'exposition actuels ne sont pas suffisamment élevés pour entraîner un cas de mauvaise santé. Tous les impacts estimés sont minimes pour la LEP de 8,5 mg/m^3 recommandée par le CER : les coûts sont de 1,5 million d'euros sur 40 ans à cette LEP et toutes les estimations présentent de faibles niveaux d'incertitude.

DE: Diese Studie unterstützt die Folgenabschätzung der Europäischen Kommission für einen möglichen Grenzwert für die Exposition am Arbeitsplatz (AGW) für Isopren im Rahmen der Richtlinie über krebserzeugende, erbgutverändernde und fortpflanzungsgefährdende Stoffe (CMRD, Richtlinie 2004/37/EK). In diesem Bericht werden Kosten und Nutzen für eine Reihe potenzieller AGW-Werte für Isopren geschätzt. Die monetarisierten Auswirkungen beziehen sich in erster Linie auf die Kosten für die Einhaltung der AGW und die vermiedenen Kosten für Gesundheitsschäden, einschließlich Leberkrebs und die beiden nicht krebsbedingten Endpunkte (Schädigung des Riechepithels und Degeneration der weißen Substanz des Rückenmarks). Isopren in seiner monomeren Form wird zur Herstellung von Gummimaterialien verwendet, und schätzungsweise 10 500 Arbeitnehmer sind in der EU Isoprenmonomer ausgesetzt. Vier Referenzgrenzwerte werden im Vergleich zur Basislinie bewertet: 1,3, 8,5, 40 und 129,4 mg/m^3. Das Kosten-Nutzen-Verhältnis für alle Optionen zeigt, dass die Kosten höher sind als der Nutzen, wobei für keine Option ein Nutzen geschätzt wird, da die derzeitigen Expositionswerte nicht hoch genug sind, um zu einer Erkrankung zu führen. Alle geschätzten Auswirkungen sind minimal für den von RAC empfohlenen AGW von 8,5 mg/m^3: die Kosten belaufen sich auf 1,5 Mio. € über 40 Jahre bei diesem AGW, und alle Schätzungen weisen einen geringen Unsicherheitsgrad auf.

EXECUTIVE SUMMARY

The Carcinogens, Mutagens and Reprotoxic substances Directive (Directive 2004/37/EC), hereinafter the CMRD, protects workers from exposure to carcinogens, mutagens or reprotoxic substances at work. The aim of this study is to support the European Commission's Impact Assessment (IA) of a potential Occupational Exposure Limit (OEL) for isoprene.

Two sectors are analysed with one main factor considered in their selection. This selection criterion for identifying sectors is that the sector should be using isoprene in its monomeric form. This criterion was used as the major use of isoprene is the manufacture of rubber materials such as polyisoprene, butyl rubber or styrene-isoprene-styrene co-polymers. Once these rubber materials are synthesised from isoprene there is minimal/no potential for exposure to isoprene monomer and so sectors using polymeric forms of isoprene were screened out of the analysis. Additionally, a further consideration was to consider sectors which may have unintentional exposure to isoprene monomer. This resulted in the inclusion of more companies in the analysis but did not increase the number of sectors with exposure. Weak evidence was found for the inclusion of a further sector relating to the manufacture of fine/speciality chemicals. Consultation with key industry players highlighted that not enough evidence exists to support the use of isoprene for this sector and inclusion in the analysis.

The costs and benefits (relative to the baseline) estimated in this report for the different policy options are summarised in Table 0-1. The benefits are shown for both Method 1 and Method 2. The costs are for the present value (PV) over 40 years with a static discount rate of 3%. They assume a 5% turnover in staff. The cost benefit ratios below for each policy option indicate higher costs than benefits although relatively speaking both of these values are minimal and will have no perceivable impacts on industrial feasibility or avoided cases of ill health. At the RAC recommended OEL of 8.5 mg/m^3 the costs are €1.5 million over 40 years whilst the benefits are value at €0 as exposures are not high enough in any sector to result in a case of ill health.

Table 0-1 Summary of monetised costs and benefits (static discount rate, additional to the baseline) (millions)

Policy option	1.3 mg/m^3	8.5 mg/m^3	40.0 mg/m^3	129.4 mg/m^3
Total benefits M1	€ 0.00	€ 0.00	€ 0.00	€ 0.00
Total benefits M2	€ 0.00	€ 0.00	€ 0.00	€ 0.00
Total costs (€ millions)	€ 1.90	€ 1.50	€ 1.40	€ 1.30
Cost benefit ratio M1	1.90/0	1.50/0	1.40/0	1.30/0
Cost benefit ratio M2	1.90/0	1.50/0	1.40/0	1.30/ 0

*Notes: *Values relate to method 1 - method 2.*

Source: Study team.

The multi-criteria analysis summarising both the monetised and qualitative impacts is shown in Table 0-2.

Table 0-2 Multi-criteria analysis (all impacts over 40 years and additional to the baseline) per policy option

Impact	Stakeholders affected	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Direct costs – adjustment					
Risk management measures - first year	Companies	€ 0	€ 0	€ 0	€ 0
Risk management measures -recurrent	Companies	€ 0	€ 0	€ 0	€ 0
Risk management measures -discontinu-ations	Companies	€ 0	€ 0	€ 0	€ 0
Risk management measures -total	Companies	€ 0	€ 0	€ 0	€ 0
Risk management measures -total per company	Companies	€ 0	€ 0	€ 0	€ 0
Monitoring (sampling and analysis)	Companies	€ 0.50 million	€ 0.19 million	€ 0.14 million	€ 0.11 million
Transposition costs	Public sector	€ 1.30 million	€ 1.20 million	€ 1.10 million	€ 1.10 million
Direct costs - administrative					
Company cost of ad-ministration burden	Companies	€ 0.15 million	€ 0.11 million	€ 0.08 million	€ 0.05 million
Direct compliance costs – total					
Adjustment, monitor-ing and administration burden costs	Companies	€ 0.65 million	€ 0.30 million	€ 0.22 million	€ 0.16 million
Adjustment, monitor-ing and administration burden costs per com-pany	Companies	€ 0.008 mil-lion	€ 0.004 mil-lion	€ 0.003 mil-lion	€ 0.002 mil-lion
Direct costs - enforcement costs					
Enforcement costs	Public sector	Enforcement costs may arise as a result of ensuring compli-ance with new OELs however these costs are not estimated as they are specific to Member States individual inspection regime.			
Indirect costs - other					
Firms exiting the mar-ket - No. of company closures	Companies	0	0	0	0
Firms discontinuing at least a part of their business - %	Companies	0	0	0	0

Impact	Stakeholders affected	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Total compliance costs as % of turnover over 40 years (including discontinuations)	Companies	Up to 0.004% (Synthetic rubber manufacture – small companies)	Up to 0.002% (Synthetic rubber manufacture – small companies)	Up to 0.001% (Synthetic rubber manufacture – small/medium companies)	Up to 0.001% (Synthetic rubber manufacture – small/medium companies)
First year compliance costs as % of turnover over 40 years (excluding discontinuations)	Companies	Same as above	Same as above	Same as above	Same as above
Employment – Jobs lost	Workers & families	0	0	0	0
Employment – Social cost	Workers & families	€ 0	€ 0	€ 0	€ 0
International competitiveness	Companies	No impact	No impact	No impact	No impact
Consumers	Consumers	No impact	No impact	No impact	No impact
Internal market Lowest to highest OEL*	Companies	1 : 1	1 : 1	1 : 4.7	1 : 15.2
Specific MSs/regions - MSs that would have to change OELs	Public sector	All	AU, BE, BG, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK	AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PL, PT, RO, SE, SI, SK	AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PT, RO, SE, SI, SK
Regulation	Companies	€ 0	€ 0	€ 0	€ 0
Direct benefits – improved well-being - health					
Reduced cases of ill health – liver cancer	Workers & families	0	0	0	0
Reduced cases of ill health – degeneration of olfactory epithelium	Workers & families	0	0	0	0
Reduced cases of ill health – degeneration of spinal cord white matter	Workers & families	0	0	0	0
Ill health avoided, incl. intangible costs (M1 to M2)	Workers & families	€ 0	€ 0	€ 0	€ 0
Direct benefits – improved well-being - safety					

Impact	Stakeholders affected	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Avoided costs	Companies	€ 0	€ 0	€ 0	€ 0
Avoided costs	Public sector	€ 0	€ 0	€ 0	€ 0
EU policy agenda	All	Contribution to the EU Green Deal: Chemical Strategy towards a toxic-free environment			
Direct benefits – improved well-being - environmental					
Environmental releases	All	No direct or indirect impacts on the environment and environmental legislation will occur under any of the policy options.			
Direct benefits – market efficiency					
Level playing field	Companies	A harmonised OEL at EU level would help to ensure a level playing field between companies operating in different EU Member States. See row on 'internal market' for how harmonisation would occur at each policy option.			
Indirect benefits					
Administrative simplification	Companies	Should all Member States have a harmonised OEL this would reduce the administrative burden for companies with operations across multiple Member States. This reduction in administrative burden however would be less likely to have significant impacts in the case of isoprene due to the estimation that all companies already have relatively consistent operating processes which would not be influenced by the implementation of any of the policy options.			
Synergy	Companies	Synergistic reduction of risk to other chemicals via regulation of isoprene is not expected because no changes in RMMs or operating procedures would be introduced as a result of implementing any of the policy options. Isoprene risk was previously reduced via synergies from the implementation of the benzene OEL.			
Corporate Social Responsibility	Companies	No major impacts are expected on the perception of companies via meeting expectations around corporate social responsibility. This is due to the fact that if OELs for isoprene were to be implemented in the EU then companies would likely not introduce any new measures due to existing compliance. As such any wider benefits of building a good corporate reputation would not be applicable.			
Avoided cost of setting OEL	Public sector	€ 2.50 million	€ 2.40 million	€ 2.30 million	€ 2.20 million
Other impacts					
Recycling – loss of business	Recycling companies	No impacts are expected to be felt by recycling companies as a result of any of the policy options.			
Impacts on fundamental rights	All	Compulsory monitoring of isoprene levels will help to ensure that the fundamental right of workers to workplace environments which respect human health is reliably enforced.			

Impact	Stakeholders affected	1.3 mg/m^3	8.5 mg/m^3	40.0 mg/m^3	129.4 mg/m^3
Impacts on digitalisation	Companies	No impacts on digitalisation are expected.			
Contributions to the UN sustainable development goals	All	In relation to the third sustainable development goal – "*good health and wellbeing - improved worker and family health*" – the above comment for impacts on fundamental rights also applies.			

*Notes: * This row indicates the ratio between the lowest national EU OEL and the OEL that would be introduced at each policy option, therefore describing the ratio of harmonisation of OELs for isoprene in the EU.*

Notes: May not sum to total due to rounding.

Source: Study team.

When considering the findings of the Multi-Criteria Analysis (MCA) in relation to the Cost Benefit Analysis (CBA) in the tables above, the quantified cost values do not change, however monetised indirect benefits in the MCA do result in an increase in the quantified benefits value for each policy option. This increase is attributed to the avoided costs that would be incurred by Member States to introduce a national OEL for isoprene and so the value is dependent on the assumption that all Member States would want to set a national OEL.

In general, the findings of this report for the introduction of OELs for isoprene do not have many associated uncertainties or issues. The findings indicate that very low impacts will be experienced as a result of OELs introduction and only low levels of uncertainty are associated around these values.

In the consultation stage, a major trade association for industrial isoprene users highlighted that industry members support and are confident in their ability to meet the RAC opinion level of 8.5 mg/m^3 whilst they also believed that investigating below this limit is not scientifically accurate. This is grounded in the fact that the RAC opinion value was not derived via an ERR but instead by the endogenous isoprene concentrations which are naturally occurrent in humans. As such the industry association argued that extrapolation downwards of this value to 1.3 mg/m^3 would not be scientifically accurate. Given however that isoprene is a non-threshold carcinogen it can be argued that any additional exposure above that of endogenous concentration will correlate to (albeit small) increases in risk.

In the current study the study team were able to use the same data sources as those stated in the RAC opinion to derive an Exposure Risk Relationship (ERR) for isoprene which in turn would allow extrapolation down to the 1.3 mg/m^3 value. There is some uncertainty in the gradient of the calculated ERR due to metabolic differences between tested animals and humans meaning that in some cases conservative assumptions were made and as such the benefits of this study may be slightly overestimated despite resulting in no cases of ill health.

Given this dispute it should acknowledged that whilst the findings of this study indicate no impacts across any of the policy options, industry would be most in favour of the 8.5 mg/m^3 level.

Résumé Exécutif

La directive sur les agents cancérigènes, mutagènes et toxiques pour la reproduction (directive 2004/37/CE), ci-après dénommée CMRD, protège les travailleurs contre l'exposition à des agents cancérigènes, mutagènes ou toxiques pour la reproduction sur le lieu de travail. L'objectif de cette étude est de soutenir l'analyse d'impact (IA) de la Commission européenne concernant une éventuelle limite d'exposition professionnelle (LEP) pour l'isoprène.

Deux secteurs sont analysés avec un facteur principal pris en compte dans leur sélection. Ce critère de sélection pour l'identification des secteurs est que le secteur doit utiliser l'isoprène sous sa forme monomère. Ce critère a été retenu car la principale utilisation de l'isoprène est la fabrication de matériaux en caoutchouc tels que le polyisoprène, le caoutchouc butyle ou les copolymères styrène-isoprène-styrène. Une fois que ces matériaux en caoutchouc sont synthétisés à partir de l'isoprène, le potentiel d'exposition au monomère d'isoprène est minime, voire nul, et les secteurs utilisant des formes polymères d'isoprène ont donc été exclus de l'analyse. En outre, une autre considération a été de prendre en compte les secteurs susceptibles d'être exposés involontairement à l'isoprène monomère. Cela a permis d'inclure davantage d'entreprises dans l'analyse, mais n'a pas augmenté le nombre de secteurs exposés. L'inclusion d'un autre secteur relatif à la fabrication de produits chimiques fins/spécialisés n'a pas été étayée par des preuves suffisantes. La consultation des principaux acteurs de l'industrie a montré qu'il n'existait pas suffisamment de preuves pour justifier l'utilisation de l'isoprène dans ce secteur et son inclusion dans l'analyse.

Les coûts et les bénéfices (par rapport à la situation de référence) estimés dans le présent rapport pour les différentes LEP cibles sont résumés dans le tableau 1. Les bénéfices sont indiqués à la fois pour la méthode 1 et la méthode 2. Les coûts correspondent à la valeur actuelle sur 40 ans avec un taux d'actualisation statique de 3 %. Ils supposent une rotation du personnel de 5 %. Les ratios coûts-avantages ci-dessous pour chaque option politique indiquent des coûts plus élevés que les avantages, bien que ces deux valeurs soient relativement minimes et n'aient pas d'impact perceptible sur la faisabilité industrielle ou les cas de maladie évités. Pour la LEP de 8,5 mg/m^3 recommandée par le CER, les coûts s'élèvent à 1,5 million d'euros sur 40 ans, tandis que les avantages sont évalués à 0 euro, car les expositions ne sont pas suffisamment élevées dans aucun secteur pour entraîner un cas de mauvaise santé.

Table 0-1 Résumé des coûts et bénéfices monétisés (taux d'actualisation statique, en plus du scénario de référence) (millions)

Option politique	1,3 mg/m^3	8,5 mg/m^3	40,0 mg/m^3	129,4 mg/m^3
Total des bénéfices M1	€ 0,00	€ 0,00	€ 0,00	€ 0,00
Total des bénéfices M2	€ 0,00	€ 0,00	€ 0,00	€ 0,00
Total des coûts (€ millions)	€ 1,90	€ 1,50	€ 1,40	€ 1,30
Rapport coût-bénéfice M1	1,90/0	1,50/0	1,40/0	1,30/0
Rapport coût-bénéfice M2	1,90/0	1,50/0	1,40/0	1,30/0

Notes : Les valeurs se rapportent à la méthode 1 - méthode 2.

Source : Équipe d'étude.

L'analyse multicritère résumant les impacts monétaires et qualitatifs est présentée dans le tableau 0-2.

Table 0-2 Analyse multicritères (tous les impacts sur 40 ans et supplémentaires par rapport à la ligne de base) par option LEP

Impact	Acteurs concernés	1,3 mg/m³	8,5 mg/m³	40,0 mg/m³	129,4 mg/m³
Coûts directs - ajustement					
Mesures de gestion des risques - première année	Entreprises	€ 0	€ 0	€ 0	€ 0
Mesures de gestion des risques - récurrent	Entreprises	€ 0	€ 0	€ 0	€ 0
Mesures de gestion des risques - cessations d'activité	Entreprises	€ 0	€ 0	€ 0	€ 0
Mesures de gestion des risques – total	Entreprises	€ 0	€ 0	€ 0	€ 0
Mesures de gestion des risques – total par entreprise	Entreprises	€ 0	€ 0	€ 0	€ 0
Surveillance (échantillonnage et analyse)	Entreprises	€ 0,50 million	€ 0,19 million	€ 0,14 million	€ 0,11 million
Coûts de transposition	Secteur public	€ 1,30 million	€ 1,20 million	€ 1,10 million	€ 1,10 million
Coûts directs - administratifs					
Coût de la charge administrative pour l'entreprise	Entreprises	€ 0,15 million	€ 0,11 million	€ 0,08 million	€ 0,05 million
Coûts directs de mise en conformité - total					
Frais d'ajustement, de contrôle et de gestion	Entreprises	€ 0,65 million	€ 0,30 million	€ 0,22 million	€ 0,16 million
Coûts de la charge d'ajustement, de suivi et d'administration par entreprise	Entreprises	€ 0,008 million	€ 0,004 million	€ 0,003 million	€ 0,002 million
Coûts directs - coûts d'exécution					
Frais d'exécution	Secteur public	Des coûts de mise en œuvre peuvent résulter de la mise en conformité avec les nouvelles LEP, mais ces coûts ne sont pas estimés car ils sont spécifiques au régime d'inspection de chaque État membre.			
Coûts indirects - autres					
Entreprises quittant le marché - Nombre de	Entreprises	0	0	0	0

Impact	Acteurs concernés	1,3 mg/m³	8,5 mg/m³	40,0 mg/m³	129,4 mg/m³
fermetures d'entreprises					
Entreprises cessant au moins une partie de leurs activités - en %.	Entreprises	0	0	0	0
Total des coûts de mise en conformité en % du chiffre d'affaires sur 40 ans (y compris les cessations d'activité)	Entreprises	Up to 0,004% (Fabrication de caoutchouc synthétique - petites entreprises)	Up to 0,002% (Fabrication de caoutchouc synthétique - petites entreprises)	Up to 0,001% (Fabrication de caoutchouc synthétique - petites/moyennes entreprises)	Up to 0,001% (Fabrication de caoutchouc synthétique - petites/moyennes entreprises)
Coûts de mise en conformité pour la première année en % du chiffre d'affaires sur 40 ans (à l'exclusion des cessations d'activité)	Entreprises	Identique au précédent	Identique au précédent	Identique au précédent	Identique au précédent
Emploi - Emplois perdus	Travailleurs et familles	0	0	0	0
Emploi - Coût social	Travailleurs et familles	€ 0	€ 0	€ 0	€ 0
Compétitivité internationale	Entreprises	Aucun impact	Aucun impact	Aucun impact	Aucun impact
Consommateurs	Entreprises	Aucun impact	Aucun impact	Aucun impact	Aucun impact
Marché intérieur De la plus basse à la plus haute LIEP*	Entreprises	1 : 1	1 : 1	1 : 4.7	1 : 15.2
États membres/régions spécifiques - États membres qui devraient modifier les LEP	Secteur public	Tous	AU, BE, BG, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK	AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PL, PT, RO, SE, SI, SK	AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PT, RO, SE, SI, SK
Règlement	Entreprises	€ 0	€ 0	€ 0	€ 0
Avantages directs - amélioration du bien-être et de la santé					
Réduction des cas de maladie – (cancer du foie)	Travailleurs et familles	0	0	0	0
Réduction des cas de mauvaise santé – (dégénérescence de l'épithélium olfactif)	Travailleurs et familles	0	0	0	0

Impact	Acteurs concernés	1,3 mg/m³	8,5 mg/m³	40,0 mg/m³	129,4 mg/m³
Réduction des cas de maladie – (dégénérescence de la substance blanche de la moelle épinière)	Travailleurs et familles	0	0	0	0
Maladies évitées, y compris les coûts intangibles (M1 à M2)	Travailleurs et familles	€ 0	€ 0	€ 0	€ 0
Avantages directs - amélioration du bien-être - sécurité					
Coûts évités	Entreprises	€ 0	€ 0	€ 0	€ 0
Coûts évités	Secteur public	€ 0	€ 0	€ 0	€ 0
Agenda politique de l'UE	Tous	Toutes les contributions au Green Deal de l'UE : Stratégie chimique pour un environnement sans substances toxiques			
Avantages directs - amélioration du bien-être - environnement					
Rejets environnementaux	Tous	Aucune des options politiques n'aura d'incidence directe ou indirecte sur l'environnement et la législation environnementale.			
Avantages directs - efficacité du marché					
Des conditions de concurrence équitables	Entreprises	Des LEP harmonisé au niveau de l'UE contribuerait à garantir des conditions de concurrence équitables entre les entreprises opérant dans différents États membres de l'UE. Voir la ligne sur le "marché intérieur" pour savoir comment l'harmonisation se ferait pour chaque option politique.			
Avantages indirects					
Simplification administrative	Entreprises	Si tous les États membres disposaient d'un LEP harmonisé, cela réduirait la charge administrative pour les entreprises qui exercent leurs activités dans plusieurs États membres. Cette réduction de la charge administrative serait toutefois moins susceptible d'avoir des effets significatifs dans le cas de l'isoprène, car on estime que toutes les entreprises ont déjà des processus opérationnels relativement cohérents qui ne seraient pas influencés par la mise en œuvre de l'une ou l'autre des options stratégiques.			
Synergie	Entreprises	On ne s'attend pas à une réduction synergique des risques liés à d'autres substances chimiques par le biais de la réglementation de l'isoprène, car la mise en œuvre de l'une ou l'autre des options stratégiques n'entraînerait aucune modification des RMM ou des procédures opérationnelles. Le risque lié à l'isoprène a déjà été réduit grâce aux synergies résultant de la mise en œuvre de la VLEP pour le benzène.			
Responsabilité sociale des entreprises	Entreprises	Aucun impact majeur n'est attendu sur la perception des entreprises en ce qui concerne la satisfaction des attentes en matière de responsabilité sociale des entreprises. Cela s'explique par le fait que si des NAEO pour l'isoprène devaient être mises en œuvre dans l'UE, les entreprises n'introduiraient probablement pas de nouvelles mesures en raison de			

Impact	Acteurs concernés	1,3 mg/m³	8,5 mg/m³	40,0 mg/m³	129,4 mg/m³
		leur conformité actuelle. Par conséquent, les avantages plus larges liés à la construction d'une bonne réputation d'entreprise ne seraient pas applicables.			
Coût évité de la mise en place de la LEP	Secteur public	€ 2,50 million	€ 2,40 million	€ 2,30 million	€ 2,20 million
Autres impacts					
Recyclage - perte d'activité	Entreprises de recyclage	Aucune des options stratégiques ne devrait avoir d'incidence sur les entreprises de recyclage.			
Impacts sur les droits fondamentaux	Tous	La surveillance obligatoire des niveaux d'isoprène contribuera à garantir que le droit fondamental des travailleurs à des environnements de travail respectueux de la santé humaine est appliqué de manière fiable.			
Impacts sur la numérisation	Entreprises	Aucun impact sur la numérisation n'est attendu.			
Contributions aux objectifs de développement durable des Nations unies	Tous	En ce qui concerne le troisième objectif de développement durable - "bonne santé et bien-être - amélioration de la santé des travailleurs et des familles" - le commentaire ci-dessus concernant les incidences sur les droits fondamentaux s'applique également.			

Notes : Cette ligne indique le rapport entre la LEP nationale la plus basse de l'UE et la LEP qui serait introduite pour chaque option politique, décrivant ainsi le ratio d'harmonisation des VLEP pour l'isoprène dans l'UE.

Notes: Les chiffres ayant été arrondis, il est possible que leur somme ne corresponde pas exactement au total indiqué.

Source : Équipe de l'étude.

Lorsque l'on examine les conclusions de l’analyse multicritères par rapport à l'analyse coûts-avantages dans les tableaux ci-dessus, les valeurs des coûts quantifiés ne changent pas, mais les avantages indirects monétisés dans l’analyse multicritères entraînent une augmentation de la valeur des avantages quantifiés pour chaque option politique. Cette augmentation est attribuée aux coûts évités qui seraient encourus par les États membres pour introduire des LEP nationaux pour l'isoprène et la valeur dépend donc de l'hypothèse selon laquelle tous les États membres voudraient fixer un LEP national.

En général, les conclusions de ce rapport concernant l'introduction des LEP pour l'isoprène n'ont pas beaucoup d'incertitudes ou de problèmes associés. Les résultats indiquent que l'introduction des LEP n'aura que très peu d'incidences et que ces valeurs ne sont associées qu'à de faibles niveaux d'incertitude.

Lors de la phase de consultation, une importante association commerciale d'utilisateurs industriels d'isoprène a souligné que les membres de l'industrie soutiennent et sont confiants dans leur capacité à respecter le niveau d'opinion du CER de 8,5 mg/m³, tout en estimant qu'enquêter en dessous de cette limite n'est pas scientifiquement exact. Cela s'explique par le fait que la valeur de l'avis du CER n'est pas dérivée d'une relation entre exposition et risque mais plutôt des concentrations endogènes d'isoprène qui sont naturellement présentes chez l'homme. L'association industrielle a donc fait valoir que l'extrapolation vers le bas de cette valeur à 1,3 mg/m³ ne serait pas scientifiquement exacte. Toutefois, étant donné que l'isoprène est un cancérogène sans seuil, on peut affirmer que toute exposition supplémentaire au-delà de la concentration endogène se traduira par une augmentation (bien que faible) du risque.

Dans l'étude actuelle, l'équipe d'étude a pu utiliser les mêmes sources de données que celles mentionnées dans l'avis du CER pour calculer une relation entre exposition et risque pour l'isoprène, ce qui permettrait d'extrapoler jusqu'à la valeur de 1,3 mg/m^3. Il existe une certaine incertitude dans le gradient de la relation entre exposition et risque calculé en raison des différences métaboliques entre les animaux testés et les humains, ce qui signifie que dans certains cas, des hypothèses conservatrices ont été faites et que, par conséquent, les avantages de cette étude peuvent être légèrement surestimés bien qu'elle n'ait donné lieu à aucun cas de mauvaise santé.

Compte tenu de ce différend, il convient de reconnaître que si les conclusions de cette étude n'indiquent aucun impact pour l'une ou l'autre des options politiques, l'industrie serait plus favorable au niveau de 8,5 mg/m^3.

Kurzfassung

Die Richtlinie über krebserzeugende, erbgutverändernde und fortpflanzungsgefährdende Stoffe (Richtlinie 2004/37/EC), im Folgenden CMRD genannt, schützt Arbeitnehmer vor der Exposition gegenüber krebserzeugenden, erbgutverändernden oder fortpflanzungsgefährdenden Stoffen bei der Arbeit. Ziel dieser Studie ist es, die Folgenabschätzung der Europäischen Kommission für einen möglichen Grenzwert für die Exposition am Arbeitsplatz (OEL) für Isopren zu unterstützen.

Es werden zwei Sektoren analysiert, wobei ein Hauptfaktor bei ihrer Auswahl berücksichtigt wird. Das Auswahlkriterium für die Identifizierung der Sektoren ist, dass der Sektor Isopren in seiner monomeren Form verwendet werden sollte. Dieses Kriterium wurde verwendet, da die Hauptverwendung von Isopren in der Herstellung von Gummimaterialien wie Polyisopren, Butylkautschuk oder Styrol-Isopren-Styrol-Copolymeren besteht. Sobald diese Gummimaterialien aus Isopren synthetisiert sind, besteht nur noch ein minimales/kein Potenzial für eine Exposition gegenüber Isoprenmonomer, so dass Sektoren, die polymere Formen von Isopren verwenden, von der Analyse ausgeschlossen wurden. Eine weitere Überlegung bestand darin, Sektoren zu berücksichtigen, in denen eine unbeabsichtigte Exposition gegenüber Isoprenmonomeren möglich ist. Dies führte dazu, dass mehr Unternehmen in die Analyse einbezogen wurden, aber die Anzahl der Sektoren mit Exposition nicht erhöht wurde. Für die Einbeziehung eines weiteren Sektors, der sich auf die Herstellung von Fein-/Spezialchemikalien bezieht, wurden schwache Hinweise gefunden. Die Konsultation der wichtigsten Industrieakteure ergab, dass es nicht genügend Beweise gibt, um die Verwendung von Isopren in diesem Sektor und die Aufnahme in die Analyse zu unterstützen.

Die in diesem Bericht für die verschiedenen Ziel-OEL geschätzten Kosten und Nutzen (im Vergleich zum Ausgangswert) sind in Tabelle 0-1 zusammengefasst. Der Nutzen ist sowohl für Methode 1 als auch für Methode 2 angegeben. Die Kosten beziehen sich auf den Gegenwartswert (PV) über 40 Jahre mit einem statischen Abzinsungssatz von 3 %. Sie gehen von einer Personalfluktuation von 5 % aus. Die nachstehenden Kosten-Nutzen-Verhältnisse für jede Option zeigen, dass die Kosten höher sind als der Nutzen, obwohl beide Werte relativ gesehen minimal sind und keine spürbaren Auswirkungen auf die industrielle Durchführbarkeit oder vermiedene Krankheitsfälle haben werden. Bei dem von RAC empfohlenen Grenzwert von 8,5 mg/m^3 belaufen sich die Kosten auf 1,5 Mio. € über einen Zeitraum von 40 Jahren, während der Nutzen mit 0 € veranschlagt wird, da die Exposition in keinem Sektor hoch genug ist, um zu einem Krankheitsfall zu führen.

Table 0-1 *Zusammenfassung der monetarisierten Kosten und des Nutzens (statischer Abzinsungssatz, zusätzlich zum Basisszenario) (in Millionen €)*

Option	1,3 mg/m³	8,5 mg/m³	40,0 mg/m³	129,4 mg/m³
Gesamtnutzen M1	€ 0,00	€ 0,00	€ 0,00	€ 0,00
Gesamtnutzen M2	€ 0,00	€ 0,00	€ 0,00	€ 0,00
Gesamtkosten (Millionen €)	€ 1,90	€ 1,50	€ 1,40	€ 1,30
Kosten-Nutzen-Verhältnis M1	1,90/0	1,50/0	1,40/0	1,30/0
Kosten-Nutzen-Verhältnis M2	1,90/0	1,50/0	1,40/0	1,30/0

Anmerkungen: Werte beziehen sich auf Methode 1 - Methode 2.

Quelle: Studienteam.

Die multikriterielle Analyse, die sowohl die monetären als auch die qualitativen Auswirkungen zusammenfasst, ist in Tabelle 0-2 dargestellt.

Tabelle 0-2 Multikriterienanalyse (alle Auswirkungen über 40 Jahre und zusätzlich zum Bassisszenario) per AGW-Option

Auswirkungen	Betroffene Stakeholders	1,3 mg/m³	8,5 mg/m³	40,0 mg/m³	129,4 mg/m³
Direkte Kosten – Anpassung					
Risikomanagement-maßnahmen - erstes Jahr	Unternehmen	€ 0	€ 0	€ 0	€ 0
Risikomanagement-maßnahmen – wiederkehrend	Unternehmen	€ 0	€ 0	€ 0	€ 0
Risikomanagement-maßnahmen – Unter-brechung	Unternehmen	€ 0	€ 0	€ 0	€ 0
Risikomanagement-maßnahmen – gesamt	Unternehmen	€ 0	€ 0	€ 0	€ 0
Risikomanagement-maßnahmen - gesamt pro Unternehmen	Unternehmen	€ 0	€ 0	€ 0	€ 0
Luftüberwachung (Probenahme und An-alyse)	Unternehmen	€ 0.50 Millionen	€ 0.19 Millionen	€ 0.14 Millionen	€ 0.11 Mil-lionen
Umsetzungskosten	Öffentlicher Sektor	€ 1.30 Millionen	€ 1.20 Millionen	€ 1.10 Millionen	€ 1.10 Mil-lionen
Direkte Kosten – Verwaltung					
Kosten des Unterneh-mens für den Verwal-tungsaufwand	Unternehmen	€ 0.15 Millionen	€ 0.11 Millionen	€ 0.08 Millionen	€ 0.05 Mil-lionen

Auswirkungen	Betroffene Stakeholders	1,3 mg/m³	8,5 mg/m³	40,0 mg/m³	129,4 mg/m³
Direkte Kosten – Einhaltung der Vorschriften (Compliance) gesamt					
Kosten für Anpassung, Überwachung und Verwaltungsaufwand	Unternehmen	€ 0.65 Millionen	€ 0.30 Millionen	€ 0.22 Millionen	€ 0.16 Millionen
Kosten für Anpassung, Überwachung und Verwaltungsaufwand pro Unternehmen	Unternehmen	€ 0.008 Millionen	€ 0.004 Millionen	€ 0.003 Millionen	€ 0.002 Millionen
Direkte Kosten - Durchsetzungskosten (enforcement)					
Durchsetzungskosten außer Umsetzung	Öffentlicher Sektor	Die Kosten für die Durchsetzung der neuen OEL können sich aus der Einhaltung der neuen Grenzwerte ergeben. Diese Kosten werden jedoch nicht geschätzt, da sie vom jeweiligen Inspektionssystem des Mitgliedstaats abhängen.			
Indirekte Kosten - Sonstige					
Unternehmen, die zumindest einen Teil ihrer Geschäftsfähigkeit aufgeben – Anzahl der Unternehmensschließungen	Unternehmen	0	0	0	0
Unternehmen, die zumindest einen Teil ihrer Geschäftsfähigkeit aufgeben - %	Unternehmen	0	0	0	0
Gesamtkosten für die Einhaltung der Vorschriften in % des Umsatzes über 40 Jahre (einschließlich Einstellung des Betriebs)	Unternehmen	Bis zu 0,004% (Herstellung von synthetischem Kautschuk - kleine Unternehmen)	Bis zu 0,002% (Herstellung von synthetischem Kautschuk - kleine Unternehmen)	Bis zu 0,001% (Herstellung von synthetischem Kautschuk – kleine/mittlere Unternehmen)	Bis zu 0,001% (Herstellung von synthetischem Kautschuk – kleine/mittlere Unternehmen)
Kosten für die Einhaltung der Vorschriften im ersten Jahr in % des Jahresumsatzes (ohne Einstellung des Betriebs)	Unternehmen	Wie oben beschreiben	Wie oben beschreiben	Wie oben beschreiben	Wie oben beschreiben
Beschäftigung - verlorene Arbeitsplätze	Arbeitnehmer & Familien	0	0	0	0
Beschäftigung - Soziale Kosten	Arbeitnehmer & Familien	€ 0	€ 0	€ 0	€ 0
Internationale Wettbewerbsfähigkeit	Unternehmen	Keine Auswirkungen	Keine Auswirkungen	Keine Auswirkungen	Keine Auswirkungen
Verbraucher	Verbraucher	Keine Auswirkungen	Keine Auswirkungen	Keine Auswirkungen	Keine Auswirkungen

Auswirkungen	Betroffene Stakeholders	1,3 mg/m³	8,5 mg/m³	40,0 mg/m³	129,4 mg/m³
Binnenmarkt Niedrigster bis höchster AGW	Unternehmen	1 : 1	1 : 1	1 : 4.7	1 : 15.2
Spezifische Mitgliedstaaten/Regionen – Mitgliedstaaten, die AGWs ändern müssten	Öffentlicher Sektor	Alle	AU, BE, BG, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK	AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PL, PT, RO, SE, SI, SK	AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PT, RO, SE, SI, SK
Verordnung	Unternehmen	€ 0	€ 0	€ 0	€ 0
Direkte Nutzen – verbessertes Wohlbefinden - Gesundheit					
Geringere Krankheitsfälle (Leberkrebs)	Arbeitnehmer & Familien	0	0	0	0
Geringere Krankheitsfälle (Degeneration des Riechepithels)	Arbeitnehmer & Familien	0	0	0	0
Geringere Krankheitsfälle (Degeneration der weißen Substanz des Rückenmarksz)	Arbeitnehmer & Familien	0	0	0	0
Krankheitsfälle vermieden, einschließlich immaterieller Kosten (M1 bis M2)	Arbeitnehmer & Familien	€ 0	€ 0	€ 0	€ 0
Direkte Nutzen – verbessertes Wohlbefinden - Sicherheit					
Vermiedene Kosten	Unternehmen	€ 0	€ 0	€ 0	€ 0
Vermiedene Kosten	Öffentlicher Sektor	€ 0	€ 0	€ 0	€ 0
Politische Agenda der EU	Alle	Beitrag zum EU Green Deal: Chemische Strategie für eine giftfreie Umwelt			
Direkte Vorteile - verbessertes Wohlbefinden - Umwelt					
Freisetzungen in die Umwelt	Alle	Keine der politischen Optionen wird direkte oder indirekte Auswirkungen auf die Umwelt und das Umweltrecht haben.			
Direkte Vorteile - Markteffizienz					
Gleiche Ausgangsbedingungen	Unternehmen	Ein harmonisierter OEL auf EU-Ebene würde dazu beitragen, gleiche Wettbewerbsbedingungen für die in verschiedenen EU-Mitgliedstaaten tätigen Unternehmen zu gewährleisten. In der Zeile "Interner Markt" wird erläutert, wie die Harmonisierung bei den einzelnen politische Optionen erfolgen würde.			
Indirekte Nutzen					

Auswirkungen	Betroffene Stakeholders	1,3 mg/m³	8,5 mg/m³	40,0 mg/m³	129,4 mg/m³
Vereinfachung der Verwaltung	Unternehmen	Sollten alle Mitgliedstaaten einen harmonisierten OEL haben, würde dies den Verwaltungsaufwand für Unternehmen, die in mehreren Mitgliedstaaten tätig sind, verringern. Diese Verringerung des Verwaltungsaufwands hätte jedoch im Fall von Isopren wahrscheinlich keine nennenswerten Auswirkungen, da davon ausgegangen wird, dass alle Unternehmen bereits über relativ einheitliche Betriebsabläufe verfügen, die durch die Umsetzung einer der politischen Optionen nicht beeinflusst würden.			
Synergie	Unternehmen	Eine synergetische Verringerung des Risikos für andere Chemikalien durch die Regulierung von Isopren ist nicht zu erwarten, da die Umsetzung einer der Optionen keine Änderungen der Risikomanagementmaßnahmen oder Betriebsverfahren mit sich bringen würde. Das Isopren-Risiko wurde bereits zuvor durch Synergien aus der Umsetzung des Benzol-OEL reduziert.			
Soziale Verantwortung der Unternehmen	Unternehmen	Es werden keine größeren Auswirkungen auf die Wahrnehmung der Unternehmen durch die Erfüllung der Erwartungen im Bereich der sozialen Verantwortung der Unternehmen erwartet. Dies liegt daran, dass die Unternehmen im Falle der Einführung von OEL für Isopren in der EU wahrscheinlich keine neuen Maßnahmen einführen würden, da sie die Vorschriften bereits erfüllen. Daher würden alle weitergehenden Vorteile, die sich aus dem Aufbau eines guten Rufs des Unternehmens ergeben, nicht zum Tragen kommen.			
Vermeidete Kosten der Festlegung eines AGW	Öffentlicher Sektor	€ 2.50 Millionen	€ 2.40 Millionen	€ 2.30 Millionen	€ 2.20 Millionen
Andere Auswirkungen					
Recycling - Verlust von Geschäftsmöglichkeiten	Recycling-Unternehmen	Es wird erwartet, dass keine der politischen Optionen Auswirkungen auf die Recyclingunternehmen haben wird.			
Auswirkungen auf die Grundrechte	Alle	Die obligatorische Überwachung der Isoprenwerte wird dazu beitragen, dass das Grundrecht der Arbeitnehmer auf ein gesundheitsgerechtes Arbeitsumfeld zuverlässig durchgesetzt wird.			
Auswirkungen auf die Digitalisierung	Unternehmen	Es werden keine Auswirkungen auf die Digitalisierung erwartet.			
Beiträge zu den UN-Zielen für nachhaltige Entwicklung	Alle	In Bezug auf das dritte Ziel für nachhaltige Entwicklung - "Gesundheit und Wohlbefinden - Verbesserung der Gesundheit von Arbeitnehmern und Familien" - gilt der obige Kommentar zu den Auswirkungen auf die Grundrechte ebenfalls.			

Anmerkungen: Die Summe kann sich aufgrund von Auf- bzw. Abrunden von der Gesamtsumme unterscheiden.

Quelle: Studienteam.

Betrachtet man die Ergebnisse der MCA in Bezug auf die KNA in den obigen Tabellen, so ändern sich die quantifizierten Kostenwerte nicht, jedoch führt der monetarisierte indirekte Nutzen in der MCA zu einem Anstieg des quantifizierten Nutzenwertes für jede politische Option. Dieser Anstieg ist auf die vermiedenen Kosten zurückzuführen, die den Mitgliedstaaten bei der Einführung eines nationalen OEL für Isopren entstehen würden, so dass der Wert von der Annahme abhängt, dass alle Mitgliedstaaten einen nationalen OEL festlegen wollen.

Im Allgemeinen sind die Ergebnisse dieses Berichts für die Einführung von OEL für Isopren nicht mit vielen Unsicherheiten oder Problemen verbunden. Die Ergebnisse deuten darauf hin, dass die Einführung von OELs nur sehr geringe Auswirkungen haben wird und nur geringe Unsicherheiten mit diesen Werten verbunden sind.

In der Konsultationsphase betonte ein großer Handelsverband für industrielle Isopren-Verwender, dass die Mitglieder der Industrie den RAC-Gutachtenwert von 8,5 mg/m^3 unterstützen und zuversichtlich sind, dass sie ihn einhalten können, während sie gleichzeitig der Meinung sind, dass Untersuchungen unterhalb dieses Grenzwertes wissenschaftlich nicht korrekt sind. Dies liegt darin begründet, dass der RAC-Gutachtenwert nicht über eine ERR abgeleitet wurde, sondern durch die endogenen Isoprenkonzentrationen, die beim Menschen natürlich vorkommen. Daher argumentierte der Industrieverband, dass eine Extrapolation dieses Wertes auf den unteren Wert von 1,3 mg/m^3 wissenschaftlich nicht korrekt sei. Da es sich bei Isopren jedoch um ein Karzinogen ohne Schwellenwert handelt, kann argumentiert werden, dass jede zusätzliche Exposition oberhalb der endogenen Konzentration mit einem (wenn auch geringen) Anstieg des Risikos einhergeht.

In der aktuellen Studie konnte das Studienteam dieselben Datenquellen wie in der Stellungnahme des Regionalen Beirats verwenden, um eine ERR für Isopren abzuleiten, die wiederum eine Extrapolation auf den Wert von 1,3 mg/m^3 ermöglicht. Der Gradient der berechneten ERR ist aufgrund der Unterschiede im Stoffwechsel von Versuchstieren und Menschen mit einer gewissen Unsicherheit behaftet, was bedeutet, dass in einigen Fällen konservative Annahmen getroffen wurden, so dass der Nutzen dieser Studie möglicherweise leicht überschätzt wird, obwohl sie zu keinen Krankheitsfällen führte.

In Anbetracht dieses Streits sollte eingeräumt werden, dass die Ergebnisse dieser Studie zwar für keine der politischen Optionen Auswirkungen erkennen lassen, die Industrie jedoch am ehesten den Wert von 8,5 mg/m^3 befürworten würde.

1 INTRODUCTION

This chapter comprises the following sections:

- Section 1.1: Political and legal context;
- Section 1.2: Background; and
- Section 1.3: The study.

1.1 Political and legal context

1.1.1 The Carcinogens, Mutagens and Reprotoxic substances Directive

The Carcinogens, Mutagens and Reprotoxic substances Directive (Directive 2004/37/EC), hereinafter the CMRD, protects workers from exposure to carcinogens, mutagens or reprotoxic substances at work.

Substances within the scope of the directive are substances that meet the criteria for classification as category 1A or 1B carcinogen, mutagen or reproductive toxicant as set out in set out in Annex I to Regulation (EC) No 1272/2008 of the European Parliament and of the Council (the CLP). Substances that meet the criteria may either have a harmonised classification and listed in Annex VI to the CLP or they may have been classified by the registrant's self-classification under REACH and listed in the Classification and Labelling Inventory (C&L Inventory) at the European Chemicals Agency (ECHA) website.

Isoprene is today within the scope of the CMRD, although no OEL has been established, as it meets the criteria for classification as category 1A or 1B carcinogen, mutagen or reproductive toxicant.

As a consequence, employers' have today a number of obligations related to isoprene within the scope of the directive which include:

- The employer shall reduce the use of the substances at the place of work by replacing them, in so far as is technically possible, with substances, mixtures or process(es) which, under their conditions of use, are not dangerous or are less dangerous to workers’ health or safety, as the case may be;
- Where it is not technically possible to replace the substance the employer shall ensure that the substances are, in so far as is technically possible, manufactured and used in a closed system;
- Where a closed system is not technically possible, the employer shall ensure that the level of exposure of workers to the substances is reduced to as low a level as is technically possible; and
- Where it is not technically possible to use or manufacture a threshold reprotoxic substance in a closed system, the employer shall ensure that the risk related to the exposure of workers to that threshold reprotoxic substance is reduced to a minimum.

The requirements for minimisation of the exposure apply today to isoprene within the scope of the directive irrespective of establishing an OEL.

The minimum requirements for protecting workers that are exposed to carcinogens and mutagens are - for some substances - expressed by an Occupational Exposure Limit values (OELs). For each OEL, Member States (MS) are required to establish a corresponding national limit value (OEL), from which they can only deviate to a lower but not to a higher value. Today, no limit values for isoprene are established at EU level.

An OEL expresses the concentration of the relevant substance in the air within the breathing zone of a worker in relation to a specified reference period as set out in Annex III to the CMRD.

Of importance for the current assessment, in the case of any activity likely to involve a risk of exposure to isoprene within the scope of the directive, the nature, degree and duration of workers' exposure shall be determined in order to make it possible to assess any risk to the workers' health or safety and to lay down the measures to be taken. The assessment shall be renewed regularly and in any event when any change occurs in the conditions which may affect workers' exposure to the substances.

To determine the degree of exposure it would typically be necessary to measure the workplace concentrations. Measurements of workplace concentrations are not specifically linked to the assessment of compliance with an OEL. The assessment shall be renewed regularly, but the CMRD does not require regular monitoring if changes in the conditions which may affect workers' exposure to the substances does not occur.

1.1.2 REACH

The substances within the scope of the study are subject to the requirements for registrations under REACH. An overview of any intermediate uses is further described in section 3.9.

Chemical Safety Reports (CSRs). As part of the registration processes for the substances within the scope of the study, companies have prepared CSRs which, among others, include an assessment of occupational exposure and environmental exposure. The CSRs have been a key information source for the current assessment.

Classification and Labelling Inventory (C&L Inventory). This database contains classification and labelling information on notified and registered substances received from manufacturers and importers (self-classification) as well as harmonised classifications as listed in the CLP. For isoprene, companies have provided this information in their C&L notifications or registration dossiers.
Where there is a difference in the classification and labelling of the substance between potential registrants, the obligatory Substance Information Exchange Forums (SIEF) shall agree on the classification and labelling. For substances without harmonised classification, the self-classifications are used as basis for the human health hazard assessment undertaken as part of the REACH registration process.

1.1.2.1 Restrictions

Isoprene currently has no restrictions listed under the REACH regulation. Additionally, isoprene has one reported Assessment of Regulatory Needs (ARN) not relating to a proposed restriction and no restriction intentions in the Registry of restriction intentions (RoI). As such it can be expected that isoprene will not be restricted under REACH in the near future.

1.1.2.2 Authorisation

Isoprene is not currently included on the candidate list or authorisation list under the REACH regulation. As such there are no authorisation requirements for this substance.

1.1.2.3 Risk management option analysis

An intention for a risk management option analysis (RMOA) was submitted for Isoprene in 2016, on account of its CMR properties. Since this intention was submitted, no RMOA has been conducted. Therefore, introducing Occupational Exposure Limits for isoprene is the only suggested regulation for control of the risks posed by this substance at EU level.

1.1.3 Other relevant legislation

1.1.3.1 Classification Labelling and Packaging (CLP) Regulation (EC) 1272/2008.

Under the CLP regulation isoprene has received multiple notified classifications and has an established harmonised classification. The hazard classes identified in this regulation are presented in Table 2-2.

1.1.3.2 Cosmetics Products Regulation (EC) 1223/2009

Under the cosmetics products regulation isoprene is on the list of prohibited substances. This regulation sets a threshold of 0% for all cosmetic products resulting in a full ban on the use of isoprene.

1.1.3.3 Biocidal Products Regulation (EU) 528/2012 & Plant Protection Products Regulation (EC) 1107/2009

In the EU, isoprene is not approved for use as an active substance in either the biocidal products or plant protection products regulations.

1.1.3.4 Human and Veterinary Medicinal Products Directives 2001/83/EC and 2004/28/EC respectively

Currently under both of the above directives there are no authorisations held for the use of isoprene in either human or veterinary medicines.

1.2 Background

1.2.1 Initiatives by European Commission

No initiatives have been introduced by the European Commission which are targeted at reducing the level of isoprene exposure. In the interests of sustainability many users of polyisoprene (the major product of isoprene) rely on naturally derived sources (trees such as *Hevea brasilienis*) to reduce demands within the oil and gas sector. More about voluntary industry initiatives can be found in section 3.6.

1.2.2 Opinion of the Committee of Risk Assessment (RAC)

On the 18 March 2022, the Committee for Risk Assessment (RAC) published its opinion on the scientific evaluation of occupational exposure limits for isoprene, which is summarised in Table 1-1 below.

Table 1-1 The outcome of the RAC evaluation to derive limit values for isoprene and the evaluation for dermal exposure and suggested notations (RAC, 2022b)

Derived limit value	**Concentration / notation**
Occupational exposure limit value (OEL) - 8-hour time weighted average (TWA)	8.5 mg/m^3 (3 ppm)
Short term exposure limit (STEL)	N/A
Biological limit value (BLV)	N/A

Derived limit value	Concentration / notation
Biological guidance value (BGV)	N/A
Notations	
Notations	None

The key conclusions of the RAC evaluation are used as starting points for the health assessment and further described in its Chapter 39.

Selected key conclusions of the evaluation are (RAC, 2022b):

- Isoprene (2-methyl-1,3-butadiene) is an intermediate in the chemical and rubber producing industry. Air-monitoring data were collected at three U.S. facilities (between 1993 and 1998) that produced isoprene monomers or polymers; 98.5% of the samples showed concentrations of less than 10 ppm (27.9 mg/m^3), and 91.3% of less than 1 ppm (2.8 mg/m^3); similar data for Europe are missing;

- Isoprene also occurs endogenously, as a basic component of so-called isoprenoids, required for the synthesis of steroids and terpenes;

- Furthermore, isoprene is produced and emitted by many species of trees, accounting for around one-third of all hydrocarbons released into the atmosphere. Nevertheless, it is rapidly degraded, with environmental concentrations reaching low (ng/m^3) levels during the daytime;

- At the workplace, isoprene is easily taken up via inhalation, while dermal uptake is negligible. Isoprene itself is not genotoxic, but is readily metabolised to a genotoxic mono- and diepoxide, predominantly in the liver;

- Whilst no epidemiological studies are available which are suitable to assess the cancer risk to humans, carcinogenicity in rats and mice has been clearly demonstrated;

- Whilst acute toxicity is low, the most sensitive chronic toxicity endpoints of proliferation of haemopoietic cells in the spleen and bone marrow myeloid hyperplasia, were reported in both sexes in mice starting at 10 ppm after long term exposure. Therefore, 10 ppm is considered the LOAEL for non-cancer effects in mice;

- The most critical adverse health effect is carcinogenicity, mediated presumably and predominantly by the isoprene-derived diepoxide. Due to differences in the epoxide hydrolase activity involved in the detoxification of DNA-reactive epoxides, mice especially, but also rats, appear to be more sensitive when compared to humans. Also, the endogenous production of isoprene, and thus also the steady-state levels of isoprene epoxides, is much lower in mice when compared to humans; and

- For the setting of an OEL, it is difficult to derive an exposure-risk relationship from animal data that would reflect the cancer risk in humans, due to the endogenous formation of isoprene and its toxic diepoxide metabolite in humans, as well as pronounced interspecies differences in metabolism. Therefore, it is proposed to follow a similar approach to DFG (2009), i.e., the identification of an exposure level, expected to be within the statistical range of the total internal isoprene levels. Based on a physiological toxicokinetic (PT) model, the respective exposure level would be 3 ppm. Taking mice carcinogenicity data as a basis, this would correspond to an additional cancer risk of 4:1000 (AGS, 2012); however, due to the far lower endogenous levels of isoprene and the higher levels of toxic isoprene derived epoxides in mice, cancer risks calculated from mice carcinogenicity data by linear extrapolation are likely to overestimate the human cancer risk.

1.2.3 Scientific Committee on Occupational Exposure Limits (SCOEL)

The SCOEL has not published any recommendations or opinions relating to the exposure of isoprene at work.

1.2.4 Advisory Committee on Safety and Health at Work (ACSH)

The ACSH has in its opinion on priority chemicals for new or revised occupational exposure limit values under EU OSH legislation from 2021 listed isoprene as a priority carcinogen under the CMRD (immediate priorities) (ACHS, 2021).

1.3 The study

This report is one of six reports elaborated within the framework of a study undertaken for the European Commission by a consortium comprising RPA Risk & Policy Analysts (United Kingdom), COWI A/S (Denmark), FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe (Germany), and EPRD Office for Economic Policy and Regional Development (Poland). The six reports are:

- Methodological note;
- Report for 1,4-dioxane;
- Report for isoprene;
- Report for polycyclic aromatic hydrocarbons (PAH);
- Report for welding fumes; and
- Report for cobalt and inorganic cobalt compounds.

Details on the methodology used across all substances are included in the Methodological note. The note also includes an initial screening of potential impacts for all impact categories.

1.3.1 Study objectives

One of the key aims of the study is to provide the Commission with the most recent, updated and robust information on a number of carcinogenic substances with the view to support the European Commission in the preparation of an Impact Assessment Report to accompany a potential proposal to amend Directive 2004/37/EC.

The general objectives with regard to these substances (except for welding fume) include a detailed assessment of the baseline scenario (past, current, and future), as well as the assessment of the impacts of introducing a new Occupational Exposure Limit (OEL) and, where appropriate, a Short-Term Exposure Limits (STEL) and a skin notation and a respiratory notation.

The specific objective of this report is to assess the impacts of introducing an OEL for isoprene under the scope of the CMRD.

1.3.2 Limit values assessed

Throughout this document the term ‘Limit Values’ is used to refer to the group of measures being proposed. This includes OELs, STELs, BLVs and notations.

OELs are 8-hour time weighted average (TWA) exposures and define a threshold beyond which workers must not be exposed. OELs are set by the European Commission. For each OEL, Member States are required to establish a corresponding national limit value, from which they can only deviate to a lower but not a higher value.

In addition to setting/reviewing OELs, the European Chemicals Agency (ECHA) has also been mandated to adopt, as appropriate, scientific opinions on the establishment of:

- biological limit values; and
- notations.

A ‘biological limit value’ (BLV) is ‘the limit of the concentration in the appropriate biological medium of the relevant agent, its metabolite, or an indicator of effect’.

A ‘notation’ is a means of alerting employers that air sampling alone is insufficient to accurately quantitate exposure and that other measures may need to be taken. For example, a ‘skin notation’ would indicate that measures need to be taken to prevent significant absorption through the skin.

Furthermore, in cases where adverse health effects are not adequately controlled by compliance with an 8-hour TWA OEL, short-term exposure limit (STEL) values, which are usually based on a 15-minute reference period, can also be established.

Within this study only 8-hour TWA OELs are assessed as the RAC opinion stated that both BLVs and STELs are not suitable measures for isoprene limit values. STELs have been discounted because the main genotoxic effects associated with isoprene exposure are systemic. This means short term exposure would not impact human health, provided that long term 8-hour TWA OEL are complied with. Meanwhile BLVs are deemed unsuitable due to the endogenous production of isoprene within humans which is variable between individuals and is similar to the level which would be expected at the RAC opinion value. As such BLVs would not return useful data and are discounted as proposed limit values.

1.3.3 Existing limit values at EU level

Currently there are no pre-existing limit values for isoprene at the EU level however, some Member States do have national OELs and STELs for isoprene. These national OELs are reviewed in section 3.1 of this report.

1.3.4 Substances within the scope of the study

Within this report, the scope shall only apply to isoprene (CAS: 78-79-5), and not to any other isomer or derived product[1]. For example, isoprene is frequently polymerised to form both homopolymer and copolymer products such as polyisoprene or butyl rubber. These polymers however would not be in scope of this report as once polymerised isoprene no longer presents any carcinogenic or mutagenic risk to human health.

[1] Please note that during consultation the scope was also expanded to include Hydrocarbons, C5 rich (CAS: 68476-55-1) due to the isoprene content within this mixture of substances.

2 BACKGROUND FOR ANALYSING THE HEALTH IMPACTS

This chapter comprises the following sections:

- Section 2.1: Summary of epidemiological and experimental data;
- Section 2.2: Deriving an Exposure Risk Relationship (carcinogenic effects) and a Dose Response Relationship (non-carcinogenic effects);
- Section 2.3: Groups at extra risk; and
- Section 2.4: Summary of background for analysing health impacts.

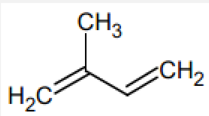
2.1 Summary of epidemiological and experimental data

2.1.1 Identity and classification

2.1.1.1 Identity

The identity and physico-chemical properties of isoprene are described in Table 2-1 below (RAC, 2022a).

Table 2-1 Identity and physico-chemical properties of isoprene (RAC, 2022a)

Endpoint	Value
IUPAC Name	2-methyl-1,3-butadiene
Synonyms	Isoprene, isopentadiene, β-methylbivinyl
EC No.	78-79-5
CAS No.	201-143-3
Chemical structure	
Chemical formula	C5H8
Appearance	colourless liquid
Boiling point	34 °C (1013.25 hPa)
Density	0.679 g/cm³ (20 °C)
Vapour pressure	63.397 kPa (21.1 °C)
Partition coefficient (log Pow)	2.42 (20 °C)
Water solubility	642 mg/L (25 °C)
Viscosity	0.21 mPa*s
Unit transformation	1 ppm = 2.83 mg/m³ (25 °C) 1 mg/m³ = 0.36 ppm

Source: (RAC, 2022a)

2.1.1.2 Classification

A harmonised classification according to Annex VI of the CLP Regulation is available for isoprene and displayed in Table 2-2.

Table 2-2 Harmonised classification of isoprene according to Annex VI to the CLP Regulation

Index No	Annex VI of CLP hazard class and category	Hazard statement code	Note
601-014-00-5	Flam. Liq. 1	H224	Note D
	Muta. 2	H341	
	Carc. 1B	H350	
	Aquatic Chronic 3	H412	

Source: (ECHA Dissemination, 2022, RAC, 2022a)

2.1.2 General toxicity profile, critical endpoints and mode of action

2.1.2.1 Toxicokinetics

2.1.2.1.1 Endogenous formation

Isoprene is formed endogenously in humans and is necessary for the synthesis of steroids and terpenes. Potential sources, from which isoprene can become endogenously available, are di-methylallyl pyrophosphate, farnesyl or geranyl residues of prenylated proteins, or squalene (RAC, 2022a). An isoprene production rate of approximately 0.2 µmol/kg body weight (bw) an hour has been published for humans by Hartwig and MAK Commission, (2015, RAC, 2022a). In this study the blood of volunteers resulted in a mean endogenous isoprene concentration of 5.2 ± 4.0 nmol/L. The isoprene blood concentrations of healthy volunteers of both sexes were determined to be 37 ± 25 nmol/L (range: 15-70 nmol/L) (Hartwig and MAK Commission, 2015, RAC, 2022a). Due to the high variability around these figures, it is not possible to accurately determine a value for the concentration of non-endogenous isoprene in volunteers blood samples. In mechanically ventilated patients mean isoprene concentrations of 10.29 ± 6.17 nmol/L (range: 0.52-24.5 nmol/L) in the venous blood and 6.68 ± 4.71 nmol/L (range: 0 -18.8 nmol/L) in arterial blood were measured (Hartwig and MAK Commission, 2015, RAC, 2022a).

Of the endogenous isoprene approx. 10% is exhaled unchanged and about 90% is further metabolised (Hartwig and MAK Commission, 2015, RAC, 2022a).

Animals have significant lower endogenous isoprene concentrations compared to humans. Isoprene blood concentrations of less than 1 nmol/L were measured in rats, rabbits, dogs, ponies, cows, and sheep (Hartwig and MAK Commission, 2015). In case of rats a 30-fold lower endogenous isoprene blood concentration was determined in comparison to human volunteers. In mice no isoprene concentrations were measured in the exhaled air (Hartwig and MAK Commission, 2015, RAC, 2022a).

2.1.2.1.2 Absorption, distribution and excretion

Human data

At workplaces, occupational exposure to isoprene can occur primarily through inhalation and dermal contact (RAC, 2022a). However, it is reported that dermal uptake is considered to be negligible and thus not contributing to the body burden (RAC, 2022b).

For isoprene, a low blood:air partition coefficient of 0.75 has been determined experimentally *in vitro*, indicating that exhalation is relevant and that isoprene's affinity for blood is low (Hartwig and MAK Commission, 2015; RAC, 2022a).

A multitude of studies exist that measured isoprene concentrations in exhaled air of volunteers (Hartwig and MAK Commission, 2015; RAC, 2022a). For example, Turner *et al.* (2006) measured a mean isoprene level of 118 ± 68 ppb (range: 0-474 ppb) (Turner *et al.*, 2006). In its evaluation MAK noted that the range of measured isoprene levels in humans is broad, which indicates that inter-individual differences exist. Additionally, the MAK Commission stated that other factors can also affect the isoprene concentration in exhaled air: *"[…] is markedly dependent on the intensity of physical activity."* (Hartwig and MAK Commission, 2015; RAC, 2022a).

Animal data

In animal studies it was observed that an increase in isoprene concentration leads to a decrease of isoprene absorption due to an increased excretion of unmetabolized isoprene at high exposure concentrations (RAC, 2022a).

Regarding dermal absorption of isoprene, no studies are available. Dermal fluxes of 0.023 or 0.026 mg/cm² an hour were calculated for a saturated aqueous isoprene solution by using a water solubility of 642 mg/L and a log K_{ow} of 2.42 and performing modelling. A total dermal absorption of 46.9 or 52.6 mg isoprene was calculated for a one-hour exposure of both hands and lower arms (ca. 2,000 cm²) (Hartwig and MAK Commission, 2015).

Male F344 rats were exposed by inhalation (nose-only) to ^{14}C radiolabelled isoprene concentrations of 0, 8, 260, 1,480 or 8,200 ppm (0, 22.6, 736, 4,188 or 23,206 mg/m³) for 6 hours and during the following 66 hours radioactivity in urine, faeces, exhaled air and remaining in the organisms was determined. After the exposure, 19%, 9.1%, 5.8% and 4.5% of the total inhaled ^{14}C concentration remained in the body at 22.6, 736, 4,188 and 23,206 mg/m³. Of the inhaled isoprene 25.3%, 12.0%, 4.7%, and 3.6% were metabolised at the respective concentrations. At all concentrations, more than 75% of metabolised isoprene was excreted via urine. At the highest concentration, 95.5% of the inhaled isoprene was excreted unchanged. The calculated mean half-life of ^{14}C in urine was 10.2 hours and is not affected by the exposure concentration. Isoprene and its metabolites were detected as ^{14}C in the nose, lungs, liver, kidney, and fat tissue. The highest ^{14}C levels were detected in the fat tissue after six hours (Hartwig and MAK Commission, 2015, RAC, 2022a).

In an inhalation study, male B6C3F1 mice were exposed nose-only to ^{14}C radiolabelled isoprene concentrations of 0, 20, 200 or 2,000 ppm (0, 57, 566, 5,660 mg/m³) for up to six hours and during the following 68 hours radioactivity in urine, faeces, exhaled air and remaining in the organisms was determined. Within 15 to 30 minutes after the start of exposure, a steady state was reached in all concentration groups. The mean isoprene concentrations in blood were 24.8, 830 or 6,800 ng/ml at 57, 566, or 5,660 mg/m³, respectively. Of the inhaled ^{14}C isoprene concentration, it was calculated that 5.9%, 8.9% and 3.8% remained in the body at 57, 566, or 5,660 mg/m³, respectively. In urine, 52% to 73% radioactivity corresponding to isoprene's metabolites was excreted (Hartwig and MAK Commission, 2015, RAC, 2022a).

2.1.2.1.3 Metabolism

In mice and rats, Peter *et al.* (1990) described saturation kinetics of isoprene metabolism for an increase in atmospheric isoprene concentrations to about 1,000 ppm (ca. 2,830 mg/m³) for rats and 2,000 ppm (ca. 5,660 mg/m³) for mice (Peter *et al.*, 1990).

Isoprene's metabolism was extensively investigated in microsomal preparations of livers from animals (mice, rat, hamster, rabbit). Microsomal monooxygenases (cytochrome P450 (CYP)), mainly CYP2E1 followed by CYP2B6, metabolised isoprene to monoepoxides (3,4-epoxy-3-

methyl-1-butene and 3,4-epoxy-2-methyl-1-butene). The main metabolite, 3,4-epoxy-3-methyl-1-butene, is then hydrolysed non-enzymatically to trans-3-methyl-1-butene-3,4-diol. 3,4-epoxy-2-methyl-1-butene, which is only formed in small amounts (14-25% of main monoepoxide), is hydrolysed by microsomal epoxide hydrolase to trans-2-methyl-1-butene-3,4-diol. In studies with microsomes from transfected cell lines, it was estimated that the dominant monoepoxide is formed at a rate five to eight times higher than that of 3,4-epoxy-2-methyl-1-butene. Both monoepoxides can be oxidised by CYP monooxygenases to a diepoxide, 2-methyl-1,2,3,4-diepoxybutane, which is mutagenic (Hartwig and MAK Commission, 2015, RAC, 2022a). Subsequently, isoprene epoxides are hydrolysed by microsomal epoxide hydrolase and conjugated via glutathione S-transferase and are thus detoxified (Hartwig and MAK Commission, 2015, RAC, 2022a).

Investigations with human liver microsomes determined a four times higher formation rate of 3,4-epoxy-3-methyl-1-butene than 3,4-epoxy-2-methyl-1-butene. In human samples, the formation of the mutagenic diepoxide from the monoepoxides via CYP2E1 occurred at similar rates (Hartwig and MAK Commission, 2015, RAC, 2022a).

In rodents the formation of ^{14}C isoprene haemoglobin adducts was observed 24 hours after the end of exposure after intraperitoneal injection or a six-hour inhalation exposure. At low concentrations, up to 30 mg/kg bw/d i.p. or 20 ppm (57 mg/m³) by inhalation, the haemoglobin adducts were formed linearly. Regarding the haemoglobin adduct formation of isoprene, RAC stated: *"The formation of haemoglobin adducts can be considered as a biomarker of exposure to reactive metabolites of isoprene with no toxicological impact." (RAC, 2022a)*.

2.1.2.1.4 Toxicokinetic modelling

A physiological toxicokinetic model (PT model) was developed from various inhalation exposures, which describe absorption, distribution, excretion and endogenous formation after isoprene exposure in mice, rats, and humans (Csanády and Filser, 2001, Filser *et al.*, 1996). The model consists of five compartments (lung, well perfused organs/tissue, fat, muscles, and liver) and was validated with experimental human data. The main site for metabolism of isoprene is the liver with 90%, approximately 10% is metabolised extrahepatically. At low isoprene exposure concentrations up to 50 ppm (141.5 mg/m³), the rate of metabolism at steady state is eight to fourteen times lower in humans than in rodents (Csanády and Filser, 2001). Also, Csanády and Filser (2001) calculated that an isoprene exposure to 10 ppm (28 mg/m³) over eight hours leads to an area under the blood curve (AUC) which is four times higher than the AUC of endogenous isoprene formation over 24 hours. Due to lack of data on the internal exposure of the carcinogenic isoprene metabolite, MAK Commission (2015) and RAC (2022b) used the PT model established by Csanády and Filser (2001) to estimate the AUC for endogenous formation of isoprene in the general population and under occupational exposure.

A physiologically based pharmacokinetic (PBPK) model was established by Bogaards *et al.* (2001) by using enzyme kinetic parameters determined *in vitro* in liver samples in order to investigate interspecies differences in enzyme activity and its effects on formation of isoprene diepoxide metabolites. The three enzyme systems analysed were CYP, epoxide hydrolase, and glutathione S-transferase. Only minor differences in enzyme activity of mice, rat, and humans were observed for CYP-mediated oxidation of isoprene as well as its monoepoxides. Relevant differences in the enzyme activity of microsomal epoxide hydrolase and glutathione S-transferase, which detoxify isoprene epoxides, were observed (Bogaards *et al.*, 2001). Compared to mice and rats, a higher hydrolysis capacity of isoprene was observed in humans, which can be interpreted as a *"[…] lower susceptibility of humans to isoprene exposure."* (RAC, 2022a, b). However, the human glutathione S-transferase has a lower activity (factor of 25 to 50) than rats or mice (Hartwig and MAK Commission, 2015, RAC, 2022a). By entering the *in vitro* data into the PBPK model, Bogaards *et al.* (2001) determined that the predicted isoprene diepoxide levels were 15-fold lower in humans compared to rats and 20-fold lower in humans compared to mice. Based on these results RAC concluded: *"However, when taking into account the intra-individual variations of enzyme activities in humans, for a worst-case scenario of an individual presenting both an extensive oxidation by cytochrome P450 and a low detoxification by epoxide hydrolase, isoprene diepoxide concentrations were predicted similar to or even higher than those predicted for the mouse and rat. Nevertheless, on average, especially the higher activity of the mitochondrial epoxide hydrolase in humans compared to mice results in lower predicted diepoxide levels in humans (Bogaards et al., 2001), expected to result in lower cancer risk." (RAC, 2022b)*.

2.1.3 Cancer endpoints – toxicological and epidemiological key studies (existing assessments)

Under CLP Regulation No 1272/2008 isoprene is classified as Carc. 1B (RAC, 2022a). The International Agency for Research of Cancer (IARC) classified isoprene as *"possibly carcinogenic to humans (Group 2B)"* based on *"sufficient evidence"* in carcinogenicity studies in experimental animals (IARC, 1994, 1999). No epidemiological studies, which assess solely the cancer risk of isoprene, are available. Several studies (e.g., meta-analysis, cohort, or case-control) from the rubber industry (the major industry relating to use of isoprene) indicate that higher cancer incidences in exposed workers exist, however the assessment did not focus on isoprene but instead on other chemicals (e.g., butadiene, styrene) (RAC, 2022a). These 'other chemicals' are frequently used in the manufacture of alternative rubber polymers such as SBR (styrene butadiene rubber) and SIS (styrene isoprene styrene) copolymers. When investigations are conducted in relation to cancer risk in the rubber industry the majority of studies focus on the evidence from combined exposure as opposed to from a single substance. This is likely due to the fact that some rubber polymers are manufactured from multiple carcinogenic monomers and facilities are likely to manufacture more than one type of rubber polymer.

For assessing carcinogenicity of isoprene, B6C3F1 mice (50 animals per sex and concentration group) were exposed to isoprene concentrations by whole body inhalation for 4 or 8 hours per day for 5 days per week up to 80 weeks with holding periods of 96 or 104 weeks (Cox *et al.*, 1996, Placke *et al.*, 1996). Male mice were exposed to isoprene concentrations of 0, 10, 70, 140, 280, 700 and 2,200 ppm (0, 28, 198, 396, 792, 1,981, and 6,226 mg/m³) and female mice to 0, 10, or 70 ppm (0, 28, 198 mg/m³). In male mice, significantly increased tumour occurrences were Harderian gland adenomas at 198 mg/m³ and above (already after 20 weeks), hepatocellular adenomas at 396 mg/m³ and above, histiocytic sarcomas at 792 mg/m³ and above, and alveolar/bronchial adenomas and carcinomas at 1,981 mg/m³. Significantly increased incidences of Harderian gland adenomas and pituitary gland adenomas were observed in female mice at 198 mg/m³. However, the pituitary gland adenomas were within the range of the historical control and thus not considered as substance related. In the spleen of female mice, a not statistically significant increase of hemangiosarcoma was seen at 198 mg/m³ (RAC, 2022a). Table 2-3 provides an overview on the incidences of selected neoplasms in male mice.

Table 2-3 Incidences of neoplasms in male B6C3F1 mice exposed to isoprene by inhalation (8 h/d, 5 d/w) for 80 weeks, data presented as reported in RAC (2022a), extracted from Placke et al. (1996) and Cox et al. (1996)

	Concentration in mg/m³					
	0	**28**	**198**	**792**	**1,981**	**19,810**
Alveolar/bronchi-olar adenoma	11/50 [a]	16/50	4/50	13/50	23/50*	30/50*
Alveolar/bronchi-olar carcinoma	0	1	2	1	7*	7*
Hepatocellular adenoma	11/50	12/50	15/50	24/50*	27/48*	30/50*
Hepatocellular carcinoma	9	6	9	16	17	16
Harderian gland adenoma	4/47	4/49	9/50	17/50*	26/49*	35/50*
Harderian gland carcinoma	0	0	0	1	3	2
Histiocytic sar-coma	0/50	2/50	2/50	4/50	2/50*	2/50

[a] Fraction of animals found to have the reported tumour type (row heading) at necropsy
* Compared to control group significantly different (P≤0.05) by Fisher exact test.
Source: RAC (2022a); Placke et al, (1996); Cox et al, (1996)

In an NTP carcinogenicity study, F344/N rats of both sexes (50 animals per sex and concentration group) were whole-body exposed to 0, 220, 700 or 7,000 ppm isoprene (0, 623, 1,981 or 19,810 mg/m³) for 6 h/d plus T_{90} (12 min), 5 d/w for 105 weeks (NTP, 1999). Compared to controls, a statistically significant increase in incidences of mammary gland fibroadenomas was observed in males at 19,810 mag/m³ and females at 623 mg/m³ and above. At 1,981 mg/m³ and above, significant increased incidences of renal tubule adenomas and interstitial cell tumours were seen in male rats. *"In addition, four mammary gland carcinomas, rarely occurring in chamber control male rats, were observed only in the groups exposed to isoprene. The carcinoma incidence was not increased in exposed female rats. Single occurrences of rarely occurring female brain tumours (e.g., malignant astrocytoma, malignant glioma, malignant medulloblastoma) were regarded as potentially substance related."* (RAC, 2022a).

Male F344/N rats (40 rats per concentration group, 30 per group in recovery period) inhaled 0, 70, 220, 700, 2,200 or 7,000 ppm isoprene (0, 198, 623, 1,981, or 6,226 mg/m³) 6 h/d plus T_{90} (12 min), 5 d/w for 6 months (26 weeks) followed by a 6-month recovery period (Melnick *et al.*, 1994, 1996, NTP, 1995). An exposure-related increase in incidences of testicular interstitial cell hyperplasia (Leydig cell hyperplasia) in comparison to controls was seen at 623 mg/m³ and above. A statistically significant increase was only noted in the highest concentration group. *"Following a 26-week recovery period, the incidence/severity of hyperplastic lesions was marginally increased in the exposed groups, over the substantially affected control group […]. An increase with increasing isoprene doses, in benign testicular interstitial cell tumours was also observed"* (RAC, 2022a).

Inhalation to isoprene concentrations of 0, 70, 220, 700, 2,200 or 7,000 ppm (0, 198, 623, 1,981, or 6,226 mg/m³) for 6 h/d, 5 d/w for six months (26 weeks) followed by a six-month recovery period led in male B6C3F1 mice to increased mortality at 1,981 mg/m³ and above at the end of exposure (Melnick *et al.*, 1994, 1996, NTP, 1995). After the 26-week recovery period, increased incidences of Harderian gland adenomas occurred in all concentration groups compared to controls, which was statistically significant at 623 mg/m³ and above. In addition, statistically significant increases were also observed for combined incidence of hepatocellular adenomas or carcinomas at 623 mg/m³ and above, alveolar/bronchial adenomas or carcinomas at 1,981 mg/m³ and above, and squamous cell papillomas or carcinomas of the forestomach in the highest concentration group (RAC, 2022a).

2.1.4 Genotoxicity

RAC considers isoprene to be a genotoxic carcinogen based on genotoxic effects seen in *in vivo* studies in animals and in *in vitro* studies only with metabolic activation in mammalian cells (RAC, 2022a).

In *in vivo* studies in mice, an increase in micronuclei of peripheral erythrocytes were observed in male animals after inhalation exposure to isoprene at 700 ppm (1,981 mg/m³; NOAEC 220 ppm (623 mg/m³)) and above for 12 days and 13 weeks and in female mice at 220 ppm (ca. 623 mg/m³; NOAEC 70 ppm (ca. 198 mg/m³)) and above for 13 weeks (RAC, 2022a). A difference in the number of aberrations was not seen in bone marrow cells (NTP, 1995). In rats exposed to up to 7,000 ppm isoprene (ca. 19,810 mg/m³) for four weeks, no increase in micronuclei was seen in lung fibroblasts (RAC, 2022a).

The subacute (12 days) inhalation exposure of male mice to isoprene resulted in increased numbers of sister chromatid exchange frequencies in the bone marrow at 220 ppm and above (ca. 623 mg/m³). However, an increase in chromosomal aberrations in the bone marrow of male mice exposed to up to 7,000 ppm isoprene (ca. 19,810 mg/m³) for 12 days was not seen (RAC, 2022a).

In mice exposed to isoprene for 6 months (26 weeks) followed by a 6-month recovery period without exposure isoprene-induced tumours of Harderian gland, lung, and forestomach were seen at 2,200 ppm (6,226 mg/m³). An increased frequency of K-ras and H-ras mutations in the tumours was observed, which RAC *"[…] considered to be an early event in tumour formation." (RAC, 2022b)*.

In Ames tests in bacteria, isoprene was not mutagenic in the presence or absence of metabolic activation. Also, isoprene's monoepoxide metabolites (3,4-epoxy-2-methyl-1-butene (=1,2-epoxy-2-methyl-3-butene) and 3,4-epoxy-3-methyl-1-butene (=1,2-epoxy-3-methyl-3-butene) did not cause mutations without metabolic activation. The diepoxide (1,2:3,4-epoxy-2-methyl-butane) was mutagenic in the strain *Salmonella typhimurium* TA100 without metabolic activation (RAC, 2022a).

In mammalian cells (Chinese hamster ovary (CHO)) neither increased incidence of chromosomal aberrations nor sister chromatid exchanges were observed (RAC, 2022a).

Isoprene led to a positive result in a Comet assay performed in peripheral blood mononuclear cells (PBMCs) or human leukaemia cells (HL60) with metabolic activation and did not induce deoxyribonucleic acid (DNA) damage without metabolic activation. Its monoepoxide, 3,4-epoxy-3-methyl-1-butene, was genotoxic in both cell types without metabolic activation (RAC, 2022a).

2.1.5 *Non-cancer endpoints – toxicological and epidemiological key studies (existing assessments)*

There is only a limited amount of data available on humans after a single exposure to isoprene, and these mainly investigated respiratory irritation and odour perception. For repeated exposure to isoprene, data are only available from studies of rubber industry workers exposed to other chemicals at the same time. Due to the limited human database, data from animal studies are also reported and used for the assessment (RAC, 2022a).

2.1.5.1 Anaemia and haematopoietic effects

In inhalation studies conducted by NTP, B6C3F1 mice were exposed to isoprene for various durations (2 weeks to 6 months, 6 h/d plus T_{90} (12 min), 5 d/w), which led to effects on haematological parameters. After subacute exposure for 2 weeks, male and female mice at all concentration groups ranging from 438 to 7,000 ppm (1,240-19,810 mg/m³) had decreased haemoglobin concentrations, haematocrit values, and erythrocyte numbers (Melnick *et al.*, 1990, NTP, 1995, RAC, 2022a). In a 13-week inhalation study, a decrease in haematocrit, haemoglobin, and erythrocyte count, increased mean cell volume (MCV) and macrocytic anaemia (indicated by the parameters mentioned beforehand, e.g. increase in MCV) were observed in both sexes at 700 ppm (1,981 mg/m³) and above (see Table 2-4) (RAC, 2022a). In females, statistically significant effects (decrease in erythrocyte count and mean cell haemoglobin) were already seen at 198 mg/m³ (see Table 2-4 below) (NTP, 1995). In male mice exposed to isoprene for 26 weeks macrocytic, nonresponsive anaemia was observed and indicated by a decrease in erythrocyte count, haemoglobin, and haematocrit values and an increase in mean cell volume at 700 ppm (1,981 mg/m³) and above (Melnick *et al.*, 1990, NTP, 1995, RAC, 2022a).

After chronic isoprene exposure (80 weeks), proliferation of haematopoietic cells in the spleen and bone marrow myeloid hyperplasia was reported for B6C3F1 mice of both sexes at all concentration groups. The female mice were exposed to 0-70 ppm isoprene (0-198 mg/m³) and males to 0-2,200 ppm isoprene (0-6,226 mg/m³) (RAC, 2022a). Significant changes in red blood cell parameters were not observed (Placke *et al.*, 1996). No further data is available. Based on the observed effect, RAC concluded: *"[…] the LOAEL for non-cancer effects is considered to be 10 ppm in mice."* (RAC, 2022a).

In general, rats are less sensitive to isoprene exposure than mice, thus a minor effect on haematological parameters in rats was only observed after subchronic exposure to isoprene. Inhalation exposure to isoprene concentrations between 70 to 7,000 ppm (19,8-19,810 mg/m³) for 13 weeks (6 h/d plus T_{90} (12 min), 5d/w) led in female F344/N rats at all concentrations and in males at 19,810 mg/m³ isoprene to a reduced number of neutrophils. Neither the leukocyte count nor the bone marrow cellularity counts were affected thus a shift of neutrophils from the circulating to the marginal pool may have occurred (RAC, 2022a). The longer exposure duration of six months did not lead to changes in haematological parameters in male rats (RAC, 2022a).

2.1.5.2 Degeneration of olfactory epithelium

Three volunteers (one woman and two men) were exposed to 278 to 27,800 mg isoprene/m³ (ca. 100-10,000 ppm) by inhalation for five minutes. The following effects were reported: limit of odour perception at 695 mg/m³, headache at 13,900 mg/m³ and above, and a marked irritation of bronchi at 27,800 mg/m³ (RAC, 2022a).

An inhalation study (published in Russian) performed with ten volunteers reported mild mucosal irritation in nose, larynx, and pharynx at 160 mg isoprene/m³ (ca. 57 ppm) and an odour threshold of 10 mg/m³ (ca. 3.6 ppm). Further details are not given (RAC, 2022a).

For 630 workers in the rubber production industry from 1965 to 1968, it is reported that with prolonged duration of employment effects on nose and the upper respiratory tract increased. The reported effects were catarrhal nasal inflammation, atrophic processes in the upper respiratory tract, degeneration of olfactory tract, and impairment of odour perception (Hartwig and MAK Commission, 2015, IARC, 1994, 1999). Due to simultaneous exposure to other chemicals (e.g., formaldehyde) the observed effects cannot be assigned to isoprene alone (RAC, 2022a).

In animal studies, isoprene was slightly irritating to rabbit skin and potentially eye irritating as reported by one study (RAC, 2022a). In mice, an exposure concentration with 50% respiratory depression (RD_{50} value) of 161,900 mg/m³ (57,200 ppm) was calculated based on decreased respiration rate and respiratory minute volume seen in a few studies (RAC, 2022a).

Repeated isoprene exposure results in clear effects on the olfactory tract in animals. After subchronic exposure for 13 weeks (6 h/d plus T_{90} (12 min), 5 d/w), degeneration of olfactory epithelium was observed in male B6C3F1 mice at the highest isoprene concentration of 19,819 mg/m³ (RAC, 2022a). In an inhalation study with prolonged exposure to isoprene for six months (26 weeks, 6 h/d plus T_{90} (12 min), 5 d/w) followed by a six-month recovery period, degenerated olfactory epithelium was seen in all male B6C3F1 mice at 19,810 mg/m³ at the end of the exposure period. After the six-month recovery period, a statistically significant increase in degeneration of olfactory epithelium was reported at 623 mg isoprene/m³ (for incidence data, see Table 2-9) (NTP, 1995, RAC, 2022a). NTP (1995) described the effects on olfactory epithelium as followed: *"Degeneration was characterized by focal loss of the olfactory epithelium, with single layers of columnar, cuboidal, or respiratory epithelial cells covering the defect. Bowman's glands were prominent and dilated and were filled with neutrophils and eosinophilic debris. Dilated Bowman's glands were lined by ciliated epithelial cells. Chronic inflammation characterized by fibrosis of the lamina propria was observed, along with mixed cell inflammatory infiltrate. Degeneration was minimal to moderate in severity and usually affected the olfactory epithelium at the dorsal meatus of the middle and posterior nasal section."*.

The chronic inhalation study conducted by Placke *et al.* (1996) reported the occurrence of a non-neoplastic lesion in male mice at 623 mg/m³ (280 ppm) and above and in female mice at the highest concentration of 198 mg/m³ (70 ppm): *"The lesion was in the dorsal meatus and consisted of focal areas of mild metaplasia of the olfactory epithelium to respiratory epithelium. The metaplastic epithelium often invaginated to form glandular patterns."* (Placke *et al.*, 1996).

In F344/N rats exposed to isoprene for 105 weeks (6 h/d plus T_{90} (12 min), 5 d/w), the NTP carcinogenicity study reported *"purulent inflammation in the nose"* of female rats in the highest concentration group (19,800 mg/m³) (RAC, 2022a).

2.1.5.3 Degeneration of spinal cord white matter

Neurological effects of isoprene were observed in male B6C3F1 mice after repeated isoprene exposure (70 to 7,000 ppm (19,8-19,810 mg/m³), 6 h/d plus T_{90} (12 min), 5 d/w) for six months (26 weeks) followed by a six-month recovery period. After the end of exposure, a decrease in grip strength of fore- and hindlimbs at 623 mg/m³ and above, and degeneration of the white matter of the spinal cord as well as impaired hindlimb function and skeletal muscle atrophy were observed at 19,810 mg/m³. After the recovery period of six months, degeneration of the white matter of the spinal cord was observed at all concentration groups (for incidence data, see Table 2-11). RAC concluded that *"No NOAEC could be identified, and 70 ppm is the LOAEC (neurological effects)."* (RAC, 2022a).

NTP (1995) characterised the lesion as follows: *"The spinal cord degeneration was a subtle lesion characterized by dilated clear spaces in the white matter; some of the clear spaces contained eosinophilic globules or "ovoids" measuring approximately 2 to 3 microns in diameter. Spinal cord degeneration most likely accounted for the hindlimb dysfunction discussed above."*.

The observed neurological effects were not seen in rats exposed to isoprene under the same conditions (concentration and duration).

2.1.5.4 Reproductive toxicity

For isoprene, no studies investigating the effects of isoprene on sexual function and fertility are available. Nevertheless, repeated dose toxicity studies in animals also investigate reproductive organs and effects. Thus, some limited data is provided.

In a 13-week inhalation study, male B6C3F1 mice exposed to isoprene (0-19,810 mg/m³, six h/d plus T_{90} (12 min), five d/w) had decreases in the absolute weight of epididymides and cauda epididymis and sperm parameters (sperm motility, sperm concentration, number of spermatids as well as sperm heads per testis) at 1,981 mg/m³. At 19,810 mg/m³ an increase in oestrous cycle length in females, a decrease in absolute testis weight and testicular atrophy in males were also noted (see Table 2-13). In the annex to the opinion, RAC states that a NOAEC of 198 mg/m³ can be identified: *"In mice, […] a NOAEC of 70 ppm isoprene was identified upon inhalation exposure for 13 weeks."* (RAC, 2022a). In F344/N rats exposed to isoprene under the same conditions as male mice no effects on testes, epididymis, sperm parameters or oestrous cycle were observed (RAC, 2022a).

Effects on reproductive organs were observed in F344/N rats exposed to isoprene for six months. *"At the end of the exposure period, an increased incidence of Leydig cell hyperplasia in the testes was observed in the highest dose (7000 ppm; 19810 mg/m³) group. After a 6-months recovery period, increased Leydig cell hyperplasia was detected in rats of all isoprene doses (LOAEC 70 ppm; 200 ppm). In addition, Leydig cell adenomas were found in the high-dose group of 7000 ppm."* (RAC, 2022a).

For male B6C3F1 mice, which were also exposed to isoprene for six months (26 weeks), testicular atrophy and decrease in absolute and relative testis weight was reported. All observed effects were reversible and not seen after the recovery period (NTP, 1995, RAC, 2022a).

2.1.5.5 Developmental toxicity

In a teratology study, pregnant Sprague Dawley rats were whole-body exposed to 0, 280, 1,400 or 7,000 ppm isoprene vapour (0, 792, 3,962, 19,810 mg/m³) from gestation days (GD) 6-19 and no effects were observed. Therefore, the identified NOAEC for maternal and developmental effects was 19,810 mg/m³ (NTP, 1995, RAC, 2022a).

A teratology study in pregnant CD-1 Swiss mice exposed to isoprene concentrations of up to 7,000 ppm (19,810 mg/m³) from GD 6-17 observed maternal toxicity (decreased body weight gain, increased absolute and relative kidney weight) at the highest concentration. Thus, the NOAEC for maternal toxicity was 3,962 mg/m³. *"In the foetuses, the occurrence of variations or reduced ossification (supernumerary ribs mainly) was increased in the dose groups 1400 ppm and 7000 ppm. In addition, the body weight of male foetuses was decreased at 1400 and 7000 ppm. In female foetuses there was a concentration-dependent decrease in the body weight of female foetuses at all doses (280, 1400, 7000 ppm)."* (see Table 2-16) (RAC, 2022a). Based on this study, RAC concluded in its opinion: *"In mice, decreased foetal weight of male foetuses and an increase of variations or reduced ossification was found, resulting in a NOAEC of 280 ppm*

(NTP, 1995). The proposed OEL of 3 ppm is at least 90-fold lower compared to the most sensitive species (mice); therefore, no extra risk during pregnancy is expected." (RAC, 2022b).

Another study in pregnant rats orally exposed to isoprene on GD 9 to 12 observed an increase in the number of resorptions, reduced foetal body weight, and reduced ossification, which were all not dose-dependent (Hartwig and MAK Commission, 2015). Due to limitations (e.g., volatile substance orally administered, control values exceptionally low, no dose-dependent effects observed), the MAK Commission (2015) considered this study not suitable for assessing developmental toxicity of isoprene (Hartwig and MAK Commission, 2015).

2.1.6 Biological monitoring – toxicological and epidemiological key studies (existing assessments)

The endogenously formed isoprene can be measured in exhaled breath of humans. A direct association between isoprene exposure and exhaled isoprene concentration in breath was not observed in humans exposed to increased isoprene concentrations (RAC, 2022a).

Studies on potential biomarkers of exposure to isoprene were conducted recently. Alwis *et al.* (2016) identified two possible candidates in urine: a mixture of N-acetyl-S-(1-[hydroxymethyl]-2-methyl-2-propen-1-yl)-L-cysteine and N-acetyl-S-(2-hydroxy-3-methyl-3-buten-1-yl)-L-cysteine) (IPM1) and N-acetyl-S-(4-hydroxy-2-methyl-2-buten-1-yl)-L-cysteine (IPM3). The analytical methods for measuring IPM1 and IPM3 were developed by the US Centre for Disease Control and Prevention (CDC). The major urinary metabolite was IPM3, which was used by Biren *et al.* (2020) as a biomarker to determine isoprene exposure in the general population of the USA. The data was collected during the 2015-2016 National Health and Nutrition Examination Survey. A correlation between smoking and higher IPM3 levels in urine was observed. In urine, significant higher IPM3 levels in smokers (39.8 µg/g creatinine) versus non-smokers (3.05 µg/g creatinine) were determined. Further correlation factors, which were investigated were sex, race, body mass index, and diet (RAC, 2022a).

Haemoglobin adducts of isoprene's metabolite could also serve as biomarker; however a published method is not available yet (RAC, 2022a).

For EU Member States, no information on the background levels of general populations to isoprene exposure are available (RAC, 2022a).

Regarding occupational isoprene exposure, no study exists that investigated the correlation between internal and external isoprene exposure (RAC, 2022a).

2.2 Deriving an Exposure Risk Relationship (carcinogenic effects) and a Dose Response Relationship (non-carcinogenic effects)

2.2.1 Starting point

The starting point of the following quantitative considerations is the evaluation performed by RAC (2022a, b).

In its opinion, RAC proposed an eight-h TWA OEL of 3 ppm (8.5 mg/m³) isoprene. The Committee neither established a STEL value, a BLV, nor assigned any notations. This OEL is considered to be protective for carcinogenic and non-carcinogenic effects (RAC, 2022b).

Regarding the mode of action, RAC considers isoprene to be *"a genotoxic carcinogen, with genotoxic effects seen in vivo, but not in vitro, indicating that metabolism plays an important role"* and further concludes that isoprene *"in principle [produces] non-threshold effects"* (RAC, 2022b).

Concerning the quantitative risk assessment RAC took the following arguments into consideration (RAC, 2022b):

- no epidemiological studies are available for assessment of cancer risk in humans;
- carcinogenicity was *"clearly demonstrated"* in animal studies (rats and mice) and is considered as the "*most critical adverse health effect"; and*
- *"For the setting of an OEL, it is difficult to derive an exposure-risk relationship from animal data that would reflect the cancer risk in humans, due to the endogenous formation of isoprene and its toxic diepoxide metabolite in humans, as well as pronounced interspecies differences in metabolism".*

Due to the species differences in metabolism and endogenous formation of isoprene, RAC choose to follow an approach proposed by the MAK Commission (2015) for deriving an OEL, which focuses on *"the identification of an exposure level, which will not exceed the statistical range of the total internal isoprene levels in humans."* (RAC, 2022a). By applying a physiological toxicokinetic model, the Area Under the Curve (AUC) for isoprene in blood for life-long endogenous formation and the additional AUC for occupational exposure to 10 ppm for 40 years was determined: *"[…] using a PT-model, the additional AUC for isoprene in the blood was estimated for a situation with occupational exposure at 10 ppm for 40 years (8 h/day, 5 days/week, 48 weeks/year). When running the PT model with the exhalation concentrations for an adult person, the life-long AUC (0-80 years) was estimated as 3.6 ± 2.8 mmol x h/l. The additional AUC for a situation with 40 years of occupational exposure at 10 ppm was estimated to be approximately 9.8 mmol x h/l (DFG, 2009)."* (RAC, 2022a).

In conclusion RAC stated: *"From this, it can be estimated that occupational exposure to one third of that concentration, i.e., 3 ppm, would be approximately at the same level as the standard deviation of the AUC for life-long endogenous isoprene formation (3.6 ± 2.8 mmol x h/l)."* and *"since the resulting isoprene levels are still within the range of endogenous formation, only little additional cancer risk is expected, provided that the proposed OEL is complied with."* (RAC, 2022a). Based on this information, the study team have assumed the little additional cancer risk would apply in cases where a person has relatively high endogenous production and therefore the combined risk with inhalation exposure from the workplace would result in isoprene levels outside the standard statistical range of internal isoprene levels.

Regarding chronic toxicity, RAC identified a LOAEC of 10 ppm (28 mg/m³) for spleen and bone marrow toxicity in mice and due to *"the pronounced species differences between mice and humans […], no further extrapolation factor is needed and the proposed OEL is considered to be protective in humans also with respect to chronic toxicity."* (RAC, 2022b).

2.2.2 ERR for carcinogenic effects

2.2.2.1 Approach

As outlined in section 2.1.3, there is sufficient evidence in experimental animals for the carcinogenic activity of isoprene. But no evidence from epidemiological studies for isoprene, due to a small database with concurrent exposure to other substances at the workplace.

In the past exposure-risk relationships for workers and the general population exposure to isoprene by inhalation have been derived by the German Committee on Hazardous Substances (Ausschuss für Gefahrstoffe (AGS, 2012)) in 2012 and by Haney *et al.* (2015).

The basic approaches for these two ERRs are presented in the following:

Ausschuss für Gefahrstoffe, Germany (AGS, 2012)

For their assessment, AGS used tumour incidence data from a carcinogenicity study in rats (NTP, 1999) and a carcinogenicity study in mice published by Placke *et al.* (1996) as well as Cox *et al.* (1996). The following tumour locations were considered by AGS: lesions of testis in male rats (interstitial cell adenoma, bilateral), fibroadenoma of mammary gland in female rats, and pituitary gland adenomas in female mice.

By using benchmark modelling and/or T25 approach the corresponding T25 concentration or $BMCL_{10}$ were calculated, converted to an exposure concentration for workers and subsequently the risks were quantified. The excess cancer risk was estimated to be 4:1,000 at 5.6 ppm (15.8 mg/m³) for testicular cancer, at 3.0 ppm (8.5 mg/m³) for mammary gland adenomas and at 2.6 ppm (7.4 mg/m³) for pituitary gland adenomas (AGS, 2012). AGS does not further discuss the derived ERR. RAC summarises: "AGS concluded that as the proposed limit value, derived from non-carcinogenic data, is the same as the concentration of the estimated tolerable residual cancer risk (4:1,000), and since the value is in the range of the load caused by endogenous isoprene, the limit value of 3 ppm can be used." (RAC, 2022b).

Haney *et al.* (2015)

Haney *et al.* (2015) performed a carcinogenic assessment and developed a unit risk factor for isoprene. The studies from NTP (1995, 1999) and Placke *et al.* (1996) were considered for the selection of the key study. As the dose-response curve for the endpoint liver carcinoma in male mice from Placke *et al.* (1996) was strongest this was selected as key study and endpoint rather than the data from the NTP studies. For deriving a unit risk factor, default assumptions are in place (e.g., 24 h/d, 7 d/w, for a lifetime) therefore the liver carcinoma data in male mice were adjusted for *"[…] differences between the exposure durations and times of response observation and the objective of characterizing exposure for 24 h/day, 7 days/week, for a lifetime"* (Haney *et al.*, 2015). Afterwards, dose-response modelling via the multistage cancer model with USEPA BMD (Software Version 3.4) was performed and the point of departure (PoD) calculated. Adjustments of the PoD by a factor of ten for species differences in metabolism and a factor of two for inhalation dosimetry were performed, resulting in a unit risk factor of 2.3E-08 per µg/m³ (equal to 6.2E-08 per ppb). For continuous lifetime exposure the 10^{-4}, 10^{-5} and 10^{-6} excess risk air concentrations were calculated (4,500 µg/m³ (1,600 ppb), 450 µg/m³ (160 ppb) and 45 µg/m³ (16 ppb)) (Haney *et al.*, 2015).

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RAC did not derive an ERR, due to the species differences in metabolism and endogenous formation of isoprene (RAC, 2022b).

Approach taken for this assessment

For the current assessment, the derivation of an ERR was necessary to estimate cancer cases above the proposed OEL. From the available literature, a point of departure (PoD) for the ERR derivation was selected. In the NTP study on toxicology and carcinogenesis of isoprene from

1999, an increased incidence of mammary gland fibroadenomas compared to controls was observed in rats, which was statistically significant at 623 mg/m³ and above in female rats and at 19,810 mg/m³ in male rats (RAC, 2022b). In male rats, significantly increased incidences of renal tubule adenomas or carcinomas and interstitial cell adenomas compared to controls were seen at 1,981 mg/m³ and above (RAC, 2022b). Placke *et al.* (1996) and Cox *et al.* (1996) observed in their chronic inhalation carcinogenicity study significantly increased incidences of Harderian gland adenomas in male and female mice and pituitary gland adenomas female mice at 198 mg/m³ and above as well as hepatocellular adenomas and carcinomas in male mice at 396 mg/m³ and above. Several other tumour types were seen at higher isoprene concentrations. Of these occurring tumour types, some are species specific and thus not suitable for assessing the human cancer risk, e.g., mammary gland fibroadenomas in rats (Rudmann *et al.*, 2012, Russo, 2015). For selecting the PoD various factors were considered (e.g., relevance for humans, incidence at lowest concentration, exceeding historical controls) and it was concluded that the increased incidence of hepatocellular adenomas and carcinomas in male mice at 396mg/m³ reported by Placke *et al.* (1996) are suitable.

Although the method of choice for calculating the PoD is benchmark dose modelling (BMD), the results of BMD-modelling of this dataset could not be used as the calculated ratio between BMDU and BMDL was larger than 50 indicating a high uncertainty (for details see Guidance on the use of benchmark dose approach in risk assessment[2]). Visual inspection of the data and graphs supported this uncertainty. Therefore, in accordance with the ECHA Guidance Chapter R.8 (2012) and its appendix on Occupational exposure limits (2019) the PoD was determined by calculating the T25 (concentration representing 25% response above background). The calculated T25 for liver adenomas and carcinomas in mice is 297 mg/m³.

Modification of dose descriptor to correct starting point

In order to consider the differences in worker and animal experimental exposure conditions, corrections according to ECHA Guidance Chapter R.8 for exposure duration (52 weeks/48 weeks, 75 years/40 years) as well as for breathing volume for an eight-hour shift and light work activity (6.7 m³/10 m³) were applied. The corresponding human T25 is 404 mg/m³.

As outlined by RAC (and several other institutions, e.g., MAK Commission and Committee on Hazardous Substances (AGS)) "*it is difficult to derive an exposure-risk relationship from animal data that would reflect the cancer risk in humans, due to the endogenous formation of isoprene and its toxic diepoxide metabolite in humans, as well as pronounced interspecies differences in metabolism*…. *Cancer risks calculated from mice carcinogenicity data by linear extrapolation are likely to overestimate the human cancer risk*." (RAC, 2022b). According to Haney *et al.* (2015) a modification of the PoD from animal studies is a suitable method to quantify exposure-risk relationship for humans. For considering the lesser susceptibility of humans than mice to isoprene exposure, Haney *et al.* (2015) multiplied by a factor of 10 for target tissue metabolite concentrations and a factor of two for inhalation dosimetry differences between mice and man. These factors are based on physiologically based pharmacokinetic (PBPK) predictions performed by Bogaards *et al.* (2001). The modified human T25 is 8,088 mg/m³.

2.2.2.2 Conclusion

Using the modified human T25 concentration of 8,088 mg/m³, linear extrapolation to the zero point in the coordinate system (see Figure 2-1) is performed to derive a concentration of:

[2] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2022.7584

- 129.4 mg/m³ for an excess cancer risk of 4:1,000;
- 12.9 mg/m³ for an excess cancer risk of 4:10,000; and
- 1.3 mg/m³ for an excess cancer risk of 4:100,000.

The calculated ERR equation is:

Equation 2-1: ERR for isoprene

$$Excess\ Cancer\ Risk\ [as\ fraction\ of\ 1] = 0.000031 * conc(isoprene)$$

where

- Excess Cancer Risk refers to the excess liver cancer risk from isoprene at a given concentration [mg/m³];

and

- conc(isoprene) is the exposure concentration given as mg isoprene/m³ (assuming continuous exposure over a work life, i.e., 40 years, 8 h/d, 5 d/week).

The ERR is shown graphically in Figure 2-1.

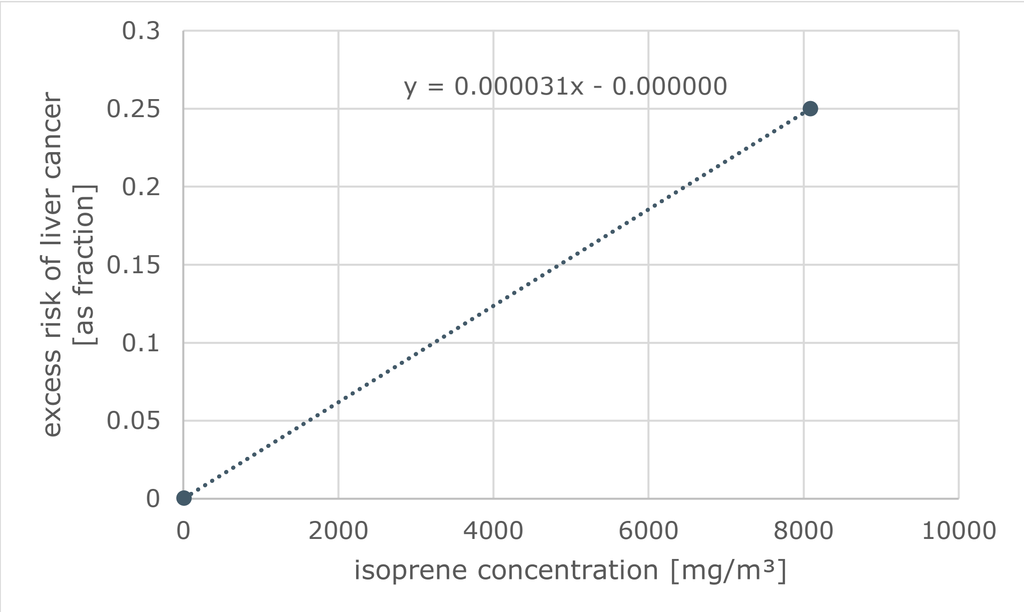

Figure 2-1: ERR for liver cancer after isoprene exposure

2.2.2.3 Discussion

1 The derived ERR is based on effects observed in a carcinogenicity study in mice due to the lack of epidemiological data. RAC considered carcinogenicity of isoprene as the most critical effect (RAC, 2022b).

A different approach to that used by AGS was used in the current assessment. The main reasons are:

- Some of the tumour types are species specific and thus not suitable for assessing the human cancer risk (e.g., fibroadenoma in rats (Rudmann *et al.*, 2012, Russo, 2015)), tumour type has a high rate of spontaneous incidence (e.g., Leydig cell adenomas in Fischer rats (AGS, 2013)), or the observed incidences did not exceed the historical control data (e.g., pituitary gland adenoma in mice (Placke *et al.*, 1996)); and

- Linear extrapolation of animal data to humans is possible by applying the factors defined by Haney *et al.* (2015) for interspecies differences in metabolism and inhalation dosimetry adjustment between mice and humans, which derived a unit risk factor for isoprene by using these factors.

Uncertainty results from the lack of human data, thus experimental data from an animal study are used to extrapolate the tumour incidence data to humans. Additionally, differences between mice and humans regarding isoprene's metabolism, endogenous formation, sensitivity, and whether tumours occur at the same site; all these also contribute to the uncertainty. Furthermore, linear extrapolation to low concentrations is always associated with a degree of uncertainty.

The approach of RAC and MAK Commission are based on a physiological toxicokinetic model, which compares the AUC for endogenous isoprene formation with the one generated from lifelong occupational exposure and the proposed OEL is in the range of the AUC from the standard deviation of endogenous concentration in humans. However, differences in metabolism of isoprene may also exist in humans. Thus, a worker, for who the AUC from endogenous isoprene formation is at the upper margin of the standard deviation and occupationally exposed to isoprene may have a slightly elevated excess cancer risk. This is the reason why it cannot be assumed that at the proposed OEL of 8.5 mg/m³ the excess cancer risk in humans equals zero. RAC addresses this in its statement: *"Furthermore, since the resulting isoprene levels are still within the range of endogenous formation, only little additional cancer risk is expected, provided that the proposed OEL is complied with."* (RAC, 2022b).

2.2.3 DRR for non-carcinogenic effects

For non-carcinogenic effects, RAC did not derive any DRRs. However, isoprene exposure causes adverse effects on several organ systems. For the current assessment, the following endpoints were evaluated and, where possible, DRRs were established:

- Anaemia;
- Degeneration of olfactory epithelium;
- Degeneration of spinal cord white matter;
- Male fertility; and
- Reduced birthweight.

A detailed discussion of each of these endpoints will be provided in the following subsections.

2.2.3.1 Anaemia

2.2.3.1.1 Approach

RAC (2022b) considered proliferation of haemopoietic cells in the spleen and bone marrow myeloid hyperplasia observed in a long-term study in mice by Placke *et al.* (1996) as the most sensitive chronic toxicity endpoints for isoprene. Therefore, RAC identified a LOAEC for non-cancer effects of 10 ppm (28 mg/m³). A DRR was not established by RAC.

As Placke *et al.* (1996) as well as Cox *et al.* (1996) do not report incidence data (or other relevant parameters) for effects on spleen and bone marrow in control and exposed groups, both studies cannot be used for deriving a DRR. The toxic effects on spleen and bone marrow after isoprene exposure can cause changes in blood components. NTP studies in mice after subacute and subchronic (for 13 weeks as well as for 6 months) exposure to isoprene reported significant changes in haematological parameters, which developed into a macrocytic anaemia with prolonged exposure (NTP, 1995). In a conservative approach, the results from the 13-week exposure study were used for the further assessment as significant results were observed at lower concentrations and both sexes were included in the study. The selection of the subchronic inhalation study in mice for deriving the DRR is further supported by the observed increased number of micronuclei detected in the peripheral blood erythrocytes in female mice, which may have been a compensation for the reduction in erythrocytes due to anaemia (see section 2.1.4) (NTP, 1999). In Table 2-4 the significant results for the relevant haematological parameters are reported.

Table 2-4 Relevant haematological parameters regarding anaemia for male and female mice exposed to isoprene in a 13-week inhalation study, data reported in NTP (1995)

	Concentration in mg/m³					
	0	**198**	**623**	**1,981**	**6,226**	**19,810**
Male mice						
Haemoglobin [g/dL]	16.8 ± 0.1	17.0 ± 0.1	16.7 ± 0.1	15.7 ± 0.1**	15.7 ± 0.1**	14.6 ± 0.1**
Erythrocytes [10^6/µL]	10.81 ± 0.06	10.80 ± 0.06	10.65 ± 0.06	9.76 ± 0.04**	9.72 ± 0.05**	8.80 ± 0.09**
Mean cell volume [fL]	44.6 ± 0.3	45.4 ± 0.3	45.2 ± 0.3	45.9 ± 0.4**	46.8 ± 0.2**	47.9 ± 0.4**
Female mice						
Haemoglobin [g/dL]	16.6 ± 0.2	16.6 ± 0.1	16.4 ± 0.1	16.0 ± 0.1**	16.0 ± 0.1**	15.7 ± 0.1**
Erythrocytes [10^6/µL]	10.79 ± 0.07	10.54 ± 0.03**	10.40 ± 0.12**	9.96 ± 0.05**	9.96 ± 0.07**	9.61 ± 0.04**
Mean cell volume [fL]	44.4 ± 0.4	44.8 ± 0.3	45.5 ± 0.2*	46.6 ± 0.2**	46.2 ± 0.1**	47.1 ± 0.2**

Data presented as mean ± standard error (SD).
* Compared to control group significantly different (P≤0.05) by Dunn's or Shirley's test.
** Compared to control group significantly different (P≤0.01) by Shirley's test.
Source: NTP, (1995)

It is not possible to directly derive the fraction of affected human individuals from the data reported in Table 2-4. Therefore, a link has to be established to human data and a transformation has to be performed to estimate the affected fraction (% individuals of total exposed).

The endpoint anaemia is an endpoint which can be linked to a respective clinical picture in humans. The haematological parameters predominately affected by anaemia are a reduction of haemoglobin concentration and the number or erythrocytes (red blood cell (RBC) count)) as well as specifically for macrocytic anaemia an increase in the mean cell volume (MCV). Table 2-5 presents the reference and pathological values for the three relevant haematological parameters associated with (macrocytic) anaemia in humans as provided by WHO and MSD Manuals.

Table 2-5 Reference and pathological values for relevant haematological parameters affected by macrocytic anaemia in humans. Data taken from (WHO, 2011; Braunstein, 2022; Padilla and Abadie 2022).

	Pathological value	Reference value
Men (adult)		
Haemoglobin [g/dL]	<14	14-17
Erythrocytes [mio./µL]	<4.5	4.2-5.9 for general population
Mean cell volume [fL]	>100	80-100 for general population
Women (adult, non-pregnant)		
Haemoglobin [g/dL]	<12	12-16
Erythrocytes/RBC count [mio./µL]	<4.0	4.2-5.9 for general population
Mean cell volume (MCV) [fL]	>100	80-100 for general population

As the pathological values of haematological parameters are lower for women than for men these values are considered in a conservative approach in the assessment. Therefore, a haemoglobin concentration below 12 g/dL, a number of erythrocytes/RBC below 4.0 mio. cells/µL and a MCV above 100 fL are considered as the borderline for a female individual affected with macrocytic anaemia. The reference values for haemoglobin concentration, RBC count, and MCV are set at 14 g/dL, 4.75 mio. cells/µL, and 90 fL. These criteria can be applied to the subchronic study of NTP (1995). According to the identified criteria for macrocytic anaemia the relevant effect on haemoglobin concentration is a 14.29% reduction, on RBC count a 15.79% reduction, and on MCV a 4.93% increase. In the NTP study the criteria are applied by transforming the relevant effect value of each parameter [%] into an analogue value in animal data, subsequently this transformed animal data is subtracted (in case of a reduction) or added (in case of an increase) to the control value of animal data. Thus, resulting in a critical effect size of 14.23 g/dL for haemoglobin concentration, 9.09 mio. cells/µL for RBC count, and 49.33 fL for MCV. For haematological parameters a normal distribution in the population is assumed (Tufts *et al.*, 1985). By using the equation for a normal distribution in Excel® and mean and standard deviation as given for each exposure group, the percentage of affected individuals with macrocytic anaemia was calculated. In case of the MCV parameter an increase is leading to the cut-off value, therefore the calculated values for %affected individuals need to be corrected by subtracting the %affected individuals from 100%. Due to saturation of the isoprene metabolism in mice at an inhalation exposure concentration of about 2,000 ppm (corresponding to 5,660 mg/m^3), the two highest exposure concentrations in the NTP study were not included in the calculation. In the following tables the data as given in the NTP study (first three columns) and affected individuals regarding haemoglobin concentration (Table 2-6), RBC count (Table 2-7), and MCV (Table 2-8) are provided as calculated in Excel®:

Table 2-6 Mean values for haemoglobin concentration in blood and standard deviation in female mice (1995) used to calculate percentage of individuals exceeding the cut-off of a normal distribution. For calculation of affected individuals above the control, a cut-off of <12 g haemoglobin/dL was set.

Concentration [mg/m³]	Haemoglobin concentration [g/dL]	Standard deviation [g/dL]	Affected individuals [%]	Affected individuals above control [%]
0	16.6	0.2	0.00	0.00
198	16.6	0.1	0.00	0.00
623	16.4	0.1	0.00	0.00
1,981	16.0	0.1	0.00	0.00

Source: NTP (1995)

Table 2-7 Mean values for erythrocytes/RBC count in blood and standard deviation in female mice (1995) used to calculate percentage of individuals exceeding the cut-off of a normal distribution. For calculation of affected individuals above the control, a cut-off of <4.0 mio. Cells/µL was set.

Concentration [mg/m³]	RBC count [mio. cells/µL]	Standard deviation [g/dL]	Affected individuals [%]	Affected individuals above control [%]
0	10.79	0.07	0.00	0.00
198	10.54	0.03	0.00	0.00
623	10.40	0.12	0.00	0.00
1,981	9.96	0.05	0.00	0.00

Source: NTP (1995)

Table 2-8 Mean values for mean cell volume (MCV) in blood and standard deviation in female mice (1995) used to calculate percentage of individuals exceeding the cut-off of a normal distribution. For calculation of affected individuals above the control, a cut-off of >100 fL was set.

Concentration [mg/m³]	MCV [fL]	Standard deviation [g/dL]	Affected individuals [%]	Affected individuals above control [%]
0	44.4	0.4	0.00	0.00
198	44.8	0.3	0.00	0.00
623	45.5	0.2	0.00	0.00
1,981	46.6	0.2	0.00	0.00

Source: NTP (1995)

2.2.3.1.2 Conclusion

Based on the available data no DRR for the endpoint anaemia can be established because the calculated "affected individuals above control group" (considered as individuals who suffer from anaemia) for all relevant three haematological parameters are zero.

In the range of the policy options for isoprene (highest option at 129.4 mg/m³) no excess risk for anaemia is expected.

2.2.3.1.3 Discussion

Regarding the endpoint "anaemia" (based on the parameters "haemoglobin concentration, erythrocytes/RBC count, MCV") derivation of a DRR is not applicable within the concentration range defined by the policy options.

The approach used for establishing a DRR for anaemia is conservative due to two reasons:

- Derivation based on data from animal studies and similar incidences in mice and humans are assumed; and
- Data from females in the animal studies as well as the pathological and reference values for the relevant haematological parameters in humans were considered.

An excess risk for anaemia after repeated exposure to isoprene within the policy options could not be determined. This highlights that observed significant effects in animal studies do not need to be associated with a higher risk in humans.

In its opinion, RAC (2022b) identified a LOAEC of 28 mg/m³ (10 ppm) for non-cancer effects based on observations made by Placke *et al.* (1996) in a long-term study in mice (proliferation of haemopoietic cells in the spleen and bone marrow myeloid hyperplasia). Unfortunately, these effects are only mentioned in the publication and neither further details nor quantitative data (e.g., data on incidence) are reported thus this study was not suitable for deriving a DRR. However, the NTP study in mice with an isoprene exposure for 13 weeks was considered to be an adequate basis for deriving a DRR.

2.2.3.2 Degeneration of olfactory epithelium

2.2.3.2.1 Approach

Workers of the rubber producing industry subjected to prolonged exposure to isoprene have experienced effects on the nose and upper respiratory tract (e.g., inflammation, degeneration of olfactory tract) (Hartwig and MAK Commission, 2015, IARC, 1994, 1999). Due to co-exposure to several chemicals (e.g., formaldehyde, dimethyldioxane), the observed effects cannot be assigned to isoprene alone (Hartwig and MAK Commission, 2015, RAC, 2022a).

With respect to irritation there are only limited human data available, which are not sufficient for a DRR derivation (see 2.1.5.2 for details). In a repeated dose toxicity study, male mice were exposed to isoprene via inhalation for six months and after a six-month recovery period a dose-dependent increase in incidences of olfactory epithelial degeneration was observed (Melnick *et al.*, 1994, NTP, 1995). In the annex to the opinion, RAC states in the summary of repeated dose toxicity that olfactory epithelial degeneration is considered as significant at 220 ppm (623 mg/m³) in this study. Although RAC specifically addressed this endpoint, neither a (local) NOAEC/LOAEC nor a DRR were derived.

Using the data provided by NTP (1995) on degeneration of olfactory epithelium in mice, the derivation of a DRR for the endpoint "degeneration of olfactory epithelium" is carried out. Significant results from the NTP study (1995) are reported in Table 2-9.

Table 2-9 Incidence of olfactory epithelial degeneration in male mice exposed to isoprene in the stop-exposure study after 6 months of exposure and 6-month recovery period, data reported in NTP

	Concentration in mg/m³					
	0	**198**	**623**	**1,981**	**6,226**	**19,810**
Number of animals examined	30	30	29	30	30	28
Olfactory epithelial degeneration	1	2	5	11	25	28
Incidence (%)	3	7	17	37	83	100
Logistic regression test #	P<0.001	P=0.510	P=0.030	P=0.001	P<0.001	P<0.001

The P value of the control incidence is associated with the trend test. P values of the exposed group incidence are for pairwise comparison between control and the respective exposure group. Lesions observed in animals dying prior to terminal kill are considered as nonfatal by the logistic regression test.
Source: NTP (1995)

Due to saturation of the isoprene metabolism in mice at an inhalation exposure concentration of about 2,000 ppm (corresponding to 5,660 mg/m³), the two highest exposure concentrations in the NTP study were not included in the dose-response modelling. Modelling of the dose-response data by NTP (1995) is performed with EFSA PROAST version v 70.0 at the EFSA R4EU portal[3] and results in a $BMCL_{10}$ of 122.0 mg/m³ (BMCU of 1,610 mg/m³). The details and the protocol of the benchmark dose modelling are documented in section 16.7.

Following ECHA Guidance Chapter R.8 (ECHA, 2012), the $BMCL_{10}$ is converted to an exposure concentration for workers by adjusting for differences in the exposure scenario:

- daily exposure instead of six hours in the experimental study versus eight hours at the workplace;
- respiratory volume of 6.7 m³ versus 10 m³ during light activity at work; and
- time extrapolation from subchronic to chronic exposure (factor of 2).

The application of a time extrapolation factor of 2 is in line with ECHA Guidance Chapter R.8 and takes into account metaplasia of the olfactory epithelium observed in mice by Placke *et al.* (1996) after chronic exposure to 198 mg/m³ isoprene and above (due to no reported incidences Placke *et al.* (1996) could not be used for DRR derivation). No further assessment factors (i.e., for inter- and intraspecies variability) are applied, in order to intentionally match an actual excess risk of 10% for degeneration of olfactory epithelium. The concentration assumed to affect 10% of the exposed population is 30.7 mg/m³.

In the literature it is reported that repeated inhalation of toxic compounds can lead to inflammation, degeneration, necrosis as well as regeneration or repair of the epithelium (Gaskell, 1990, Hastings and Miller, 1997, Renne *et al.*, 2009). The NTP study (1995) reported that degenerated olfactory epithelium in mice was for example replaced by respiratory cells, Bowman's glands were affected, and chronic inflammation of lamina propria, where sensory cells as well as their support cells (e.g., Bowman gland's) are located, was observed. According to Gaskell *et al.*

[3] Found at: https://www.efsa.europa.eu/en

(1990) repeatedly damaged olfactory epithelium may regenerate *"[…] but there is not complete resolution, as it does so in a disorganized fashion with atypical arrangements of the neural elements."* Further Ramos *et al.* (2018) reported that degeneration and epithelial changes are *"Often accompanied by loss of axon bundles in subjacent lamina propria."* (Ramos *et al.*, 2018).

Jafek *et al.* (2002) reported that patients diagnosed with post-viral olfactory disease and suffering from partial (hyposmia) or total loss of olfaction had a "patchy" olfactory epithelium interspersed with respiratory epithelium. The regenerated epithelium was markedly disorganised and either had none or a very reduced number of receptors (neurons) in ansomic patients whereas only a reduction in receptors was seen in hyposomic patients (Jafek *et al.*, 2002).

For the further assessment, the observed effects on olfactory epithelium in mice are assigned to partial or total loss of olfaction (hyposmia or ansomia) in humans. This attribution is supported by observations of workers in the rubber manufacturing industry, who have been exposed to isoprene, among other chemicals, and have noticed a deterioration in their ability to smell (Hartwig and MAK Commission, 2015; IARC, 1994, 1999).

2.2.3.2.2 Conclusion

The DRR for degeneration of olfactory epithelium is created from the points in the following table (Table 2-10).

Table 2-10 DRR for degeneration of olfactory epithelium of isoprene

	Isoprene concentration [mg/m³]	**Affected individuals above control group [%]**
Starting point (proposed OEL by RAC)	8.5	0.0
Adjusted $BMCL_{10}$	30.7	10.0

Source: Study team

If a DNEL derived according to ECHA Guidance Chapter R.8 (2012) was used as a starting point, it would have been below the proposed OEL.

Figure 2-2 presents the "affected individuals above control group", which are considered as individuals suffering from partial or total loss of olfaction, plotted against the isoprene concentration in air.

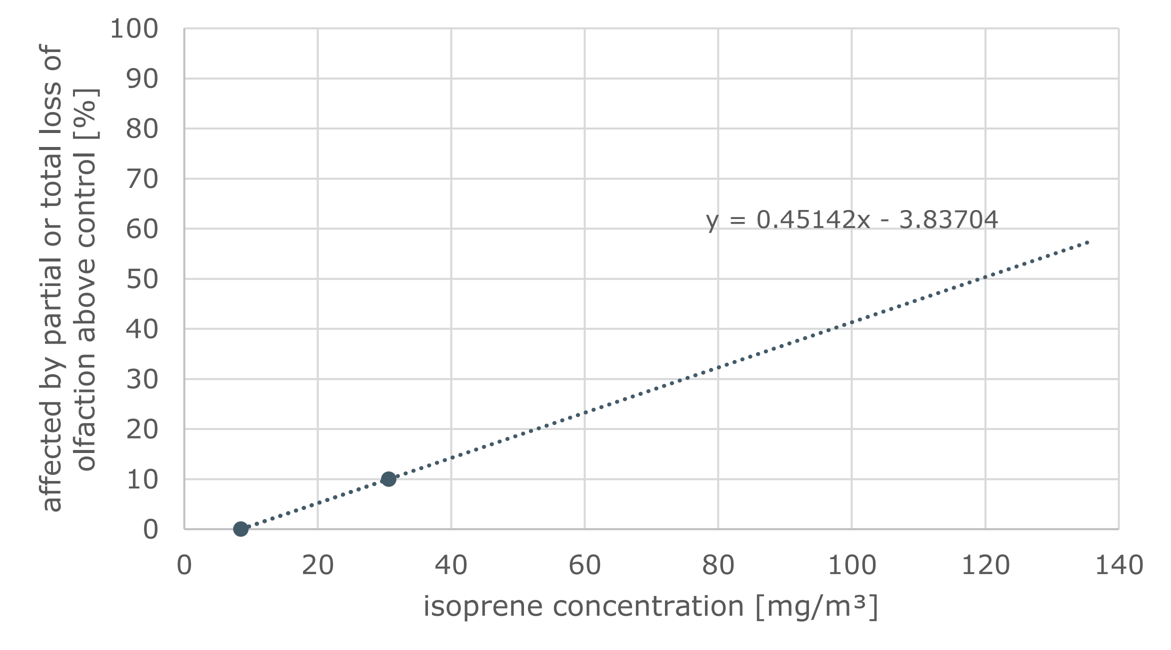

Figure 2-2: DRR for the endpoint degeneration of olfactory epithelium after isoprene exposure

The endpoint degeneration of olfactory epithelium in mice is interpreted as a partial or total loss of olfaction in humans. For estimating the incidence of partial or total loss of olfaction at concentrations above 8.5 mg/m³ a simple linear approach is proposed, which can be described with the following equation:

Equation 2-2: DRR for isoprene (endpoint degeneration of olfactory epithelium)

$$Incidence(conc) = 0.45142 * conc - 3.83704$$

where

- Incidence(conc) refers to the incidence of partial or total loss of olfaction [%];

and

- conc is the human exposure concentration given as mg isoprene/m³ for workplace scenario (8 h/d, 5 d/w).

With an isoprene concentration valid from 8.5 to 129.4 mg/m³.

At the highest policy option of 129.4 mg/m³ the affected individuals above the control group are estimated with this DRR to be 54.6% for partial or total loss of olfaction.

As no information on the exposure duration of workers exposed to isoprene is available, the MinEx of 1 day (0 years) and MaxEx of 1 year is assumed.

2.2.3.2.3 Discussion

Degeneration of olfactory epithelium is a relevant toxicological endpoint when considering effects after exposure to isoprene. The DRR given for this endpoint is based on a subchronic inhalation study in mice (NTP, 1995). According to the derived DRR more than half of the workers may be affected by partial or total loss of olfaction (based on the endpoint "degeneration of olfactory epithelium") at the highest policy option.

If instead of benchmark modelling, a NOAEC of 198 mg/m³ is used as a point of departure, the same assessment factors are applied (duration and respiratory volume of workers (*6/8 *6.7/10) and assessment factors of 2 (subchronic to chronic exposure)), which results in a human exposure concentration of 49.7 mg/m³. This is similar to the one derived by benchmark modelling (30.7 mg/m³), which is the preferred approach by ECHA and RAC (ECHA, 2012).

There is some uncertainty regarding the derived DRR as experimental data from an animal study are used and observed incidences in mice are extrapolated to humans on an equal basis. However, it is known from experience with rubber industry workers that effects on the olfactory epithelium and deterioration of olfaction can occur after years of exposure to isoprene and other chemicals (Hartwig and MAK Commission, 2015, IARC, 1994, 1999). This is also supported by Schwartz *et al.* (1989), who tested the olfactory function of 731 workers exposed to acrylates and methyl acrylates. If the data was evaluated as a nested case-control study examining cumulative effects some associations were noted as given by Hastings *et al.* (1997): *"(1) olfactory dysfunction increased with cumulative exposure, (2) the effects appeared to be reversible, and (3) the highest relative risk of olfactory dysfunction occurred in the group of workers who had never smoked"*. It may be that the partial or total loss of olfaction is of lesser clinical importance, nevertheless it cannot be estimated to which degree life quality, job duties and safety (olfaction as a warning system for high exposure) are affected (Schwartz *et al.*, 1989).

2.2.3.3 Degeneration of spinal cord white matter

2.2.3.3.1 Approach

RAC did not establish a DRR for this endpoint (RAC, 2022b). However, a LOAEC for neurological effects of 70 ppm (198 mg/m³) isoprene from a subchronic inhalation study NTP (1995) with six months (26 weeks) exposure followed by a six-month recovery period in mice was stated by RAC (RAC, 2022a). Degeneration of spinal cord white matter was regarded as the most critical effect, which was dose-dependent and significant already at the lowest concentration group (RAC, 2022a, b). In Table 2-11 the significant results regarding this endpoint from the NTP study are presented.

Table 2-11 Incidence of degeneration of spinal cord white matter in male mice exposed to isoprene in the stop-exposure study after 6 months of exposure and 6-month recovery period, data reported in NTP (1995)

	Concentration in mg/m³					
	0	**198**	**623**	**1,981**	**6,226**	**19,810**
Number of animals examined	30	30	29	30	29	28
Spinal cord degeneration	4	20	19	28	17	13
Incidence (%)	13	67	66	93	59	46
Incidence (%) minus control	0	53	52	80	45	33
Logistic regression test #	P=0.522N	P<0.001	P<0.001	P<0.001	P<0.001	P=0.005

The P value of the control incidence is associated with the trend test. P values of the exposed group incidence are for pairwise comparison between control and the respective exposure group. Lesions observed in animals dying prior to terminal kill are considered as nonfatal by the logistic regression test. N is the notation for a negative trend test.
Source: NTP (1995)

Due to lack of human data for this endpoint the identified LOAEC for neurological effects based on data from the NTP study in mice is used for deriving a DRR.

According to the ECHA Guidance Chapter R.8 (ECHA, 2012), the LOAEC (198 mg/m³) is converted to an exposure concentration for workers (human LOAEC) by adjusting for differences in the exposure scenario:

- daily exposure instead of six hours in the experimental study versus eight hours at the workplace;
- respiratory volume of 6.7 m³ versus 10 m³ during light activity at work; and
- time extrapolation from subchronic to chronic exposure (factor of 2).

No further assessment factors (i.e., for inter- and intraspecies variability) are applied, in order to intentionally match an actual excess risk of 10% for degeneration of spinal cord white matter. The adjusted human LOAEC is 49.8 mg/m³.

The observed degeneration of spinal cord white matter in mice cannot be exclusively assigned to a specific disease or disorder in humans. As white matter is impaired, which is a central component of the central nervous system (CNS) and consists mainly of myelinated axons, its function to transmit information (action potentials) between neurons in various areas in the CNS becomes affected. A group of disorders that leads to a loss of structure or function of neurons are called neurodegenerative diseases, e.g., multiple sclerosis, amyotrophic lateral sclerosis, and Parkinson’s disease. These are serious diseases that usually occur at an advanced age, have complex developmental processes, or can be caused by various triggers (e.g., genetic inheritance). Compared to neurodegenerative diseases, the observed effect on spinal cord white matter in mice is not as severe and thus this effect is assigned to a milder form of neurodegenerative disorders for the current assessment.

2.2.3.3.2 Conclusion

The DRR for degeneration of spinal cord white matter is created from the points in Table 2-12.

Table 2-12 DRR for degeneration of spinal cord white matter of isoprene

	Isoprene concentration [mg/m³]	Affected individuals above control group [%]
Starting point (proposed OEL by RAC)	8.5	0.0
Adjusted LOAEC	49.8	53.33

Source: Study team

If a DNEL derived according to ECHA Guidance Chapter R.8 (2012) was used as a starting point, it would have been below the proposed OEL.

Figure 2-3 presents the “affected individuals above control group”, which are considered as individuals suffering from a milder form of neurodegenerative disorders, plotted against the isoprene concentration in air.

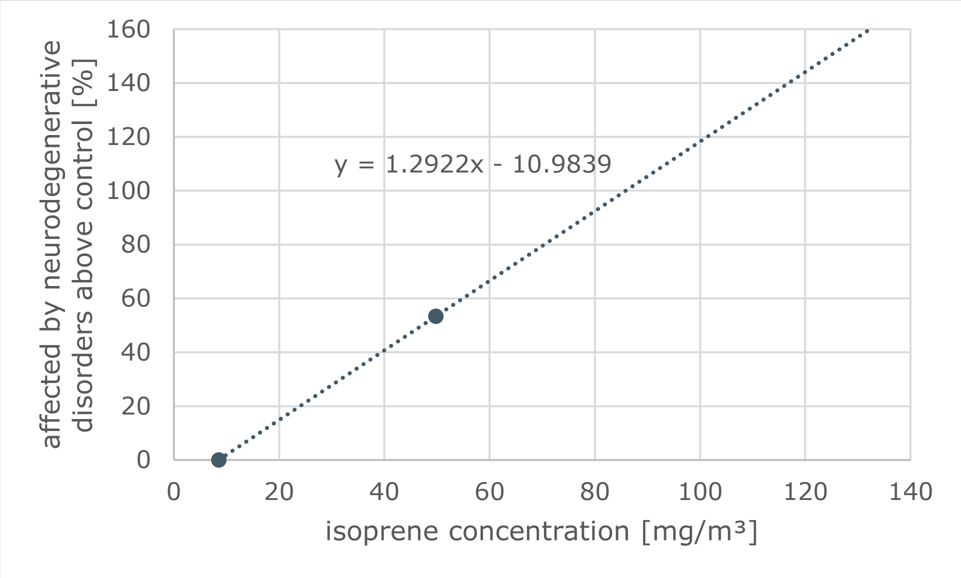

Figure 2-3: DRR for the endpoint degeneration of spinal cord white matter after isoprene exposure

The endpoint "degeneration of spinal cord white matter" in mice is interpreted as suffering from a milder form of neurodegenerative disorders in humans. For estimating the incidence of being affected by neurodegenerative disorders at concentrations above 8.5 mg/m³ a simple linear approach is proposed, which can be described with the following equation:

Equation 2-3: DRR for isoprene (endpoint degeneration of spinal cord white matter)

$$Incidence(conc) = 1.2922 * conc - 10.9839$$

where

- Incidence(conc) refers to the incidence of neurodegenerative disorders [%];

and

- conc is the human exposure concentration given as mg isoprene/m³ for workplace scenario (8 h/d, 5 d/w).

With an isoprene concentration valid from 8.5 to 129.4 mg/m³.

At the highest policy option of 129.4 mg/m³ all exposed workers (156.2%) would be affected from a milder form of neurodegenerative disorders. An isoprene concentration of 88.4 mg/m³ results in 100% affected workers.

As no information on the exposure duration of workers exposed to isoprene is available, the default values for MinEx of 1 day (0 years) and MaxEx of 1 year are assumed.

2.2.3.3.3 Discussion

As the basis for deriving the DRR for the endpoint "degeneration of spinal cord white matter" served observations made in mice after subchronic exposure to isoprene (NTP, 1995). The assignment of a human disease to this endpoint proved to be challenging because the observed effect is not clearly assignable to one of the typical neurodegenerative diseases (e.g., multiple sclerosis). NTP (1995) stated "incidences of minimal spinal cord degeneration" were noted in all exposure groups after the recovery period. Thus, a milder form of a neurodegenerative disorder was regarded as adequate for the assignment although a high uncertainty remains.

Further limitations of the derived DRR are that it is based on animal data and not data on workers or humans. Also, the assumption was made that the occurred incidences in mice are transferred to humans at an equal rate, an overestimation of the risk is likely. As mice is the most sensitive species for chronic toxicity to isoprene, using mice data for the derivation of a DRR is conservative.

NTP (1995) did not address the impact of time and the increased incidences of degeneration of spinal cord white matter in mice after a six-month recovery period. Therefore, further details cannot be presented in this assessment.

To conclude, despite of those uncertainties, the derived DRR provides a plausible approach to address dose dependent neurodegenerative disorders from occupational isoprene exposure.

2.2.3.4 Male fertility

2.2.3.4.1 Approach

RAC did not develop a DRR for this endpoint. However, in the annex to its opinion RAC stated a LOAEC and a NOAEC of 70 ppm (198 mg/m³) for increased Leydig cell hyperplasia in F344/N rats after six months (26 weeks) exposure to isoprene and a six-month recovery period (LOAEC) and observed effects on testes in mice after 13-week exposure to isoprene (NOAEC). According to the German ERB-Leitfaden by AGS (2013), Leydig cell adenomas and their mode of origin are of less relevance for humans since these tumours occur more frequently in rats than in humans and especially Fischer rats (e.g., F344/N) have a high spontaneous incidence, which can reach almost 100%. Additionally, the mice data are more conservative as a NOAEC is identified. Therefore, the data from the rat study are not considered adequate for deriving a DRR.

The 13-week inhalation study performed by NTP (1995) in mice observed effects on testes *"including decreases in the absolute weight of epididymides and cauda epididymides, sperm motility, sperm concentration, and number of spermatids and sperm heads per testis […] at 700 ppm"* (Melnick *et al.*, 1994, NTP, 1995). In absence of human data, the subchronic NTP study in mice was also used as the basis for the derivation of a DRR for the endpoint male fertility. In Table 2-13 are reported the significant results for effects on testes in mice.

Table 2-13 Relevant effects on testes in male mice exposed to isoprene in a 13-week inhalation study, data reported in NTP (1995)

	Concentration in mg/m³			
	0	**198**	**1,981**	**19,810**
Weights [g]				
Left epididymis	0.043 ± 0.001	0.043 ± 0.002	0.038 ± 0.001**	0.030 ± 0.001**
Left cauda epididymis	0.015 ± 0.001	0.014 ± 0.001	0.013 ± 0.001*	0.009 ± 0.001**
Left testis	0.113 ± 0.003	0.122 ± 0.005	0.107 ± 0.001	0.071 ± 0.003**
Spermatid measurements				
Spermatid heads [10^7/g testis]	19.87 ± 0.57	18.46 ± 0.84	18.67 ± 0.82	17.29 ± 0.69*
Spermatid heads [10^7/testis]	2.25 ± 0.09	2.24 ± 0.09	1.99 ± 0.07*	1.22 ± 0.06**

	Concentration in mg/m³			
	0	198	1,981	19,810
Spermatid count [mean/10^{-4} mL suspension]	70.43 ± 2.67	69.88 ± 2.94	62.13 ± 2.33*	38.08 ± 2.00**
Epididymal spermatozoal measurements				
Motility [%]	94.38 ± 0.49	92.93 ± 1.26	89.05 ± 1.23**	72.40 ± 2.28**
Concentration [10^6/ g cauda epididymal tissue]	1353.4 ± 135	1374.4 ± 83.7	707.3 ± 132**	161.9 ± 29.7**

Data presented as mean ± standard error (SD).
* Compared to control group significantly different (P≤0.05) by Shirley's test.
** Compared to control group significantly different (P≤0.01) by Shirley's test.
Source: NTP, (1995)

It is not possible to directly derive the fraction of affected human individuals from the data reported in Table 2-13. Therefore, a link has to be established to human data and a transformation has to be performed to estimate the affected fraction (% individuals of total exposed).

The parameter "reduced total sperm motility" observed in mice is an endpoint that can be linked to corresponding observations in humans. WHO (2021) provides information on the distribution of this parameter in the human male population based on data from 3,488 healthy individuals and defines the parameter "total sperm motility" to include both progressive and non-progressive sperm (see Table 2-14). In 2010, WHO regarded the 5th percentile as a limit to judge on abnormal low cases of sperm motility (WHO, 2010). Recently, WHO (2021) published updated data on total sperm motility in humans without maintaining this strict criterion. Nevertheless, for evaluating the endpoint "reduced total sperm motility" the strict criterion is applied to assess the relevance of the observed decrease in total sperm motility observed in mice in the NTP study. When using the more recent data by WHO (2021), the criterion results in a reduction of total motile sperm of 22% (50th percentile minus 5th percentile, see Table 2-14).

Table 2-14 Distribution in human males for the parameter total sperm motility (in %, normally distributed) (WHO, 2021)

5th percentile	50th percentile	95th percentile
42%	64%	90%

Source: WHO, (2021)

By applying the reduction of 22% in total motility sperm to the male mice data in the NTP study from 1995 and then subtracting the transformed value from the control, a critical effect size of 73.6% sperm motility is calculated. For further calculation it is assumed that sperm motility is normally distributed in the population. Using the normal distribution equation in Excel® and the mean and standard deviation given for each exposure group, the percentage of affected individuals (sperm motility below 5th percentile) was calculated. The highest isoprene concentration has to be omitted from further calculations due to isoprene's saturated metabolisms in mice above 2,000 ppm (corresponding to 5,660 mg/m³). Table 2-15 presents the data as provided in the NTP study (first three columns, highest concentration not reported) and the affected individuals with total sperm count below the 5th percentile as calculated in Excel®:

Table 2-15 Mean values for sperm motility (in %) and standard deviation in male mice (NTP, 1995) used to calculate the affected individuals above the control. Assuming a normal distribution, the cut-off criteria is set as the 5th percentile of a healthy male population.

Concentration [mg/m³]	sperm motility [%]	Standard deviation [%]	Affected individuals [%]	Affected individuals above control [%]
0	94.38	0.49	0.00	0.00
198	92.93	1.26	0.00	0.00
1,981	89.05	1.23	0.00	0.00

Source: NTP, (1995)

2.2.3.4.2 Conclusion

The derivation of a DRR for the endpoint "male fertility" is not possible because the calculated "affected individuals above control group" (considered as individuals who suffer from infertility) at the two relevant isoprene concentrations within the policy options of this assessment are zero.

In the range of the policy options (highest option for isoprene is 129.4 mg/m³) no excess risk for male infertility is expected.

2.2.3.4.3 Discussion

Regarding the endpoint "male fertility" (based on the parameter "reduced sperm motility") derivation of a DRR is not applicable within the concentration range defined by the policy options.

The limitations of the used approach for deriving a DRR are the lack of human data, using experimental data from mice and assuming equal incidences between mice and humans for this endpoint. Because the calculated excess risk for isoprene concentrations within the policy option is zero, a DRR for this endpoint could not be derived.

2.2.3.5 Reduced birthweight

2.2.3.5.1 Approach

For this endpoint RAC did not derive a DRR. RAC stated in its opinion that *"[…] some minor findings […] have been reported at higher doses"* and *"In mice, decreased foetal weight of male foetuses and an increase of variations or reduced ossification was found, resulting in a NOAEC of 280 ppm."* (RAC, 2022b). To verify the observed developmental effects at a lower isoprene concentration, the current assessment also includes the endpoint "reduced birthweight" and checked if the derivation of a DRR is possible.

No human data for this endpoint is available thus a teratology study performed by NTP (1995) in pregnant CD-1 Swiss mice was used as the basis for the derivation of a DRR. The overall incidence of foetal variations/reduced ossifications was not statistically significant different between exposed and control groups. At the highest tested concentrations (19,810 mg/m³), a significant increase of foetuses per litter with variations/reduced ossifications was seen. However, as this effect was only observed at the highest isoprene concentration in mice it is not considered for the current assessment. The significant results regarding foetal body weight observed in the teratology study in mice are presented in Table 2-16.

Table 2-16 Relevant developmental effects observed in mice after maternal exposure to isoprene on gestation days 6 to 17, data reported in NTP (1995)

	Concentration in mg/m³			
	0	**792**	**3,962**	**19,810**
Average foetal body weight per litter [g]				
Live male foetuses	1.37 ± 0.11	1.30 ± 0.10	1.23 ± 0.10*	1.16 ± 0.12*
Live female foetuses	1.32 ± 0.10	1.25 ± 0.10*	1.20 ± 0.10*	1.12 ± 0.13*

Data presented as mean ± standard error (SD).
* Compared to control group significantly different (P≤0.05) by Tukey's *t*-test.
Source: NTP, (1995)

In the annex to the opinion, RAC (2022a) refers to an argument by the MAK Commission (2015) that pregnant mice in the lowest concentration group on average delivered more live foetuses than controls, which may explain the reduced body weights of foetuses. However, it is unclear if this observation shall be regarded as a developmental effect or not. Additionally, the observed maternal toxicity with a NOAEC of 3,962 mg/m³ (1,400 ppm) is rather high and in comparison, to repeated dose toxicity studies a lower NOAEC is expected (Hartwig and MAK Commission, 2015, RAC, 2022a).

It is not possible to derive directly the fraction of affected human individuals from the data reported in Table 2-16. Therefore, a link has to be established to human data and a transformation has to be performed to estimate the affected fraction (% individuals of total exposed).

The endpoint "reduced birthweight" is an endpoint which can be linked to a respective clinical picture in humans. In newborns, a reduced birthweight below 2500 g is regarded as underweight[4]. Neuhauser *et al.* (2013) provide reference percentiles for birthweight of newborns from the National Health Interview and Examination Survey for Children and Adolescents (KiGGS) and provided a median value (50th percentile) of 3.39 kg for newborn girls and 3.53 kg for newborn boys in Germany (Neuhauser *et al.*, 2013). For evaluating the endpoint "reduced birthweight" the criterion of a birthweight below 2.5 kg is considered as underweight and applied to assess the relevance of the observed decrease in foetal body weight in mice in the teratology study. In the teratology study, birthweight data from female foetuses was lower compared to male foetuses and thus used for this assessment. Using the criterion and applying it to the data published by Neuhauser *et al.* (2013) (median value of 3.39 minus 2.5 kg = 0.89 kg, which corresponds to a reduction of 26.25%; 26.25% applied to female mice data) results in a reduction in female foetal body weight of 0.347 g (26.25% of 1.32 g), which is considered as an underweight female mice foetus. By applying the reduction of 0.347 g in foetal body weight to the female mice data and then subtracting the transformed value from the control, a critical effect size of 0.973 g is calculated. For further calculation it is assumed that reduction in body weight is normally distributed in the population. Using the normal distribution equation in Excel® and the mean and standard deviation given for each exposure group, the percentage of affected individuals (reduced foetal body weight below the underweight criterion) was calculated. The highest isoprene concentration has to be omitted from further calculations due to isoprene's saturated metabolisms in mice above 2,000 ppm (corresponding to 5,660 mg/m³). Table 2-17 presents the data as provided in the teratology study (first three columns, highest concentration

[4] https://www.pschyrembel.de/Neugeborenes/K0F47

not reported) and the affected individuals with reduced birthweight below the criterion of 2.5 kg as calculated in Excel®:

Table 2-17 Mean values for live foetal body weight (in g) and standard deviation in female mice (1995) used to calculate the affected individuals above the control. Assuming a normal distribution, the cut-off criteria is set as 0.973 g for underweight body weight.

Concentration [mg/m³]	Foetal body weight [g]	Standard deviation [g]	Affected individuals [%]	Affected individuals above control [%]
0	1.32	0.10	0.026	0.0
792	1.25	0.10	0.284	0.258
3,962	1.20	0.10	1.174	1.148

Source: NTP, (1995)

According to the ECHA Guidance Chapter R.8 (ECHA, 2012), the NOAEC (792 mg/m³) can be converted to a Derived No-effect Level (DNEL) for developmental effects, a concentration where no effects are expected by adjusting for:

- daily exposure instead of six hours in the experimental study versus eight hours at the workplace;
- exposure per week instead of seven days in the experimental study versus five days at the workplace;
- respiratory volume of 6.7 m³ versus 10 m³ during light activity at work;
- interspecies differences (factor of 2.5); and
- intraspecies differences (factor of 5).

A time extrapolation factor does not need to be applied. The calculated DNEL for developmental toxicity is 44.57 mg/m³.

2.2.3.5.2 Conclusion

The DRR for reduced birthweight is created from the points in the following table (Table 2-18).

Table 2-18 DRR for reduced birthweight of isoprene

	Isoprene concentration [mg/m³]	Affected individuals above control group [%]
Starting point (DNEL(DevTox))	44.6	0.0
Adjusted isoprene concentration for 792 mg/m³	557.2	0.258
Adjusted isoprene concentration for 3,962 mg/m³	2,787.3	1.148

Source: Study team

Figure 2-4 presents the “affected individuals above control group”, which are considered as individuals suffering from reduced birthweight, plotted against the isoprene concentration in air.

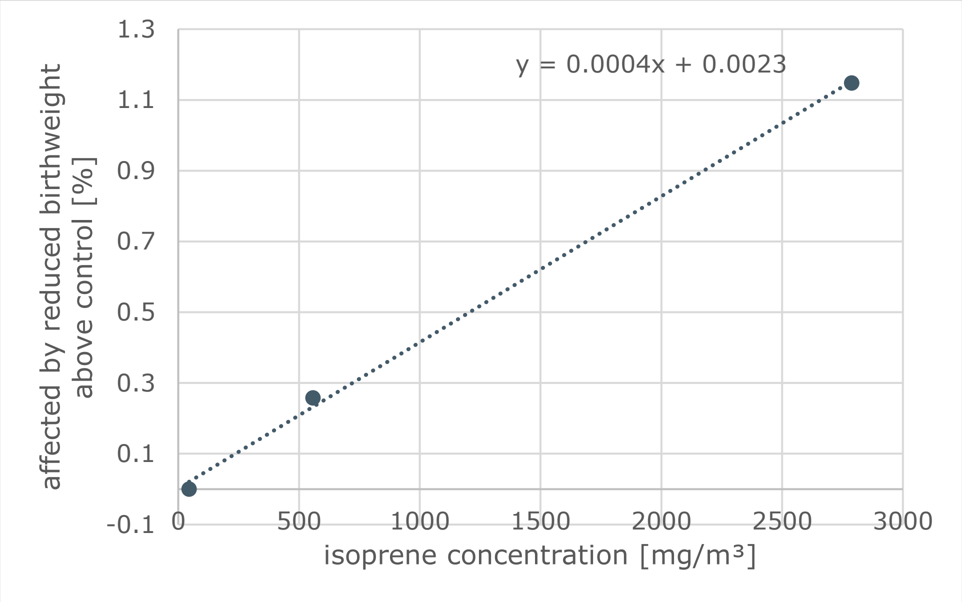

Figure 2-4: DRR for the endpoint reduced birthweight after isoprene exposure

The endpoint reduced birthweight in mice is interpreted as a reduced/underweight birthweight in humans. For estimating the incidence of reduced birthweight at concentrations above the DNEL for developmental effects (44.57 mg/m³) a simple linear approach is proposed, which can be described with the following equation:

Equation 2-4: DRR for isoprene (endpoint reduced birthweight)

$$Incidence(conc) = 0.0004 * conc + 0.0023$$

where

- Incidence(conc) refers to the incidence of reduced birthweight [%];

and

- conc is the human exposure concentration given as mg isoprene/m³ for workplace scenario (8 h/d, 5 d/w).

With an isoprene concentration valid from 44.6 to 129.4 mg/m³.

With the DRR for reduced birthweight an excess risk of 0.056% is calculated at the highest policy option of 129.4 mg/m³.

As no information on the exposure duration of workers exposed to isoprene is available, the MinEx of 1 day (0 years) and MaxEx of 1 year is assumed to include a full pregnancy period.

2.2.3.5.3 Discussion

It has to be emphasised that the data basis for deriving a DRR for this endpoint is associated with uncertainties. Neither observations nor data from humans are available thus the derivation is based on animal data. Further studies, which support the results from the study in mice are not available.

However, a conservative approach was chosen for DRR derivation as similar incidences in mice and humans are assumed and the selected data are from female mice which are more sensitive than male mice. Also in humans, female newborns have a lighter birthweight than male newborns as shown in Neuhauser *et al.* (2013).

Furthermore, pregnant women are usually excepted from workplaces with high exposure to chemicals and hazardous substances. Thus, the number of pregnant women, who are exposed to these high isoprene concentrations should be very limited.

2.3 Groups at extra risk

No specific groups at extra risk were identified by RAC (RAC, 2022b).

2.4 Summary of background for analysing health impacts

2.4.1 Summary of exposure, uptake and health effects

2.4.1.1 Routes of exposure and toxicokinetics

Occupational exposure to isoprene may occur primarily via inhalation or dermal contact during the production and usage of isoprene or synthetic rubber at industrial sites (RAC, 2022a). The dermal uptake is regarded as negligible (RAC, 2022b). However, isoprene can also be found in the air as it is produced and emitted by vegetation (RAC, 2022a). Isoprene is endogenously formed in humans with an estimated rate of approx. 0.2 µmol/kg bw and necessary for the synthesis of steroids and terpenes (RAC, 2022a).

It is mainly in the liver (90%) that isoprene is metabolised to monoepoxides which can be further oxidised to a diepoxide. This diepoxide is mutagenic. Subsequently, isoprene epoxides are broken down and conjugated by enzymes which results in a loss of toxicity (Hartwig and MAK Commission, 2015, RAC, 2022a). Studies observed interspecies differences in enzyme activity and its effects on the formation of the toxic isoprene metabolite. It was observed that especially mice and rats are more susceptible to isoprene and its metabolism to the mutagenic diepoxide than humans (Peter *et al.*, 1990; RAC, 2022a).

2.4.1.2 Adverse health effects

Isoprene has a harmonised classification for carcinogenicity (Carc. 1B) and mutagenicity (Muta. 2). There are no epidemiological studies on exposure to isoprene alone. However, a small database exists for rubber industry workers exposed to isoprene and other chemicals at the same time. There is sufficient evidence for the carcinogenic activity of isoprene from experimental animal studies. RAC considered the carcinogenicity of isoprene *"[…] as the critical health effect."* (RAC, 2022a).

The considerations in the RAC opinion report identified the increase in the number of cells in the spleen and increased cell growth of haemopietic cells in bone marrow as the most sensitive toxicity endpoints from chronic exposure. For these endpoints the Lowest Observed Adverse Effect Concentration (LOAEC) was 10 ppm (28 mg/m^3).

Additionally, repeated exposure to isoprene has been found to cause adverse effects on several organ systems. Based on these adverse effects, the following endpoints were evaluated:

- Anaemia;
- Degeneration of olfactory epithelium;
- Degeneration of spinal cord white matter;
- Male fertility; and
- and reduced birthweight.

In the following table the most relevant carcinogenic and non-carcinogenic endpoints are listed.

Table 2-19 Relevant carcinogenic and non-carcinogenic endpoints and their use for deriving ERRs and DRRs

Endpoint	Assessment
Liver cancer	Considered quantitatively for ERR
Other cancer sites (testis, mammary gland, pituitary gland)	Not considered (not suitable for human cancer risk assessment or observed incidences did not exceed the historical control data)
Anaemia	Not considered quantitatively for DRR (no excess risk expected in concentration range of policy options)
Degeneration of olfactory epithelium	Considered quantitatively for DRR
Degeneration of spinal cord white matter	Considered quantitatively for DRR
Reproductive toxicity – male fertility	Not considered quantitatively for DRR (no excess risk expected in concentration range of policy options)
Reproductive toxicity - developmental toxicity (reduced birthweight)	Considered quantitatively for DRR (only relevant at highest policy option)

Source: Study team

2.4.2 Summary of ERR and DRR

RAC did not derive an ERR, due to the species differences in metabolism and endogenous formation of isoprene (RAC, 2022b). For the current assessment an ERR was derived based on effects observed in a carcinogenicity study in mice due to the lack of epidemiological data. By using a modified human T25 concentration of 8,088 mg/m³ and performing linear extrapolation to the zero point in the coordinate system derivation of the following concentrations was performed:

- 129.4 mg/m³ for an excess cancer risk of 4 : 1,000
- 12.9 mg/m³ for an excess cancer risk of 4 : 10,000
- 1.3 mg/m³ for an excess cancer risk of 4 : 100,000.

The following equation was calculated:

$$Excess\ Cancer\ Risk\ [as\ fraction\ of\ 1] = 0.000031 * conc(isoprene)$$

With exposure concentrations of isoprene (conc(isoprene)) given as mg isoprene/m³ (assuming continuous exposure over a work life, i.e., 40 years, 8 h/d, 5 d/week).

DRRs for isoprene were derived for the following endpoints:

- Degeneration of olfactory epithelium (considered as individuals suffering from partial or total loss of olfaction)

$$Incidence(conc) = 0.45142 * conc - 3.83704$$

With c valid from ≥ 8.5 mg/m³ to 129.4 mg/m³.

- Degeneration of spinal cord white matter (considered as individuals suffering from a milder form of neurodegenerative disorders)

$$Incidence(conc) = 1.2922 * conc - 10.9839$$

With c valid from ≥ 8.5 mg/m³ to 129.4 mg/m³.

- Reduced birthweight

$$Incidence(conc) = 0.0004 * conc + 0.0023$$

With c valid from ≥ 44.6 mg/m³ to 129.4 mg/m³.

- Anaemia (no excess risk is expected in the concentration range considered in the policy options)

- Male fertility (no excess risk is expected in the concentration range considered in the policy options)

3 CURRENT SITUATION

This chapter comprises the following sections:

- Section 3.1: Existing national limits;
- Section 3.2: Relevant sectors, processes and uses;
- Section 3.3: Exposure concentrations;
- Section 3.4: Exposed workforce;
- Section 3.5: Current risk management measures;
- Section 3.6: Voluntary industry initiatives;
- Section 3.7: Examples of good/best practice;
- Section 3.8: Standard monitoring methods/tools;
- Section 3.9: Intermediate uses not covered by certain REACH procedures;
- Section 3.10: Market analysis;
- Section 3.11: Alternatives;
- Section 3.12: Current disease burden (CDB); and
- Section 3.13: Summary of the current situation.

3.1 Existing national limits

3.1.1 OELs and STELs in Member States

The existing OELs and STELs in Member States are shown in Table 16-15.

3.1.2 BLVs in Member States

For isoprene, no BLVs are established (RAC, 2022a).

3.1.3 Minimum, maximum and average national OELs

The table below provides a summary of the above data regarding national OELs for isoprene. National OELs currently exist in five Member States with relatively large variability. If limit values are being assessed for Europe and not just EU Member States, then Switzerland have implemented OELs and STEL values in line with the DFG German values. The highest value of 100 mg/m^3 is currently in place in Poland, whilst the lowest national OEL of 8.4 mg/m^3 is in place in Germany (as proposed by AGS). Poland recently conducted a further review of isoprene exposure limits and has proposed to reduce the OEL to 8 mg/m^3. This is on account of the degradation of spinal cord white matter endpoint as opposed to cases of liver cancer (Klimczak and Kilanowicz-Sapota, 2023). Germany has two OELs in place based on data from both AGS and DFG, resulting in the OELs of 8.4 and 8.5 mg/m^3 as highlighted above.

The median value for Europe is based on the regulations in Latvia and gives a value of 40 mg/m^3 (14.36 ppm). This value is largely in line with that of the arithmetic mean for the EU

Member States national OELs. This mean is calculated as approximately 45.7 mg/m³ (approximately 16.42 ppm) and so largely reflects the median value.

Table 3-1 Maximum, minimum and average of OELs for isoprene in those EU Member States where an OEL exists

Maximum, minimum and averages	Isoprene OEL (mg/m³)
Maximum	100 (35.89 ppm)
Minimum	8.4 (3 ppm)
Median	40 (14.36 ppm)
Mode	40 (14.36 ppm)
Mean	45.7 (16.42 ppm) (approximate)

Source: Study team analysis

3.2 Relevant uses, processes and sectors

3.2.1 Summary of REACH registration data

Isoprene is a registered substance under the REACH regulation, as such users of this substance have a requirement to submit data relating to the use and risks posed by the substance. Table 3-2 below indicates summary information of the registration information for isoprene within the EU. The table also includes registration information for Hydrocarbons, C5-rich which is relevant due to the inclusion of isoprene in this mixture following the steam cracking process.

Table 3-2 Summary of REACH registrations for isoprene.

Substance	EC No	Registered tonnage, t/year	Registration type	Status	Consortium
Isoprene	201-143-3	≥ 100,000 to < 1,000,000 tonnes	Full	Active	Lower Olefins and Aromatics Research Consortium
Hydrocarbons, C5-rich	270-695-5	≥ 1,000,000 to < 10,000,000 tonnes	Full	Active	Lower Olefins and Aromatics Research Consortium

Source: ECHA (2023a), ECHA (2023b)

3.2.2 Manufacture of isoprene

Isoprene is a short chain hydrocarbon and is manufactured via the steam cracking of the naphtha fraction of crude oil. As the steam cracking process is random in its approach to splitting the carbon backbone of longer chain hydrocarbons, isoprene is often unintentionally produced as a byproduct. The steam cracking of naphtha is usually focussed on the production of more widely used chemicals such as ethylene and propylene (Ezinkwo *et al.*, 2013). Following the steam cracking process, a mixture known as Pyrolysis Gasoline is produced containing hydrocarbons with chain length between five to ten carbons. From this a mixture of carbon five (C5) rich hydrocarbons, which comprises around 25% of the PyGas stream, is refined via fractionation. This mixture is given its own CAS (Chemicals Abstracts Service) number (CAS: 68476-55-1) and entry in the ECHA chemicals data base, meaning that registrants of this C5 stream may also be unintentional producers/users of isoprene[5]. In order to manufacture pure isoprene, further refining of this C5 rich mixture is required.

The C5 feedstock typically contains around 10-30% isoprene content (Ezikwo *et al*, 2013; Study Team Consultation), however via consultation with petrochemical industry stakeholders it has been indicated that some steam cracking processes maybe conducted with varying conditions resulting in lower isoprene content in the C5 stream (<1-5%).

Other methods for the production of isoprene via chemical synthesis (i.e. dehydration of isopentane or synthesis from isobutylene and formaldehyde) have been cited in literature, however it is believed that the primary method for isoprene production remains the steam cracking of the naphtha fraction of crude oil (Kothandaraman *et al*, 2022; OECD, 2005). Consultation with industry also highlighted that the synthetic manufacture of isoprene is currently only expected to be conducted in Russia where fuel prices are low enough to make it cost effective.

Note should also be made of the natural production of isoprene which occurs via biosynthetic pathways in both plants and animals (McGenity *et al*, 2018). This means that in some cases plants may also act as a source of naturally derived isoprene, as opposed to isoprene derived from synthetic or petrochemical pathways. Consultation with industry highlighted this extraction as highly uneconomical and therefore very unlikely to be conducted at industrial scale. As such, the main actors involved in the production of isoprene in the EU are expected to primarily be those in the petrochemical industry.

3.2.3 Overview of key intentional uses

Isoprene as a monomer has relatively limited intentional uses and is primary used as an intermediate in the polymerisation of various synthetic rubbers such as polyisoprene, styrene-isoprene-styrene copolymer, and butyl rubber. These rubber elastomers have significantly wider uses than that of the isoprene monomer itself. It is approximated that the polymerisation to form these elastomeric polymers accounts for over 95% of all isoprene use within the EU (RAC, 2022a). Other uses listed in the registration dossier for isoprene indicate the use of isoprene as a fuel. Following consultation with industry associations and petrochemical companies this use is likely associated with the unintentional use of isoprene in pyrolysis gasoline mix which is occasionally included in fuels.

In addition, isoprene may be used as speciality chemicals, derivatives and other intermediates for use in other products such as pharmaceuticals and flavours/perfumes (RAC, 2022a; Shell, 2023). For the purposes of this study these end uses are grouped together as ‘other’ end uses and account for less than 5% of total isoprene use. It has been noted that isoprene used for these end uses may be supplied via petrochemical production, however it may also be possible to extract useful isoprene derivatives (terpenoids) direct from natural sources avoiding the need to synthesise these from isoprene monomer. In the latter method no isoprene exposure would be expected as a result of these processes. It has been reported via consultation with major pharmaceutical manufacturers that monomeric isoprene is not being used and so it is likely that the natural extraction of isoprene derivatives is more commonly used than chemical synthesis from monomeric isoprene. This study therefore concludes that whilst it is possible that isoprene is used in niche pharmaceutical and flavouring/perfume applications it is not possible to further investigate these uses due to limited data availability.

[5] Please note that further consultation is ongoing in order to address the impacts of isoprene exposure via PyGas in industrial settings.

Polyisoprene, and other polymers containing isoprene can be used in many applications for rubber goods. To illustrate this, a range of example products using isoprene containing substances are highlighted in Table 3-3 below.

Table 3-3 End uses of isoprene-based polymers.

Polyisoprene	Styrene-isoprene rubber	Butyl rubber
Adhesives	Hardeners in plastics and structural adhesives	Tire inner tubes
Paints/coatings	Hotmelt adhesives	Wire and cable insulation
Shoe soles	Sealants	Steam hoses
Vehicle tires	Gasket materials	Mechanical goods
Elastic films	Rubber bands	Adhesives
Medical equipment	Childrens toys	Tubeless tires
Textile threads	Roofing/road surfacing	
Baby bottle nipples	Shoe soles	
Rubber bands		
Hoses		
Pressure sensitive adhesives		
Electrochemical cells		
Protective gloves		

Sources: ScienceDirect (2023a, 2023b), Kent Elastomer (2024), Consultation

In addition to the production of polyisoprene from polymerisation of naphtha cracked isoprene, polyisoprene can also be produced via natural processes. The rubber tree, *Hevea brasiliensis*, naturally produces polyisoprene which can also be applied to many of the applications mentioned in the table above. This natural rubber product however contains latex which is a common allergenic and so cannot be used in applications which may result in exposure of those who have a latex allergy. However, for applications where latex exposure is less of a risk, polyisoprene from natural sources could be argued as being more sustainable than naptha derived polyisoprene due to reduce fossil fuel dependence. It can also be argued although that the farming of *Hevea brasiliensis* is still not a sustainable solution due to associated impacts relating to deforestation and reductions in biodiversity. These considerations are often acknowledged by users of polyisoprene, especially within the tire industry.

3.2.4 Processes unintentionally generating isoprene

As previously mentioned in section 3.2.2 the manufacture of isoprene is often an unintentional process, whilst the main production operation is conducted to gain monomers for ethylene and propylene production. Even in situations where the intended product is the PyGas mixture, isoprene is not always the intended extraction product of this mixture. PyGas is more often used for production of aromatics such as Benzene, Toluene and Xylenes. Via consultation it was identified that all steam crackers operating in Europe would be unintentionally producing isoprene yet relatively few petrochemical companies in Europe are refining isoprene within the EU (estimated at one large petrochemical company via consultation).

Additionally, it was investigated if the processing/degradation of polyisoprene or other synthetic rubbers might result in unintentional release of isoprene monomer. Once polymerised however isoprene is stabilised within the polymer matrix and is unable to re-release the monomeric unit even when subject to heating and transforming processes associated with the processing/end of life of synthetic rubber compounds. This means that there is relatively limited scope for the unintentional production of isoprene outside of the steam cracking process used in its original manufacture.

This has been confirmed in an old OECD report on isoprene which states, "*Isoprene monomer residual concentration was not detectable in isoprene-derived polymer samples at an analytical sensitivity of 0.1 ppm in work conducted prior to June 1998. Subsequent work in latter 1998, with an increased analytical sensitivity of 0.02 ppm, that evaluated polyisoprene samples demonstrated that 17 out of 19 samples had no detectable isoprene monomer residual, while 2 samples contained between 0.04 and 0.02 ppm. Consequently, potential for consumer exposure will be negligible"* (OECD, 2005). Based on these findings, it can be concluded that over 20 years later it is not believed that residual isoprene monomer exposure will cause any significant risks to human health.

It has been noted in literature that polyisoprene products are also thermally stable to temperatures of around 300°C at which point only limited isomerisation is observed within the polymer material (Jiang *et al*, 2000). This means that, in the uses stated above, it is highly unlikely that any polyisoprene products will result in the re-release of isoprene once polymerised and in elastomeric form.

3.2.5 Presence of isoprene as impurity

Via consultation, one respondent indicated that isoprene may be present as an impurity in the raw materials involved in a chemical synthesis operation. In this operation the raw material is identified as benzene and isoprene is present in very small quantities as an impurity. This impurity is likely due to similarities in the chemical properties and molecular weights of isoprene (C_5H_8) and benzene (C_6H_6), making it difficult to ensure complete separation of these hydrocarbons throughout the preceding refining process. In this specific case, the risks of isoprene are relatively low due to the small quantity in the raw product and due to the process being tailored to control benzene exposure, which requires far stricter levels of exposure control than for isoprene.

This trend of co-exposure between isoprene and other hydrocarbons has also been documented in studies conducted looking at exposure within the rubber industry (RAC, 2022b). In these studies, exposure effects have not been able to be successfully attributed to isoprene only often due to the presence of other hydrocarbons such as butadiene, styrene or benzene as mentioned above.

3.2.6 Overview of sectors

3.2.6.1 Sources of information about sectors using isoprene

In this section, sources relating to the use of isoprene in various sectors are summarised.

The main sources of information relating to the sectors of use for isoprene have been published in literature and information is also available via company websites. In the ECHA scientific report on isoprene the main source cited in relation to end use sectors is Asghar *et al* (2020), who identify the growth in the isoprene market due to demand in the tires, conveyor belts, hoses, moulded rubber and medical equipment industry. These sectors are all subsectors of the wider rubber industry and so can all be grouped under the rubber industry.

Many other sources also corroborate rubber polymers as the main use of isoprene such as OECD (2005), Shell (2023), and Kothandaraman *et al* (2022) who all highlight the primary use of isoprene as a monomer in the production of synthetic rubber products.

Information relating to the use of isoprene in the 'other' uses, previously described as speciality chemicals, derivatives and other intermediates, highlights that isoprene may be used in very low quantities for these end uses, although it is not common practice. As such no reliable data has been able to be gathered via industry to determine the impacts of this 'other' end use sector.

3.2.6.2 Sectors of use (SU) in REACH registration dossiers

Within the REACH registration dossier, the main sectors can be implied based off existing knowledge and the data on uses. These are highlighted under the life cycle description which references the following uses of isoprene:

- Polymer production/polymer processing/use as a monomer in the polymerisation process;
- Industrial use as an intermediate in the synthesis of chemical substances/use as an intermediate;
- Manufacture of the substance; and
- Use as a fuel.

From these uses stated and the known information from the literature/consultation, the REACH registration data likely refers to the use of isoprene in the manufacture of rubber polymers, the synthesis of speciality chemicals, derivatives, and intermediates, and its use as a fuel additive as part of post extraction PyGas products.

3.2.6.3 Summary of sector data sources

Based on the available literature and consultation efforts, the following table has been produced to highlight the key sectors which may be related to the use of isoprene in an industrial setting. This summary has been produced based on both isoprene and its downstream supply chain (i.e. the use of isoprene in the manufacture of rubber products and the subsequent use of isoprene rubbers in industries for the manufacture of final articles).

Table 3-4 Summary of sectors using isoprene according to data sources

NACE	Name	Consultation	REACH SU	RAC	IARC	OECD	NTP	CSRs	Leber (2001)	Lynch (2001)	Garate *et al* (2011)
Type of data		E, W, M	M	M	W, M	W, M	W, M	E, M	E, M	M	M
Year		2023	2023	2022	1999	2005	2021	2023	2001	2001	2011
C15.20	Manufacture of footwear					X					
C19.20	Manufacture of refined petroleum products	X	X	X	X	X	X	X	X	X	
C20.16	Manufacture of plastics in primary forms										X
C20.17	Manufacture of synthetic rubber in primary forms	X	X	X	X	X	X	X	X	X	
C20.30	Manufacture of paints, varnishes and similar coatings, printing ink and mastics					X					
C20.42	Manufacture of perfumes and toilet preparations					X					
C20.52	Manufacture of glue					X					

NACE	Name	Consultation	REACH SU	RAC	IARC	OECD	NTP	CSRs	Leber (2001)	Lynch (2001)	Garate *et al* (2011)
C21.10	Manufacture of basic pharmaceutical products			X		X					
C21.20	Manufacture of basic pharmaceutical preparations			X		X					
C22.11	Manufacture of rubber tyres and tubes; retreading and rebuilding of rubber tyres			X	X		X				
C28.96	Manufacture of plastics and rubber machinery			X							
C32.50	Manufacture of medical and dental instruments and supplies			X							

Consultation responses include response received to data in the questionnaire and meetings with industry associations
W = workers, E = exposure, M = mention

3.2.7 Criteria for selection of sectors for further analysis

Following the identification of the above sectors in Table 3-4 as an initial step, these need to be filtered for relevance to occupational exposures for isoprene specifically. Therefore, the previously identified sectors have been filtered based on the following criteria:

- The sector should involve the potential for exposure to isoprene in its monomeric form.

This should be used to filter the above sections as many sources of information relate to the use of polymeric rubbers derived from isoprene. These sectors often do not have any exposure to isoprene in its monomeric form and so do not present any human health risks. For this reason, sectors which may only result in exposure to polymeric forms isoprene will not be further investigated in this report.

3.2.8 Identified sectors with risk of exposure to isoprene

By applying the criterion set out in section 3.2.7, sectors in which there is a risk of exposure to isoprene can be identified. Over 95% of all isoprene produced is used in the manufacture of elastomeric polymers for the rubber industry (RAC, 2022a) and so many industries listed above may be removed by the criteria outlined in 3.2.7.

Investigation into the 'other' end uses relating to pharmaceuticals and flavours/perfumes which may contain isoprene was also conducted via consultation. Based on feedback from the pharmaceutical industry it has been noted that isoprene monomer could theoretically be used but no consultation data are available to support this use. It is also expected, based on end uses and alternative sources of isoprene derivatives, that this situation is the same for use in flavours and perfumes.

As such the list of sectors to be further investigated is presented in Table 3-5.

Table 3-5 Gross list of identified sectors with potential risk of exposure to isoprene

Sector (NACE Code)	NACE description	Specific activity
C19.20	Manufacture of refined petroleum products	Steam cracking and refining of isoprene monomer
C20.17	Manufacture of synthetic rubber in primary forms	Polymerisation of isoprene monomer into synthetic rubber

Source: Study team

3.2.9 Uses of sectors excluded from analysis

Given the criterion outlined in section 3.2.7 and the information gathered throughout the study (via consultation and literature review) the following sectors have been excluded from further analysis as these sectors are believed/known to only relate to exposure to polymeric forms of isoprene.

Table 3-6 Uses and sectors excluded from analysis

Use or sector	Source of information on use or sector	Reasons for exclusion
Manufacture of tires	RAC, IARC, NTP	Based on the exclusion criteria that sectors must be using isoprene as a monomer the manufacture of tires (despite being the largest end use of polyisoprene) is excluded from further analysis. The manufacture of tires is a key driver in the production of isoprene globally.
Manufacture of plastics	Garate *et al*. (2011)	This end use applies to the use of styrene-isoprene-styrene in the manufacture of epoxide resins. As this is the polymeric form of isoprene no exposure to the monomer is expected and so this is excluded from further analysis.
Manufacture of rubber products (excluding tires) i.e. footwear, adhesives, rubber machinery	RAC, OECD, NTP	The manufacture of rubber goods relates to the processing of synthetic rubbers such as polyisoprene, butyl rubber and styrene-isoprene-styrene block copolymer. As such this industry would not result in any exposure of workers to isoprene and so is excluded from further analysis.
Manufacture of glue	OECD	The manufacture of glue (including other adhesives) relates to the use of polymeric forms of isoprene such as polyisoprene and styrene-isoprene-styrene block copolymers. As such no exposure to isoprene monomer is likely to occur and so this sector is excluded from further analysis.

Source: Study team

The above sectors which are excluded due to their use of polymeric isoprene can be justified by the fact that previous studies have indicated very low levels of residual isoprene within the finalised polymer (OECD, 2005). Additionally, Jiang *et al*. (2000) indicated that isoprene is unlikely to be re-released from its polymeric form unless heated above 300ºC at which temperature, the chemical structure of polyisoprene would begin to change leading to loss of useful properties and so it is highly unlikely this would occur in polymer processing. Therefore, the risks of exposure to isoprene monomer from polymeric isoprene are considered to be very low/nil.

As mentioned in the section above 'other' end uses relating to pharmaceuticals and flavours/perfumes are unable to be further explored in this study due to a lack of data. However, based on the limited consultation, it is likely any isoprene monomer used in these sectors is in very low quantities and for niche applications only. Whilst this is not enough to determine the potential exposure levels it can be used to assume that the potential numbers of workers exposed may be very low and thus may not pose a significant health risk.

3.2.10 Sectors taken forward for analysis

Due to the relatively limited time that isoprene spends in its monomeric form throughout its supply chains the main sector of interest can be identified as the chemicals industry, specifically the refining of crude oil and the polymerisation of isoprene to synthetic rubber in primary forms. These two parts of the chemicals sector are reflected by the following NACE codes and will form the main focus of study.

Table 3-7 Analysed sectors with risk of exposure to isoprene

NACE code	Short name for sector	NACE description
C19.20	Manufacture of refined petroleum products	This class includes the manufacture of liquid or gaseous fuels or other products from crude petroleum, bituminous minerals or their fractionation products. Petroleum refining involves one or more of the following activities: fractionation; straight distillation of crude oil; and cracking.
C20.17	Manufacture of synthetic rubber in primary forms	This class includes: Manufacture of synthetic rubber in primary forms Synthetic rubber Factice Manufacture of mixtures of synthetic rubber and natural rubber or rubber-like gums (e.g. balata)

Source: Study team, Eurostat (2008)

3.3 Exposure concentrations

3.3.1 Data sources

The findings of the study team in relation to existing data on occupational exposure to isoprene have highlighted a significant lack of available data. This is also reflected in the findings of the RAC (2022a) when preparing their scientific report on isoprene, in which only one US based exposure study was referenced. The usefulness of this study however is relatively limited as, in addition to the study being conducted in the US as opposed to the EU, it also draws on data published in 2001 and so is also likely outdated. Since this time the study teams findings indicate that there have been no publicly available exposure data published in relation to the occupational exposure of isoprene. This is again supported by the findings of ECHA who also state that "similar up-to-date studies within the EU were not found" (RAC, 2022a).

Throughout this study, some exposure data were able to be gathered via consultation with industry, however the majority of those contacted did not have any measured exposure data for isoprene. The combination of consultation and literature data will be further examined in the following sections of this report.

3.3.2 Inhalable vs. respirable fraction

Not relevant for isoprene.

3.3.3 Exposure data from national databases

As expressed above in section 3.3.1 there are currently no national databases which contain exposure data relating to isoprene.

3.3.4 Exposure data by sector

In the following sections, an overview of the available exposure data is presented for each of the sectors taken forward in the study analysis. As noted earlier in section 3.3.1, the availability of data for isoprene exposure has been relatively limited and so, in addition to one US based study, the main source of information has been derived via consultation with industry stakeholders.

3.3.4.1 Manufacture of refined petroleum products

The findings from the US study from Lynch (2001) and Leber (2001) highlighted that even in 1993-1998, the majority of exposure levels were lower than the proposed OEL by the RAC of 8.5mg/m^3. Based on air monitoring methods at three US based facilities it was found that 91.3% of all monitoring data were below 2.79mg/m^3 (1ppm). A further reported finding indicated that 98.5% of all samples were below 27.86mg/m^3 (10ppm). Whilst the latter is above the RAC opinion value this data does indicate that, 22 years ago, in a major western developed country, the majority of air monitoring measurements indicated workplace isoprene levels below that of the current RAC opinion.

CSR data has also been extracted as a part of this study. The data included in the table below equate to an average value of the total exposure concentrations stated in the submitted CSR. This average has been calculated for all processes which are not involving the use of full closed systems (PROC1) and has been adjusted based on the use of RPE for these processes (see section 3.3.6).

From the consultation, some data relating to occupational exposure of isoprene in petroleum refineries were highlighted alongside data being provided from submitted CSR. This data is included in the table below including data from literature.

Table 3-8 Exposure concentrations to isoprene from published sources and stakeholder consultation

Sector/ process	n	Mean	Median	95th percentile	Range		Location	Reference (Source)
					Min	Max		
NACE C19.20/ Closed system manufacture of isoprene monomer (including uses relating to transfer, testing and maintenance (PROC1, PROC8b, PROC15, PROC 28)	95	-	-	-	<0.009	0.015	EEA	Consultation 1
NACE C19.20/ Sampling of samples to be analysed (PROC9)	-	0.026	-	-	-	-	EEA	Consultation 2
NACE C19.20/ Manual maintenance of refining machinery (PROC8b)	-	0.026	-	-	-	-	EEA	Consultation 3
NACE C19.20 and C20.17/ Combined monomer production and polymerisation of isoprene	-	-	-	27.86 (98.5th percentile)	-	-	US	Leber (2001), Lynch (2001)
NACE C19.20/ Manufacture, formulation and	-	0.199	-	-	-	-	EEA	CSR, (2023)

Sector/ process	n	Mean	Median	95th percentile	Range		Location	Reference (Source)
					Min	Max		
distribution (PROC2,3,4,5, 8a,8b,9,14,15)								

Source: Study team from published sources and stakeholder consultation.

3.3.4.2 Manufacture of synthetic rubber in primary forms

The studies mentioned in the section above also apply to this sector as the studies were conducted across the US rubber production industry involving both the production of isoprene and synthetic isoprene rubbers. Lynch (2001) reported that the polymerisation process (manufacture of synthetic rubber in primary forms) results in higher exposure levels than the refining of isoprene as raw material. This is due to the need for more frequent maintenance of polymerisation equipment than the monomer production machinery.

Alike section 3.3.4.1 above, the below table provides an overview of the consultation data, CSR data and available literature exposure data for use in this study, relevant to the polymerisation of isoprene into synthetic rubber in primary forms. CSR data has again been calculated as an average of data shared for non PROC1 processes and has had an adjustment applied for the use of RPE.

Table 3-9 Exposure concentrations to isoprene from published sources and stakeholder consultation

Sector/ process	n	Mean	Median	95th percentile	Range		Location	Reference (Source)
					Min	Max		
NACE C20.17/ Closed system polymerisation and transfer of substances at dedicated facilities (PROC1 and PROC8b)	79	-	-	-	<0.152	<0.152	EEA	Consultation 1
NACE C20.17/ Used as a laboratory reagent for testing (PROC15) in the polymer production process	32	-	-	-	<0.152	<0.152	EEA	Consultation 2
NACE C20.17/ Manual maintenance of polymerisation machinery (PROC 28)	42	-	-	-	<0.152	<0.152	EEA	Consultation 3

Sector/ process	n	Mean	Median	95th percentile	Range		Location	Reference (Source)
					Min	Max		
NACE C20.17/ Closed system polymerisation (PROC1)	6	-	-	-	<0.061	<0.112	EEA	Consultation 4
NACE C20.17/ Transfer of substance at dedicated facilities (PROC8b)	6	-	-	-	<0.061	1.277	EEA	Consultation 5
NACE C19.20 and C20.17/ Combined monomer production and polymerisation of isoprene	-	-	-	27.86 (98.5^{th} percentile)	-	-	US	Leber (2001), Lynch (2001)
NACE C20.17/ Polymer production, use as an intermediate, polymer processing (PROC2,3,4,5, 6,8a,8b,9,13,14 ,15)	-	0.248	-	-	-	-	EEA	CSR, (2023)

Source: Study team from published sources and stakeholder consultation.

3.3.5 Summary of exposure data by sector

Given that the above data is mainly sourced via consultation, CSRs and from air monitoring measurements taken within the last 3 years, the consultation/CSR data is expected to present the most accurate interpretation of the current exposure. As such the findings highlighted by Leber (2001) and Lynch (2001) will not be used in any further analysis of exposure data with the report solely relying on data derived from consultation/CSRs. This is due to the outdated nature of this study and the fact that the survey was conducted in the wrong geographical region, meaning the inclusion of this data would likely disrupt the accuracy of the report findings.

3.3.6 Exposure levels with and without respiratory protective equipment (RPE)

The exposure data gathered as a part of this study has been gathered using methods such as the withdrawn OSHA 07 methodology (OSHA, 2000). This method indicates the use of a personal sampling pump however diffusive samplers for stationary sampling have also been developed for isoprene measurements. Measurements shared in consultation were gathered via a mix of stationary air sampling and personal air sampling. Based on data provided and OSHA methodology it can be expected that the exposure data gathered represent exposure concentrations before any RPE has been used. Consultation also indicates that RPE is used significantly across both sectors investigated in this report to control exposure levels at high-risk processes.

Data gathered via the sharing of confidential CSRs has also been used in the derivation of exposure concentrations for this study. This data showed predicted exposure concentrations for various processes although it did not account for the use of RPE under any of these. As such the CSR data has had a 95% efficient RPE applied to better reflect the true exposure values which workers may experience. This is based on the data found in consultation which indicated that across both sectors all workers at points of high risk of exposure (i.e. those not involving closed systems) are required to wear RPE.

As consultation data largely accounts for measurements around closed systems where RPE is not required and as the CSR data accounts for all processes but with RPE applied as an adjustment factor, these datasets can be seen as being representative of the true exposure concentrations workers would experience in these two sectors.

3.3.7 Trends in exposure concentrations

It has been reported by Lynch (2001) that numerous engineering and work-practice improvements had been implemented over the study period which had resulted in significant decreases in worker exposures. Assuming that this trend of continued improvements has been continued post 2001 it could be expected that current day exposures to isoprene would be significantly lower than those reported in section 3.3.4 above. The introduction of other non-binding targets such as the AIHA WEEL of 2ppm, implemented in 2004, may also indicate the industries continued efforts to reduce worker exposure (AIHA, 2021). The gathered exposure data via consultation also appear to support this trend.

In the current situation, however, it is not expected that isoprene exposure concentrations will significantly reduce in future years. This is based on consultation data which indicate risk management measures (RMMs) in both sectors are currently implemented to the most extent possible i.e. fully closed systems with 80-100% effective RPE required in high risk tasks (see section 3.5.4). Given these measures, there is very little feasibility for companies in either sector to be able to further reduce exposure concentrations in future years and so from the present values no significant change is expected.

3.3.8 Summary of exposure concentrations used for the further analysis

The following table provides a summary of the exposure data to be taken forward in this assessment. This data has been derived from the consultation data as shared in section 3.3.4 and will form the basis of the benefits side of the cost benefits analysis.

Table 3-10 Summary of exposure concentrations by sectors for isoprene used for the further analysis – without adjustment for the use of RPE. All values in mg/m³.

Sector		AM	Median	P75	P90	P95	Max
C19.20	Manufacture of refined petroleum products	0.20	0.11	0.23	0.44	0.65	1.36
C20.17	Manufacture of synthetic rubber in primary forms	0.25	0.21	0.31	0.43	0.52	0.76

Source: Study team on basis of information presented in this section.

Please note that whilst the value of MAX (the maximum given value) is given in this table, this does not equate to the P100 percentile. This is because the data has been modelled via a log normal distribution and as such it is not possible to calculate such a value.

3.3.9 Values used in the benefits and costs models

In both the benefits and costs models, the exposed workers or enterprises with exposed workers are split into five groups representing the groups shown in Table 3-11. The exposure level assumed to be experienced by this group is calculated as shown in Table 3-11.

Table 3-11 Calculation of exposure levels (inhalable) used in benefits and costs models

Percentiles	Proportion of workers or enterprises	Calculation for exposure level assumed for modelling
0 – 50	50%	50^{th} percentile
51 – 75	25%	Mean of 50^{th} and 75^{th} percentiles
76 – 90	15%	Mean of 75^{th} and 90^{th} percentiles
91 – 95	5%	Mean of 90^{th} and 95^{th} percentiles
96 – 100	5%	Geometric mean of 95^{th} and 100^{th} percentiles

3.4 Exposed workforce

3.4.1 Introduction

This section provides an overview of the expected workforce believed to be exposed to isoprene within the EU. This is based off the pre-established sectors of use, data gathered via consultation and literature and combined with data derived from Eurostat. In order to use the Eurostat data throughout this section specific informed assumptions have needed to be made. Where assumptions have been made these have been informed by the data gathered via consultation with industry and therefore are grounded in the real-world situation to deliver a realistic best estimate.

3.4.2 Data on exposed workforce from national databases

The study team have found no national databases which have current data relating to the number of exposed workers to isoprene in the EU. When the scope of this investigation was expanded it was found that in past studies such as the National Occupational Exposure Survey (NOES) conducted in the United States over 1981-1983, 3,700 workers were identified with potential isoprene exposure (IARC, 1999; NTP, 2021). Previous iterations of this same survey however did indicate significantly higher numbers of exposed workers (58,000) in a study conducted between 1972-1974 (NTP, 2021). In the context of the current study however neither of these national surveys are within the correct geographical area or the timeframe and are therefore of little benefit to predict worker numbers.

3.4.3 Average number of exposed workers per company (consultation)

Based on consultation with industry, the following data were gathered concerning workers employed at industrial sites which may have potential for exposure to isoprene. The table below provides a summary of the average (arithmetic mean) and minimum/maximum values found in the consultation for each sector.

Table 3-12 Survey result for average number of exposed workers per company

Sector	Number of workers per company exposed to isoprene Average (min - max)	Percentage of workers in companies exposed to isoprene Average (min - max)
Manufacture of refined petroleum products	106 (10-288)	28% (0.8%-84.7%)
Manufacture of synthetic rubber in primary forms	70 (1-260)	10% (0.3%-38.2%)

Source: Study team on basis of stakeholder responses.

3.4.4 Exposed workforce by sector

The following sections of this report provide a deeper insight into the total number of workers in each of the relevant sectors as identified by Eurostat (and therefore taken as an extrapolation of the total EU situation). Before correction this data is likely an overestimate of the true value for the number of workers exposed to isoprene in the EU because data in Eurostat are derived from NACE codes. Relevant NACE codes are not specific to operations relating to isoprene and often include the production of a wider range of products, meaning correction factors will need to be applied to ensure the data only reflect companies manufacturing/using isoprene. If wider information were available this section would also provide an overview of worker data gathered from literature sources, however given the limited availability of data only values from Eurostat and the consultation can be illustrated.

3.4.4.1 Manufacture of refined petroleum products

Using the NACE code of C19.20 the following data have been extracted from Eurostat. This data provides an overview of the total number of workers in the EU employed in industries classified under NACE 19.20.

Table 3-13 Data available for the number of workers involved in the manufacture of refined petroleum products.

Number	Description	Comment
164,143	C19.20 Manufacture of refined petroleum products	Total number of employee for all enterprises within NACE code.

Source: Eurostat (2020)

Based on the data extracted above it can be observed that there is a significantly higher proportion of workers linked to this NACE code than were identified via the consultation. This is due to the aforementioned overestimate where not every company involved in the manufacture of refined petroleum products is likely to have a risk of isoprene exposure. Based on consultation data, 18 companies in Europe are likely to be producing isoprene (both intentionally or unintentionally), whilst, in total, the NACE code covers 821 unique enterprises.

The 18 companies mentioned above were highlighted to the study team via consultation and publicly available data sets. Initial screening into these companies revealed that all would be classified as large companies with no SMEs manufacturing isoprene. Based on this knowledge the Eurostat average number of workers in large companies for NACE C19.20 can be multiplied by the number of companies to derive the number of workers in companies producing isoprene in the EU. The total workers deemed relevant to isoprene refining companies is therefore estimated at 36,666.

Whilst 36,666 can be seen as the number of employees in companies refining isoprene, this figure still does not represent the number of workers with exposure to isoprene. To calculate this, data from the consultation was used to estimate a total percentage of the refinery workforce who may have potential to be exposed via higher risk operations such as maintenance or filling. This derived an approximate exposed percentage of 28% which, when applied to the number of employees in relevant companies to isoprene, results in a total exposed workforce of 10,266.

3.4.4.2 Manufacture of synthetic rubber in primary forms

The approach for this sectors calculation is the same as above and is reliant on worker data from Eurostat. This Eurostat data is summarised in the table below, highlighting the total workers involved in the NACE code C20.17.

Table 3-14 Data available for the number of workers involved in the manufacture of synthetic rubber in primary forms.

Number	Description	Comment
8,970	C20.17 Manufacture of synthetic rubber in primary forms	Total number of employee for all enterprises within NACE code.

Source: Eurostat (2020)

The number of workers determined to be relevant in this NACE code is again higher than the number of workers determined via consultation due to the same reasons as above (not all companies in this NACE code will be relevant to isoprene). To determine the number of workers applicable to companies using isoprene, the number of companies with active registrations (split by SME classification) was multiplied by the average number of workers per company size for the C20.17 NACE code. This results in a total of 2,726 workers at synthetic rubber production sites using isoprene in the EU.

Alike the methodology for refineries, this number of workers was adjusted to calculate the true value of those workers with potential exposure to isoprene. For companies conducting polymerisation processes involving isoprene the proportion of exposed workers was estimated at approximately 10% which when applied to the data above results in 273 exposed workers to isoprene in this industry sector.

3.4.5 Trends in exposed workers

By reviewing Eurostat data for previous years and analysing industry trends, the study team has been able to investigate the change in the number of workers employed in each sector relevant for isoprene. The table below indicates for each sector the annual compound employee growth rate and uses this to estimate the number of workers who may be exposed to isoprene in each sector in both five years and ten years' time. These timeframes are selected in place of the 40 years elsewhere used in this report since it would not be reliable to assume the current compound annual growth rates (CAGR) would remain consistent over 40 years. As such, using five and ten years means the data is more likely an accurate reflection of the employee growth as opposed to projections over 40 years which would be highly unreliable.

Table 3-15 Estimated number of workers exposed in five and ten years based on current growth rate.

Sector		Number of exposed workers currently	Annual compound growth rate (%)	Number of workers exposed in 5 years	Number of workers exposed in 10 years
C19.20	Manufacture of refined petroleum products	10,266	-6	7,534	5,529
C20.17	Manufacture of synthetic rubber in primary forms	273	7	383	537
Total		10,539		7,987	6,066

Source: Study team based on Eurostat information and Ding et al (2022)

The growth rate of -6% attributed to C19.20 is based on predictions from McKinsey & Co (Ding *et al*., 2022), the refinery capacity in Europe will, depending on scenario, decrease by 19-58% (current trajectory of 46%) of the 2019 capacity by 2040. As a consequence of the ban of sale of new diesel and gasoline driven cars and vans from 2035, the decrease is expected to continue after 2040. The 6% reduction per year corresponds to these figures and as such employee numbers are expected to further reflect this trend.

The growth rate for C20.17 has been extracted for the entire NACE code and so also includes companies not producing isoprene-based rubber products. The value of 7% however is well supported by market reports which indicate similar levels of growth in the isoprene market (Grand View Research, 2023; Markets and Markets, 2017) and so 7% can be taken as a realistic change in employees for C20.17.

Combined the data highlight both increasing and decreasing worker numbers across the two sectors with an overall decrease in exposed workers occurring across both industries. This is contrary to the market growth of isoprene in Europe (Grand View Research, 2023; Markets and Markets, 2017). The decrease in exposed workforce is therefore attributed largely to the closure of refineries in Europe which would result in unintentional exposure to isoprene as opposed to a direct result of the isoprene market.

3.4.6 Summary of exposed workforce

To summarise the above information, the following tables provide an overview of the total employees in each of the relevant NACE code sectors, the number of workers in companies using/producing isoprene and the number of those workers with potential for exposure to isoprene.

Table 3-16 Estimated number of workers in the EU27 exposed to isoprene in key sectors.

Sector		Number of exposed workers	Total number of workers in NACE code	% of all workers in NACE code
C19.20	Manufacture of refined petroleum products	10,266	164,143	6%
C20.17	Manufacture of synthetic rubber in primary forms	273	8,970	3%
Total		**10,539**	**173,113**	

Source: Study team based on information presented in this section.

Table 3-17 Estimated number of workers in the EU27 exposed to isoprene and companies with exposed workers in key sectors.

Sector		Number of exposed workers	Number of companies with exposed workers	Total number of workers in companies	Number exposed per company	Percentage exposed in companies
C19.20	Manufacture of refined petroleum products	10,266	18	33,666	570	28%
C20.17	Manufacture of synthetic rubber in primary forms	273	62	2,726	4	10%
Total		**10,539**	**80**	**36,392**	**132**	

Source: Study team based on information presented in this section.

Based on the information above, it can be observed that, of the two sectors, the manufacture of isoprene monomer via refining of petroleum is likely to expose more workers to isoprene than the subsequent polymerisation process. In total it can be estimated that 10,539 workers in the EU may be exposed to isoprene across a total of 80 different companies. This equates to an average of 132 workers with exposure to isoprene per company identified as producing/using the substance.

3.5 Current risk management measures (RMMs)

3.5.1 Types of RMMs

A number of different types of risk management measures can be applied within an industrial setting in order to help reduce exposure to hazardous chemicals in the workplace. A hierarchy of the different measures which may be used is described in the CMRD and is highlighted in the table below.

Table 3-18 Hierarchy of measures to be applied by the employers, as listed in the CMRD

Type of measure	Measures specified in the CMD
Reducing the quantities of the chemical agents used (substitution and material reduction)	(a) limitation of the quantities of a carcinogen or mutagen at the place of work;
Reducing the number of workers exposed	(b) keeping as low as possible the number of workers exposed or likely to be exposed;
Reducing the concentration of the chemical agents at the workplace	(c) design of work processes and engineering control measures so as to avoid or minimise the release of carcinogens or mutagens into the place of work;
	(d) evacuation of carcinogens or mutagens at source, local extraction system or general ventilation, all such methods to be appropriate and compatible with the need to protect public health and the environment;
	(e) use of existing appropriate procedures for the measurement of carcinogens or mutagens, in particular for the early detection of abnormal exposures resulting from an unforeseeable event or an accident;
	(f) application of suitable working procedures and methods;

Type of measure	Measures specified in the CMD
Reducing the exposure of workers by protective measures	(g) collective protection measures and/or, where exposure cannot be avoided by other means, individual protection measures;
	(h) hygiene measures, in particular regular cleaning of floors, walls and other surfaces;
	(i) information for workers;
	(j) demarcation of risk areas and use of adequate warning and safety signs including 'no smoking' signs in areas where workers are exposed or likely to be exposed to carcinogens or mutagens;
	(k) drawing up plans to deal with emergencies likely to result in abnormally high exposure;
Other measures	(l) means for safe storage, handling and transportation, in particular by using sealed and clearly and visibly labelled containers.

Source: CMRD

It can be observed that based on this hierarchy, companies should first aim to reduce the use of hazardous substances via quantity or concentration, then aim to reduce the number of workers and then finally introduce physical protective measures to ensure worker protection.

3.5.2 Current use of RMMs by sector

3.5.2.1 Data from Chemical Safety Reports (CSRs)

For both manufacture of isoprene as well as use in polymerisation processes, the Process Categories (PROCs) in the REACH registration dossiers suggest relatively controlled activities with limited occupational exposure reflective of the exposure concentrations highlighted in section 3.3.4.

3.5.3 Data from questionnaire survey

The following table indicates the variety of responses received in the consultation when respondents were asked about the current RMMs they are using. The data were gathered on a process-by-process basis and so the counts shown in brackets indicate the use of this specific RMM in one process within that industries overall operations. The percentages represent this as a proportion of the total processes within that industry using this RMM.

Table 3-19 Companies' use of RMMs for individual process by sector based on consultation survey

Values	C19.20	C20.17
Substitution		
Discontinuation	14% (1)	60% (3)
Reduce use		
Reduce workers		
Rotate workers		
Redesign		
Closed systems	86% (6)	60% (3)
Partial hood		

Values	C19.20	C20.17
Open hoods		40% (2)
General ventilation	71% (5)	80% (4)
Pressurised control cabs	57% (4)	20% (1)
Simple control cabs		
RPE	71% (5)	40% (2)
HEPA		
Masks		40% (2)
Goggles	71% (5)	60% (3)
Gloves	71% (5)	100% (5)
Continuous measurement to detect unusual exposures		
Training	71% (5)	100% (5)
Cleaning	71% (5)	60% (3)
Creating a culture of safety	71% (5)	60% (3)
Personal hygiene (e.g. daily cleaning of work clothing, obligatory shower)	71% (5)	60% (3)
Provision of separate storage facilities for work clothes	71% (5)	100% (5)
Total number of processes analysed in sector	7	5

Source: Consultation survey

3.5.4 Use of personal protective equipment

Via consultation with industry conducting the refining of isoprene the frequent use of PPE has been reported. This is mainly in the form of RPE (respiratory protective equipment) used at any point where exposure to isoprene may occur. This was referred to by one respondent as being contained in an analytical plan. Within this plan, all fixed points where exposure may occur are documented and the plan indicates that "*All activities that can involve a potential exposure are performed with a complete facial mask worn.*" Based on the responses given, this facemask is likely to provide significant protection from exposure as it was cited that RPE used could be either oxygen fed or negative pressure respirators, which can be assumed to have 80% to 100% efficiency (Johnson *et al*, 1994). In addition to this, protective gloves and goggles have been stated as being used as well as daily cleaning of work clothing.

In the interview consultation phase, less information was gathered for the use of PPE in sites conducting the polymerisation of isoprene into synthetic rubbers. However, based on the survey responses highlighted in section 3.5.3 above, it can still be observed that workers at these sites do use PPE in their operations. Specifically in the manual maintenance of equipment and the transfer of a substance (including filling/unloading equipment), all companies mentioned the use of either oxygen fed or negative pressure respirators alongside gloves and visors/goggles. It was also stated that for operations involved the manufacture within closed systems these PPE measures were also required.

The only process mentioned in polymerisation sites in which RPE was not required was the use of isoprene as a laboratory reagent which is believed to be conducted as testing. It was stated however that this process was conducted in a closed system with both general and local exhaust ventilation and so exposures are still predicted to be relatively low.

3.5.5 Technical measures

The main technical measure in place across the industry is the presence of closed system production. Closed systems are found to be present across all the production processes in both the refining of isoprene and the polymerisation of isoprene. This fact is also well documented in literature (OECD, 2005; Lynch, 2001).

In the refining of isoprene, the technical measures mentioned also included the presence of pressurised control cabs and general ventilation. It can be expected that pressured control cabs can operate at around 100% efficiency whilst general ventilation is a less effective measure. In combination with the closed system processes and RPE/PPE requirements, it can be expected that these RMMs are significantly reducing the potential isoprene exposure for workers within refineries.

At sites conducting polymerisation activities the main additional technical measures are general ventilation, open hood ventilation and pressurised control cabs. As previously stated, these pressurised control cabs are highly efficient at the reducing emissions whilst open hood ventilation can be assumed to have an efficiency of around 80%. It should also be mentioned that in the consultation one respondent indicated that the filling operations for the closed system via dry break fittings in open air. As this is an open-air process still conducted with RPE (as mentioned in section 3.5.4) then it can be expected worker exposures to isoprene are minimal.

3.6 Voluntary industry initiatives

Given the lack of available data and the limited number of responses to consultation efforts it has been hard to gather a full understanding of the extent of voluntary initiatives across industry using isoprene. Attention should however be drawn to one petrochemical refinery operating in Europe who highlighted that they have implemented a company wide OEL for isoprene based on the US Workplace Environmental Exposure Levels (WEELs). The WEEL limit for isoprene was last updated in the US in 2004 to a level of 2 ppm (5.7 mg/m^3) and so this is the value used as a voluntary OEL by the respondent. In order to ensure this voluntary standard is met, the respondent carries out routine air monitoring measurements at two of its four sites associated with isoprene manufacture. Based on the data from these sites and similarities in the process, an extrapolation of very low risk of exceeding these limits can be assumed for the other two sites.

Given the low levels of exposure as reflected in section 3.4 it is not expected that many companies will be implementing further voluntary initiatives in relation to isoprene due to the already low exposures and extensive controls already in place.

3.7 Examples of good/best practice

3.7.1 Use of Respiratory Protective Equipment (RPE)

Despite both sectors investigated in this report having fully enclosed systems and methods for purging the closed system, the use of RPE has also been identified by all respondents. This RPE whilst recommended would not be required in order to have exposure below the 4:100,000 level for isoprene and as such is an example of best practice to reduce exposures to as low as possible. This RPE was stated by one respondent as being used in any operations for which there is an elevated risk of exposure in relation to the normal continuous closed operations. These events may be maintenance or filling operations which require the closed system to be opened. The RPE used does vary in efficiency with some companies using oxygen fed masks (assumed to be 100%

efficient when used correctly) and others using negative pressure full/half face respirators (estimated to be around 80% efficient (Johnson *et al*, 1994)).

3.7.2 Closed system sampling

Again, via consultation it was mentioned that companies involved in the refining of isoprene are likely to conduct sampling of products using closed system apparatus. Sampling is usually one of the main processes that may relate to worker exposure and so the use of closed systems to conduct this process is a significant benefit in helping to reduce potential worker exposure. Whilst this sampling could be seen as best practice for industry, it is likely to come at significant cost as conversion to full enclosure of processes are often entail high costs. It is however expected that steam crackers and refineries will be operated by large companies who would be better positioned to absorb these costs than smaller SME companies.

3.7.3 Options for making good practice available to stakeholders

Based on consultation data it is understood that best practice for stakeholders is currently the established and accepted methodology. As such very few efforts would be required to make best practice available to stakeholder due to already widespread adoption of suitable risk management measures in the industry.

3.8 Standard monitoring methods/tools

3.8.1 Compliance monitoring

Procedures for monitoring of contaminants in the workplace are typically established by national guidelines prepared by the national working environment authorities. These guidelines would typically refer to European standards to be used for the monitoring.

As concerns the monitoring of substances in the workplace, guidelines refer to two European standards:

- EN 482:2012+A1:2015 : Workplace exposure. General requirements for the performance of procedures for the measurement of chemical agents.

- EN 689:2018+AC:2019: Workplace exposure. Measurement of exposure by inhalation to chemical agents. Strategy for testing compliance with occupational exposure limit values.

The strategy described in EN 689:2018 gives a procedure for the employer to overcome the problem of variability and to use a relatively small number of measurements to demonstrate with a high degree of confidence that workers are unlikely to be exposed to concentrations exceeding the OELs. The procedures are further described in the Methodological Note.

As described in the Methodological Note, in order to undertake the screening tests, ideally an analytical method with a limit of quantification (LOQ) at 0.1 * OEL would be required; otherwise, it will be necessary to undertake more tests and the costs of monitoring increases. For the lowest of the reference values proposed by RAC this would correspond to 0.1 μg/m^3 for the inhalable fraction and 0.05 μg/m^3 for the respirable fraction.

3.8.2 Available analytical methods

Currently there is only one published method which specifically identifies relevant sampling and analysis of isoprene air concentrations in the workplace. This method (OSHA 07) covered methods for the analysis of a large range of organic vapours using activated carbon sampling and gas chromatography with flame ionisation detection (OSHA, 2000). The method was previously accepted but has been withdrawn from use since 2017 in favour of returning to substance specific methodologies. Isoprene however has never had a substance specific methodology and therefore currently has no validated method for its sampling. Based on consultation data it has been indicated that this withdrawn methodology is still used in the measurement of isoprene concentrations. The OSHA method is outlined in Table 3-20.

Sampling methods should have a validation from a relevant testing body in order demonstrate compliance with the requirements of the standard EN 482 or the potential to meet these requirements for some of the proposed OELs. This validation is currently not granted for the OSHA 07 methodology however based on consultation and wider reading it could be expected that the method would still result in accurate data for isoprene monitoring.

One method for the sampling of isoprene is outlined by Sigma Aldrich using Radiello® samplers (Sigma-Aldrich, 2009). The technique generally reflects that of the OSHA 07 methodology although in place of flame ionisation detection (FID) this method uses mass spectrometry. This method is suitable for both 1,3-butadiene and isoprene and as such the OSHA method 56 for the identification of 1,3-butadiene may also be suitable for isoprene. Consultation with sampler providers highlighted that isoprene is more likely to give a reliable result than 1,3-butadiene as the potential for reverse diffusion off the activated carbon is less for isoprene. As mentioned previously this method has not been officially validated for the sampling of isoprene and as so despite likely providing accurate measurements cannot do so via a ‘valid’ methodology.

A further unvalidated methodology for determination of levels of isoprene in workplace air has been investigated by Wasilewski and Kowalska (2023). In this method the same approach of using an activated carbon diffuse sampler, desorption with carbon disulfide (CS_2) and GC-FID was investigated to determine the limits of detection and quantification. The study findings indicate that the method meets the requirements of EN 482 and has a good level of precision for determination of isoprene concentrations. From this the calculated LOQ was derived at 0.2 mg/m^3 and the Limit of Detection (LOD) was derived at 0.06 mg/m^3. Based on the findings of this study it could be extrapolated that whilst the methodology is not validated this may still be a suitable method for measurement of isoprene concentrations due to compliance with EN 482 and LOQ below the lowest policy option.

Personal sampling of isoprene is also possible as products are available which can be attached to workers during activities (Advanced Chemical Sensors, 2018). From consultation it was found that the badge sampler 525AT from Assay Technology could be used to collect isoprene however the analysis method for isoprene has not been developed by Assay Technology for these samplers. As such the samplers may be provided to other labs who would likely follow the OSHA 07 analysis method. Other similar personal samplers are stated to be suitable for OSHA method 58 which relates specifically to volatile hydrocarbons in coal tar pitch. Isoprene is not a component of coal tar pitch and so there is speculation as to whether these other products are suitable for isoprene sampling.

Table 3-20 Overview of sampling and analytical methods for monitoring of isoprene in workplace air

No	Method/ Fraction	Analytical Technique	LOQ and sampling volume and time	Similar methods/ comments
1	OSHA 07 / air	GC/FID with CS_2 desorption	0.009 - 0.2 mg/m^3 (volume not stated, 8 hours)	OSHA 56, MDHS 63-2, MDHS 53-2, NIOSH 1024 / methods for butadiene sampling

Note: GC – Gas chromatography, FID – Flame ionisation detection, MS – Mass spectrometry, CS_2 carbon disulphide

It should also be noted that via consultation multiple limits of quantification (LOQ) were shared relating to OSHA 07 and no LOQ was published in the original method (OSHA, 2000). This is important as the upper bound of 0.2 mg/m^3 is higher than the recommended LOQ of 10% of the lowest OEL (0.13 mg/m^3).

In Watson *et al* (2011), it is however discussed that using a time-of-flight mass spectrometer in place of FID or quadrupole Mass Spectrometer may be able to allow isoprene measurements with a detection limit of < 10 ppt (0.00003 mg/m^3) under the specific conditions used in the test method. This method does also involve the use of a piston pump to sample 0.5 L air at an increased rate over natural diffusive collection methods. Given the level of precision able to be achieved in this methodology it is highly likely that methods such as this would allow quantification of isoprene at 10% of the lowest OEL.

3.8.3 Summary of monitoring methods/tools

Overall, the methodology currently used for the monitoring of isoprene in the workplace is observed as withdrawn and so is not determined to be a valid methodology. Despite this lack of a validated analysis method, sampling methods do exist for isoprene in the form of both personal and stationary samplers. Via consultation and literature, these samplers can be confirmed to be suitable for the collection of isoprene workplace air samples, with a greater confidence than that of 1,3-Butadiene, which does have a validated method based on these samplers (OSHA 56). In terms of analysis, this is likely still conducted via the method presented in OSHA 07 with potential for advances in this method, presented in Watson *et al* (2011), to be implemented. These advances relate to the use of thermal desorption as opposed to CS_2 desorption and the use of time-of-flight mass spectrometry in place of FID. Should these advances be introduced then it would be possible for the LOD to reach < 3 x10^{-5} mg/m^3 (< 10 ppt) making it highly likely that the LOQ would be below 10% of the most stringent policy option (0.13 mg/m^3).

Via consultation with Member State Authorities (MSA) additional data were gathered on the lowest level of practically achievable quantification. All respondents indicated the methodology used would be the same as that issued in OSHA-07 using activated carbon diffusive samplers, thermal desorption or desorption with CS_2 followed by GC-FID analysis. The LOQ for this method was stated by MSA as between 0.0001 and 25 mg/m^3. Based on the data reported in the OSHA methodology and in literature it is decided that some values within this range are likely inaccurate and as such the true LOQ is likely in the range of 0.0001-0.8 mg/m^3.

3.9 Intermediate uses not covered by certain REACH procedures

Under REACH, an intermediate is a substance that is manufactured for and consumed in or used for chemical processing in order to be transformed into another substance (REACH Article 3(15)). Substances used as intermediates would not be covered by parts of the REACH registration.

Substances which are used as on-site isolated intermediates are not subject to authorisation, and are exempted from restriction (ECHA, 2023). Transported isolated intermediates are not subject to authorisation but may be subject to evaluation and restriction. Residues of the isolated intermediates, which are not transformed into another substance in a manufacturing process, will be typically discarded or disposed of as waste or recycled as intermediates and are not subject to neither authorisation nor restrictions.

Isoprene is used as an intermediate within the EU as the monomer is produced as an intermediate substance in the manufacture of polymeric compounds. However, the registrations held for isoprene within the EU are not specific to that of an intermediate substance and instead have the full registration requirements.

3.10 Market analysis

3.10.1 Sources of data on enterprises with exposed workers

Alike the earlier sections of this report, the availability of public data on the numbers of enterprises with exposed workers to isoprene is very limited. As such the main sources of information used to calculate the number of companies per sector have been Eurostat and the consultation. This is reflected in section 3.4 earlier relating to the estimation of exposed workers.

For refineries producing isoprene monomer the consultation with a European Industry association provides an exact figure for the number of relevant companies manufacturing isoprene within the EU. As this data was direct from and overarching industry association with good visibility across the industry the data has been taken to be accurate and representative for the EU. The study team however are continuing to look into data sources for any companies who are unintentionally producing isoprene as a byproduct in products such as PyGas.

The consultation in relation to downstream polymerisation facilities however did not yield such results and so less accurate estimates were needed to be derived via the Eurostat information platform. In this case the number of companies for the NACE code C20.17 was extracted, and assumptions were made to derive estimates of the proportion of the total NACE code relevant to the use of isoprene.

3.10.2 Study team analysis of Eurostat, survey and industry data

3.10.2.1 Manufacture of refined petroleum products

In the case of refineries, as previously mentioned, Eurostat was not used to derive the actual values for the number of enterprises operating with isoprene in the EU. However, in order to derive other values from the Eurostat data it is still important to establish the proportion of the total NACE code data which is relevant to those companies refining isoprene. By applying the data shared of three large companies against the total number of enterprises in the NACE code it was derived that <0.5% of the total NACE code would be applicable to those refineries specifically producing isoprene monomer. As the data shared were also in reference to three large companies the SME split for refineries was not required to be conducted.

3.10.2.2 Manufacture of synthetic rubber in primary forms

In the calculation of the total enterprises relevant for the polymerisation process the NACE code of C20.17 manufacture of synthetic rubber in primary forms was used as a starting point. In addition to this the total number of EU registrants for isoprene was extracted from the latest update of the registration dossier. Those companies involved in the refining of isoprene were removed from the total number of registrants leaving the value of 62 companies believed to be involved in the manufacture of synthetic rubber using isoprene as a monomer. By applying this data in the same way as above to the Eurostat data it was calculated that approximately 35% of the total NACE code data would be applicable to those companies using isoprene. Section 3.10.3 below provides a summary of the data derived based on these calculations.

3.10.3 Summary of enterprises with exposed workers

Table 3-21 Estimated number of EU enterprises with workers exposed to isoprene using Eurostat, survey and industry data

Sector		Number of enterprises in EU (Eurostat)	% of enterprises with exposed workers	Estimated enterprises with exposed workers in EU
C19.20	Manufacture of refined petroleum products	821	2%	18
C20.17	Manufacture of synthetic rubber in primary forms	179	35%	62

Source: Study team on basis of stakeholder result and Eurostat Structural Business Statistics.

3.10.4 Enterprises with exposed workers by sector and by size of enterprise

Table 3-22 Distribution of EU enterprises by sector and by size of enterprise according to Eurostat

Sector		Total number of enterprises	Percentage of enterprises		
			Small <50 employees	Medium 50-249 employees	Large >249 employees
C19.20	Manufacture of refined petroleum products	821	83%	8%	9%
C20.17	Manufacture of synthetic rubber in primary forms	179	85%	11%	4%

Source: Study team on basis of stakeholder result and Eurostat Structural Business Statistics.

Table 3-23 Estimated number of EU enterprises with exposed workers by sector and by size of enterprise

Sector		Number of enterprises			
		Small <50 employees	Medium 50-249 employees	Large >249 employees	Total
C19.20	Manufacture of refined petroleum products	-	-	18	18
C20.17	Manufacture of synthetic rubber in primary forms	53	7	2	62

Source: Study team on basis of stakeholder result and Eurostat Structural Business Statistics.

3.10.5 Enterprises with exposed workers by Member State

Table 3-24 Estimated number of EU enterprises with exposed workers by Member State

Member State	Total number of enterprises with exposed workers
Belgium	2
Bulgaria	-
Czechia	-
Denmark	-
Germany	9
Estonia	-
Ireland	-
Greece	1
Spain	15
France	4
Croatia	-
Italy	11
Cyprus	-
Latvia	-
Lithuania	-
Luxembourg	-
Hungary	1
Malta	-
Netherlands	4
Austria	1
Poland	6
Portugal	-
Romania	3
Slovenia	-
Slovakia	17
Finland	1
Sweden	1
Grand total	**76**

Source: Study team on basis of stakeholder result and Eurostat Structural Business Statistics.

Note: The total sum of enterprises may not equal the total number of enterprises with exposed workers due to rounding

Table 3-25 Estimated number of EU enterprises with exposed workers by key sector and by Member State

Member State	C19.20 Manufacture of refined petroleum products	C20.17 Manufacture of syn-thetic rubber in primary forms
Belgium	-	2
Bulgaria	-	-

Member State	C19.20 Manufacture of refined petroleum products	C20.17 Manufacture of synthetic rubber in primary forms
Czechia	-	-
Denmark	-	-
Germany	2	7
Estonia	-	-
Ireland	-	-
Greece	1	-
Spain	-	15
France	-	4
Croatia	-	-
Italy	7	4
Cyprus	-	-
Latvia	-	-
Lithuania	-	-
Luxembourg	-	-
Hungary	-	1
Malta	-	-
Netherlands	1	3
Austria	-	1
Poland	3	3
Portugal	-	-
Romania	1	2
Slovenia	-	-
Slovakia	-	17
Finland	-	1
Sweden	-	1
Total	**15**	**61**

Source: Study team on basis of stakeholder result and Eurostat Structural Business Statistics.

Note: The total sum of enterprises may not equal the total number of enterprises with exposed workers due to rounding

3.10.6 Cross border aspects

As a part of this study, it should also be considered that in some cases, differences in OEL values between individual Member States may create difficulties in harmonising processes to meet required OELs. For example, a company operating in one Member State may have different OELs to another Member State where they also have operations. This means companies may have difficulty in implementing RMMs, as they may be required in one Member State but not others. This may be the case for companies with multiple sites within the EU if the Member States operated within have national OELs (Bulgaria, Germany, Latvia, Lithuania and Poland).

In the case of isoprene, however, the impacts of introduced OELs are expected to be low/nil due to the exposure concentrations, summarised in section 3.3, indicating levels below the 4:100,000 excess cancer risk value (see section 2.2). Due to this fact, it is not expected that the implementation of new OELs or the existing national OELs would create any issues for companies operating in multiple different nations.

3.10.7 Market trends

As previously conducted in the exposed workforce section (3.4), the Eurostat data and Ding *et al*, (2022) can also be extrapolated to include a growth rate in the number of businesses in the EU using isoprene. As such, this growth rate can be applied to the estimated number of companies using isoprene in the EU to predict future changes in the number of companies using isoprene who are operational in each of the two sectors. The table below highlights the outputs of the changing trends in enterprise growth/decline and sets out estimates of the number of companies being operation in both five and ten years time.

Table 3-26 Estimated number of companies using isoprene in 5 and 10 years based on current growth rate.

Sector		Number of enterprises currently using isoprene	Annual compound growth rate (%)	Number of companies using isoprene in 5 years	Number of companies using isoprene in 10 years
C19.20	Manufacture of refined petroleum products	18	-6	13	10
C20.17	Manufacture of synthetic rubber in primary forms	62	2	68	76
Total		80		81	86

Source: Study team based on Eurostat information and Ding et al. (2022)

Based on these trends, it can be observed that the number of new entrants into the market will increase in those producing isoprene rubber but will decrease for those manufacturing isoprene monomer. These numbers appear in contrast to the predicted market growth for isoprene which can be estimated at 7% (see section 4.5), however these figures are specific to numbers of companies not isoprene production. As such it can be expected that whilst some new companies will enter the market, this will likely be in tandem with existing companies scaling up their production to meet the higher market projections. This is likely realistic as the primary decline in the companies involved in the refining of isoprene monomer is driven by decreasing demand for vehicle fuels (petrol, diesel), not decreasing demand for wider petrochemical products (Ding *et al*, 2022).

3.11 Alternatives

Substitution is a key risk management measure for companies having difficulty achieving an OEL. Therefore, it is important to know whether alternatives exist for isoprene. The possible alternatives are discussed below.

3.11.1 Manufacture of refined petroleum products

As this sector is responsible for the production of isoprene and not for the use of isoprene, an analysis of alternatives is not applicable.

3.11.2 Manufacture of synthetic rubber in primary forms

As previously mentioned in this report, isoprene is not the only monomer used in the manufacture of synthetic rubbers and therefore in the event of not being able to meet a new OEL, companies manufacturing rubber in primary forms would likely replace their current isoprene rubber manufacture with manufacture of other primary rubber chemistries. This switch would be based on whether downstream use applications would be able to substitute isoprene containing rubbers for other rubber chemistries and thus increase demand of alternatives.

Whether a downstream use can substitute away from isoprene containing rubbers will depend on the specific requirements of the use as different rubber chemistries have different offerings of technical properties. A comparison of different rubber chemistries is given in Table 3-27 below.

Table 3-27 Comparison of rubber chemistries

	Natural rubber	Styrene Butadiene Rubber (SBR)	Ethylene Propylene Diene Methylene (EPDM)	Butyl Rubber (IIR)	Neoprene	Nitrile	Silicone	Viton (FKM)	Poly-urethane
Abrasion resistance	4	3	3	2	3	3	1	2	4
Chemical resistance	3	3	4	3	2	2	2	4	2
Compression set properties	3	3	3	2	2	3	3	3	2
Electrical properties	4	4	3	4	2	2	4	2	3
Flame resistance	1	1	1	1	3	1	3	4	1
Heat resistance	1	2	4	3	3	3	4	4	2
Low temperature properties	4	3	3	3	3	3	4	2	3
Oil resistance	1	1	1	1	3	4	2	4	3
Ozone resistance	1	1	4	4	3	2	4	4	4
Permeability to gases	1	3	3	4	3	3	1	3	3
Physical strength properties	4	3	3	3	3	3	2	3	4
Water resistance	3	3	4	2	2	3	2	4	2

Source: Walker Rubber, (2022)

Notes: 1 = poor performance, 2 = fair performance, 3 = good performance, 4 = excellent performance

(Please note that these categorisations are to be used for comparison purposes only)

Based on this comparison, it can be noted that each rubber chemistry may pose a unique technical offering based on the combination of properties. For example, butyl rubber is the only chemistry which was determined to have excellent gaseous impermeability and so this chemistry is likely preferred for applications involving gas sealing. Meanwhile natural rubber (polyisoprene) and polyurethane indicate the greatest physical strength and abrasion resistance and so may be preferred in higher wear applications. In determining whether an alternative chemistry is a suitable replacement for an isoprene based rubber, the required properties of the end use would need to be considered to shortlist those with suitable criteria. In some cases, alternatives may result in a decrease in performance however, would still be above the acceptable level required for the specific end use.

From the table above the main benefits of isoprene containing rubbers could be summarised as follows:

- Polyisoprene/Natural rubber;
  - Excellent physical strength and abrasion resistance
  - Excellent low temperature flexibility
  - Excellent electrical insulative properties
- Butyl rubber; and
  - Excellent weathering resistance
  - Excellent low gas permeability
  - Excellent electrical insulative properties
- SIS copolymer (Encyclopaedia Britanica, 2023).
  - High levels of elasticity
  - Excellent compression set properties
  - Excellent adhesive properties

The applications in which isoprene rubbers are used would likely be based on those which require the beneficial properties listed above. As such alternatives to these chemistries should be able to offer a suitable level of performance in these key areas. For polyisoprene, polyurethane may be able to be seen as a suitable alternative for specific applications based on high levels of strength and abrasion resistance although may not be suitable for applications with potential chemical exposure due to lower levels of chemical resistance.

For butyl rubber, one of the main applications is inner tubes in tires and so low gas permeability is a key criteria. Based on the comparison in Table 3-28, no other chemistries would be able to deliver comparable gas permeability, however rubbers such EPDM may still be suitable depending on if the loss of performance is still acceptable by industry. 3.1

Finally for Styrene-Isoprene-Styrene (SIS) copolymers, the offering of other rubber chemistries may not be able to fulfil the full requirements of these rubber products based on the combination of unique compression set, elasticity and adhesive properties. Neoprene is potentially the closest alternative examined and is identified as having good adhesive properties but is unable to provide as comparable compression set properties.

The data provided above however are based on a high-level comparison of specific rubber chemistries and as such may not represent the unique situation of specific end uses. As such any conclusions drawn from this data on the availability of alternatives should be treated with caution due to the omission of specific requirements for rubber in stated end uses.

A key note in the analysis of alternatives should also be the availability of polyisoprene from natural sources. Naturally derived polyisoprene has better physical strength than synthetic polyisoprene but lower levels of processability, due to the presence of naturally occurring impurities. Largely speaking natural polyisoprene can be seen as a reasonable alternative for synthetic polyisoprene except in applications where processing or combination with other rubber chemistries would be required. Additionally, naturally derived polyisoprene often contains latex which limits its applications in end uses which involve human contact (medical devices, rubber bands, condoms) due to potential for allergic reactions (Kent Elastomer, 2024). Many tire companies currently mix natural and synthetic polyisoprene in products (40% natural, 60% synthetic (Michelin, 2023)) as this is seen as a more sustainable solution than using solely polyisoprene manufactured from petrochemicals. There are however environmental concerns surrounding the production of natural polyisoprene as the cultivation of *Hevea brasilienis* can often lead to deforestation and loss of biodiversity.

3.11.3 Summary of availability of alternatives by sector

A summary of availability of alternatives by sector is provided in the table below.

Table 3-28 Summary of alternatives by sector

Sector		Availability of alternatives
C19.20	Manufacture of refined petroleum products	Not applicable as this sector is producing isoprene not using it.
C20.17	Manufacture of synthetic rubber in primary forms	Alternative rubber chemistries may be manufactured in place of isoprene based rubber polymers. The demand for these other rubber chemistries may in part be influenced by the potential for downstream use to substitute. In many cases substitution may be possible although this is dependent on the specific requirements of the end use and the combined properties of alternative rubber chemistries. It is likely that some substitutions may be possible whilst more technically demanding applications may have limited/no availability of alternatives.

Source: Study team summary on the basis of information presented in this section.

3.12 Current disease burden (CDB)

In this section the current burden of disease for liver cancer, degeneration of the olfactory epithelium and degeneration of spinal cord white matter is estimated using the data in the preceding sections for exposed workers, combined with data on exposure concentrations and the exposure response relationship (ERR) and dose response relationship (DRR). The data are combined with data on past trends in exposure concentrations and exposed workforce, latency and workforce turnover.

No calculations for the disease burden (past, current or future) of the reduced birthweight endpoint have been conducted in this assessment. This is because the gradient of the reduced birthweight DRR is significantly low and the DNEL is above three of the four policy options, meaning no cases would be expected even at relatively high concentration levels. In addition to this the full extent of the health impact of reduced birthweight is not fully understood and as such would be difficult to quantify in this assessment. Due to these factors, reduced birthweight has not been further assessed.

3.12.1 Past trend in exposure concentrations and exposed workforce

Based on the limited data available for past isoprene concentrations, the main source of information for this section is the study conducted in the US between the years of 1993-1998 as summarised by Leber (2001) and Lynch (2001). The use of this data however does come with assumptions which must be considered. The first of these is that to calculate the current burden of disease from past exposure it must be considered that US exposure data are being used as a proxy and so may not represent the real EU situation. Secondly the data gathered in this study were relating to both the polymerisation and monomer production processes and so the exposure levels for each sector are in this case the same, whilst in reality, it is likely that higher exposures occurred in the polymer production process (Lynch, 2001).

3.12.2 Latency and workforce turnover

The time required for the endpoints to develop over an average working life takes into account the minimum and maximum time required to develop the condition (MinEx and MaxEx) and the distribution of new cases between these two points in time, combined with the latency period with which the effects are diagnosed.

The MinEx and MaxEx for the two endpoints and the latency are summarised in Table 3-29.

Table 3-29 Latency and maximum exposure duration to develop a condition (MaxEx)

Endpoint	MinEx (years)	MaxEx (years)	Latency (years)
Liver cancer	0	40	18
Degeneration of olfactory epithelium	0	1	0
Degeneration of spinal cord white matter	0	1	0

Source: See Methodological note for more details

The workforce turnover is 5% per year and a static discount rate of 3% is used.

3.12.3 Current disease burden

The current burden of disease (i.e. the number of cases diagnosed in 2023) is estimated on the basis of historical exposure. For example, if the cancer endpoint has an average latency of 18 years, as is the case with liver cancer, the model assumes that the cases diagnosed in 2023 reflect the risk that occurred 18 years ago in 2005, due to latency, and thus reflects the number of workers exposed in 2005 and the exposure concentrations in 2005.

However, the estimation of the current disease burden due to past exposure was based on data from 1993-1998 provided in the study by Lynch (2001) and Leber (2001), as described in Section 3.3.4.1, because this was the only available data for isoprene exposure levels in the past. Hence, the estimated current burden of disease could be an overestimation, assuming that the concentration levels have been decreasing over time.

Table 3-30 Current burden of disease due to past exposure (based upon data from 1993-1998 to present day)

Endpoint	New cases per year (incidence) in 2023
Liver cancer	0.007
Degeneration of olfactory epithelium	0
Degeneration of spinal cord white matter	0

Source: Study team

3.12.4 Comparison with data on recognised cases and epidemiological data

Given that there is currently no available data to indicate the current recognised cases of ill health due to isoprene exposure or any human studies on the effects of isoprene exposure, it is not possible to compare the outputs of the CDB model to observed cases. In lieu of this however the trends in exposure concentrations over the time period indicate a significant decrease in the possibility for isoprene exposure at dangerous levels for human health and therefore any cases of ill health due to isoprene exposure currently experienced are likely to continue to decline over future years. As such, the levels calculated in section 3.12.3 above are likely to be an overestimate of the future situation.

3.13 Summary of the current situation

3.13.1 Risk to workers' health

In general, the current risks to workers health attributed to isoprene exposure can be expected to be relatively low. This is due to the following reasons:

- the number of sectors using isoprene as a monomer is relatively small leading to a relatively low number of exposed workers being exposed to the substance;
- the exposure levels of isoprene to workers are expected to be below the 4:100,000 excess risk for cancer (as derived in the ERR, see section 2.2); and
- the Risk Management Measures (RMMs) currently used by industry are established as closed system processes where Respiratory Protective Equipment (RPE) is still required to be worn, resulting in further reductions in exposure.

The following tables provide a summary of the data illustrated in the previous sections.

Table 3-31 Summary of estimates taken forward for the assessment of options

Carcinogen	Exposed workforce (number of workers)	Health effects caused	Major occupational exposure route
Isoprene	10,539	Liver Cancer Degeneration of Olfactory epithelium	Inhalation

Carcinogen	Exposed workforce (number of workers)	Health effects caused	Major occupational exposure route
		Degeneration of spinal cord white matter Reduced birthweight	

Source: Study team

Table 3-32 Summary of exposure concentrations (not adjusted for the use of RPE), exposed workforce and number of companies by sectors for isoprene

Sector		Exposure concentration mg/m³			Number of exposed workers	Number of companies
		AM	Median	P95		
C19.20	Manufacture of refined petroleum products	0.20	0.11	0.65	10,266	18
C20.17	Manufacture of synthetic rubber in primary forms	0.25	0.21	0.52	273	62

Source: Study team.

Whilst the tables above indicate the current situation with regard to exposure, numbers of workers and health effects, the current burden of disease has also been highlighted. The table below provides a brief summary of the calculated current burden relating to exposures to isoprene from previous events. This data is not derived from consultation but from literature and as such must be viewed with a certain level of caution. This is due to the fact that the cited study was conducted in the US and not within any EU country meaning that past exposure levels are a proxy for the actual EU situation. The exposed workforce has also been calculated on the assumption that growth rates in workers across both investigated sectors have remain constant since the study publication in 2001.

In addition to the above exposure data from Leber (2001) and Lynch (2001) from a US study into the refining and polymerisation of isoprene were combined with known Eurostat data to model the current burden of disease from past isoprene exposure. This data does come with the caveats that exposure is from the US and thus seen as a proxy for the EU and the data were gathered across both sectors. The results of the modelling however can still be seen as a good estimate of the current number of cases of different isoprene end points experienced today. The table below provides a summary of these estimated cases.

Table 3-33 Current disease burden related to occupational exposure to isoprene (number of cases)

Carcinogen	Health effects caused	Current disease burden (number of cases) *
Isoprene	Liver cancer	0.007
	Degeneration of olfactory epithelium	0

Carcinogen	Health effects caused	Current disease burden (number of cases) *
	Degeneration of spinal cord white matter	0

* *Incidence in 2023*

Source: Study team.

3.13.2 Relationship with other EU policies

In relation to isoprene and, as previously mentioned in section 3.3.7, a number of EU policies/initiatives may have an impact on the future use of isoprene within the EU. For example, the REPowerEU plan involves a significant shift away from the use of Russian oil. In order to do this, the EU will be looking to rapidly upscale the 'green transition' towards more renewable sources of energy. As the EU makes this transition it can be expected that EU demand for oil would decline resulting in a lowering of the need for the refining of petroleum products. Given that substances such as polyisoprene can also be produced from natural sources, it seems possible that in realising the REPowerEU plan isoprene production from crude oil and subsequent polymerisation activities could be reduced.

However, it is hard to estimate the extent to which natural polyisoprene may replace synthetic polyisoprene as natural polyisoprene also has negative impacts. These impacts are currently set to be addressed in the new EU Deforestation-Free regulation (EUDR), in which companies placing products on the market must prove that products do not contribute to global deforestation (European Commission, 2022). Deforestation is commonly seen as the most significant negative impact associated with the production of natural rubber and so this supply may also be limited in the EU once the EUDR is adopted.

In combination with this the EU Circular Economy Action Plan set out ambitious goals to increase the recyclability and quantity of recycled goods within the EU market. Given that the operations studied in this report result in the contribution of new products entering the market it could be expected that this action plan will drive a decrease in the amount of virgin isoprene products being introduced into the market. Again, this action plan could therefore result in a decline in the EU industry relating to the manufacture and polymerisation of isoprene.

3.13.3 National OELs

Within the EU Member States national OELs do exist for five different Member States. These are Bulgaria, Germany, Latvia, Lithuania and Poland. The range of these national OELs is highlighted in the table below. Of these values, Germany has the lowest national OEL of 8.4mg/m^3 whilst Poland has the highest value of 100mg/m^3 [6]. The other three Member States all share a value of 40mg/m^3.

[6] Poland has conducted a recent study recommending a change in national OEL to 8 mg/m^3 (Klimczak and Kilanowicz-Sapota, 2022). After this is implemented the new highest value in the EU will be 40 mg/m^3 in Latvia, Lithuania and Bulgaria.

Table 3-34 Summary of national OELs in EU Member States

Carcinogen	Lowest (strictest) national binding OEL (mg/m^3)	Highest (least strict) national binding OEL (mg/m^3)	Member States with no OEL
Isoprene	8.4	100	AT, BE, HR, CY, CZ, DK, EE, FI, FR, EL, HU, IE, IT, LU, MT, NL, PT, RO, SK, SI, ES, SE

Source: Study team on the basis of section 3.1.

3.13.4 Potential for lowering exposure to isoprene

In general, the industry using isoprene is well adapted to minimising the risks posed. In the case of refineries, this can be largely attributed to the fact that, alongside isoprene production, steam cracking results in the production of other aromatic compounds, many of which pose significantly higher risks to human health than isoprene. For example, respondents in the consultation mentioned that benzene is also present in the fraction of hydrocarbons which isoprene is produced in and therefore RMMs are tailored to the pre-existing EU OEL for Benzene (3.2mg/m^3 (1ppm)).

Across both refineries and polymerisation sites using isoprene, it has been identified that production occurs in closed systems and that RPE is used when conducting any activities which may result in isoprene exposure. Where possible, it has been noted that some companies have made efforts to move as many processes as possible into closed systems. For example, it was mentioned in consultation that a company has ensured that all testing is also conducted in closed systems reducing the need for the system to be opened. Certain activities such as maintenance and filling of closed system equipment are less able to be completely enclosed however, where these processes occur, workers have been found to have good ventilation and adequate RPE to ensure exposures are minimal.

Overall, industrial initiatives to reduce isoprene exposure can be seen as effective and are extensive measures that could be considered to be delivering protection with 100% efficiency (closed systems production, oxygen fed respirators/high efficiency RPE). As such the potential for industry to further reduce exposures is likely low given the pre-existing but extensive measures already implemented.

4 BASELINE SCENARIO

The baseline scenario describes how the problem is expected to evolve in case no action is taken at EU level.

This chapter comprises the following sections:

- Section 4.1: Impact of the implementation of other OELs;
- Section 4.2: Effects of forthcoming changes in national OELs or protective regulation, self-regulatory initiatives;
- Section 4.3: Effects of REACH;
- Section 4.4: Effects of EU Strategic Foresight megatrends;
- Section 4.5: Future trend in use of the substance[s];
- Section 4.6: Future trend in exposure concentrations due to technical improvements;
- Section 4.7: Future trend in exposed workforce;
- Section 4.8: Other factors of importance for the baseline;
- Section 4.9: Future disease burden (FDB); and
- Section 4.10: Summary of the baseline scenario.

4.1 Impact of the implementation of other OELs

In the production of isoprene via steam cracking, other aromatic compounds are produced and contained in the PyGas mixture formed. One of the aromatic compounds is benzene which has been regulated under the CMRD since its initial publication in 2004. At present the OEL implemented in the EU is set at 1 ppm (3.25 mg/m^3) however, in a recent amendment to the CMRD (2022), this level is set to be reduced to 0.2 ppm (0.66 mg/m^3) by April 2026. This OEL is likely to influence future exposures to isoprene in steam crackers as RMMs will need to be introduced to further reduce benzene exposure which in turn will impact the RMMs in place for isoprene, as these substances are produced in via the same equipment. This however is on the assumption that the reduction in the Benzene OEL is able to be achieved by industry. In the event that steam crackers are unable to meet the new benzene OEL this could result in discontinuations which would mean that the subsequent production of isoprene would also be discontinued. The effects of the OEL for benzene on isoprene exposures will therefore be determined by the response of industry to a lower benzene OEL coming into force in 2026[7].

In addition to the introduction of an OEL for isoprene, the proposed OEL for PAHs may also impact the potential for occupational exposures to isoprene. This is based on the fact that PAHs are also produced unintentionally in the cracking and refining of crude oil. As such if controls are introduced to limit the potential for occupational exposure to PAHs at crackers/refineries, then these controls

[7] Note: The benzene OEL is set to be decreased in stages with an initial decrease from 1 ppm (3.25 mg/m^3) to 0.5 ppm (1.65 mg/m^3) on 5 April 2024 and then the further decrease to 0.2 ppm (0.66 mg/m^3) on 5 April 2026.

would also likely further reduce occupational exposures to isoprene. In the petrochemical production industry however, it is well established that RMMs currently relate to the most extreme forms of protection i.e. closed systems with RPE essential for high risk tasks. As such it may be possible that if OELs suggested for PAHs require further reductions in worker exposure that this could result in the industries inability to meet these limits and the subsequent closure of operations. Should this be the case then, isoprene manufacture (both intentional and unintentional) would likely cease in the EU.

In the ongoing work relating to PAH OELs petrochemicals companies may only see major discontinuations under the lowest policy option (at the time of writing; 05/07/2023). It is also expected that as the petrochemicals industry is financially stable and able to absorb high costs meaning discontinuations may be less likely than predicted in the models. As such the impact of discontinuations and subsequent risks to isoprene production are likely low.

Despite the above, OELs for benzene and PAH have not been factored into the baseline for isoprene. As isoprene exposure concentrations are already at a level which would incur no significant human health risks then the effects of changes to PAH and benzene OELs will not impact the current or future burden of disease for isoprene. These other OELs would therefore not impact the baseline for isoprene.

4.2 Effects of forthcoming changes in national OELs or protective regulation, self-regulatory initiatives

At the time of writing this report, changes or introductions of new national OELs, protective regulations or self-regulatory initiatives within industry using isoprene are not expected. As such it is not expected that any changes to the use of isoprene in the EU will occur as a result of future binding/non-binding initiatives. This means that the use of isoprene in the EU will largely be dictated not by regulation but instead by changes in market supply and demand (see section 4.5).

4.3 Effects of REACH

Under the EU REACH regulation, isoprene is currently not listed on the registry of SVHC intentions, or on the candidate list for authorisation. As such, under a baseline scenario, it is not expected that isoprene use will be impacted by REACH authorisation. In terms of REACH restriction, isoprene is also not listed on the registry of restriction intentions until outcome and so restriction of the use of isoprene is also unlikely. It is reported by ECHA that isoprene does have an ongoing assessment of regulatory needs however the study team believes this entry is now out of date based on the latest update dated 24 November 2021. Overall, it can be expected that without an OEL introduced, isoprene use will not be impacted in the future via the REACH regulation.

4.4 Effects of megatrends

Based on the megatrends identified by the European Commission, these may have impacts of the future of the EU isoprene market. Specifically, the trends relating to growing consumption, shifting health challenges and accelerating technological change may be linked into sectors which are currently using isoprene-based products. In terms of consumption, it has been observed that car ownership in the EU has been constantly increasing based on data from 2013 to 2021. In addition to this, the acceleration of technical changes to the automotive system is pushing markets towards significantly increased production of hybrid and battery electric vehicles. These two trends combined means a significant demand for tires which are typically manufactured using polyisoprene and therefore, these megatrends are likely to continue to drive growth in the EU isoprene market. Another key end use of isoprene rubber is in medical devices. Given the megatrend of shifting health challenges it could be expected that constant development of new medical devices/equipment may be needed, some of which is likely to involve parts manufactured via polyisoprene or other isoprene containing rubbers. Given this megatrend, it is also likely that isoprene use will remain important in the medical sector unless a suitable alternative can be identified in the future.

Overall, megatrends will likely be responsible for driving an increase in isoprene use as further described in section 4.5 below.

4.5 Future trend in use of the isoprene

A literature review of publicly available data from market reports has been conducted to assist with the validation of the Eurostat data in relation to changes in the isoprene market within the EU. Based on data from a short literature review of independent market reports, the global Compound Annual Growth Rate (CAGR) of the isoprene market can be estimated at roughly 7% (range 6.8% to 7.8%). This growth is mainly driven by the demand for rubber used in the automotive industry which is set to see significant growth via the transition to electric vehicles. Given the scale of the automotive industry in Europe and the fact that key players in the tire industry are based in Europe (Michelin, Pirelli), it is likely that this growth rate can be seen as reflective of the EU situation. Given this growth could be expected in the EU it is likely that demand for isoprene will continue to increase over future years resulting in increased production and use.

This demand however may in part be mitigated by the potential for use of natural polyisoprene which currently represents around 40% of the polyisoprene content in tires. The use of natural polyisoprene may increase in the future as this is seen as a more sustainable source than polymerisation via petrochemical isoprene and as such helps drive towards manufacturers sustainability goals. This replacement however is hard to predict as natural polyisoprene can also be argued as having other negative environmental impacts associated with deforestation and biodiversity loss.

4.6 Future trend in exposure concentrations due to technical improvements

Within the manufacture of isoprene via petrochemical processes (cracking and refining), the current technology used is based on fully closed systems with limited potential for exposure via operations such as maintenance. When these higher risk processes are conducted, workers are required to wear protective respiratory protective equipment (RPE) with ranging efficiency between roughly 80% and 100%. These measures represent the higher end of exposure reduction via technical measures and as such future trends could be expected to show relatively little change from today's levels.

4.7 Future trend in exposed workforce

Based on the data in section 3.4.5, the total number of workers exposed to isoprene is set to decline in future years. This is driven by the decrease of refinery capacity in the EU over future years despite demand for isoprene containing rubbers for medical devices, tires and other rubber applications increasing. Given this demand the isoprene market is set to grow at an approximate value of 7% CAGR and so it can be assumed that whilst refinery capacity may close (resulting in a decrease of indirectly exposed workforce), refineries producing isoprene monomer and other important petrochemical products may remain open.

It can therefore be expected that lower numbers of workers may be exposed to isoprene in future years (see Table 3-15). Given the estimated trend in exposure concentrations and the current levels of exposure, this decrease in workers exposed is unlikely to result in any significant changes to cases of ill health. For more information on this conclusion see section 4.9.

4.8 Other factors of importance for the baseline

Limited availability of data is a factor that should be considered when reviewing the findings of this report, especially in relation to the baseline scenario. Concerns have been raised throughout the project relating to the lack of available data for isoprene. In the baseline scenario key exposure data are derived from only one study reported by Leber (2001) and Lynch (2001) alongside consultation data where multiple responses were from the same company and CSR data which is entirely modelled

Based on consultation with industry, the effects of the Covid-19 pandemic were largely not felt by either polymerisation plants or steam crackers/refineries. In all responses, it is noted that production continued under relatively normal conditions despite lockdown regulations. As such no recovery period from Covid is anticipated for the industry and the pandemic can be seen as having no impacts on the baseline scenario.

A further consideration in relation to the future use of isoprene however should be the drive to a circular economy as set out in the EU action plan. Under the circular economy action plan, it is noted that the potential for chemical recycling will continue to be explored and that treatment of end-of-life vehicles may have mandatory rules implemented for the recycling of specific components. In the case of isoprene used in polyisoprene rubber products, this drive to circular economy and advances in chemical recycling could lead to future supplies of isoprene rubber being from recycled products. At present, this is still not a technically viable process.

4.9 Future disease burden (FDB)

4.9.1 Future disease burden

The future disease burden is given below as the number of cases generated by exposure over the next 40 years (and not the number of cases occurring in the next 40 years). Latency may cause many of the cases caused by exposure in the next 40 years, particularly of cancer, to occur beyond the 40-year period. For this reason, the number of cases is not divided by 40 to indicate a number of cases per year as this would be misleading.

Table 4-1 Baseline future burden of disease; staff turnover of 5% for all sectors

Endpoint	Number of cases over 40 years
Liver cancer	0.03
Degeneration of olfactory epithelium	0
Degeneration of spinal cord white matter	0

Source: Study team.

In Table 4-2, the number of cases is distributed on the sectors, where exposure takes place. It can be seen from the table that the number of liver cancer cases will not reach a full case over a 40-year period and 67.4% of the total cases will be within C19.20 sector. No cases of degeneration of olfactory epithelium and degeneration of spinal cord white matter have been estimated.

Table 4-2 Baseline future burden of disease; staff turnover of 5% for all sectors and trend in workforce of 1% for C19.20 and 7% for C20.17 per year

Sector		Number of cases over 40 years			Percent of total cases	Trend in exposure *
		Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter		
C19.20	Manufacture of refined petroleum products	0.02	-	-	67.4%	0
C20.17	Manufacture of synthetic rubber in primary forms	0.01	-	-	32.6%	0

** Multiply of trend in workforce and exposure concentration*

Source: Study team.

Table 4-3 presents baseline future burden of disease based on two methods.

Table 4-3 Baseline future burden of disease (PV40), 5% turnover of workforce a year, 3% static discount rate

Sector		PV40 over 40 years, static discount rate Range of Method 1 – Method 2 (€ million)			
		Liver cancer M1 – M2	Degeneration of olfactory epithelium M1 – M2	Degeneration of spinal cord white matter M1 – M2	Total Low – high
C19.20	Manufacture of refined petroleum products	€ 0.035 - € 0.028	€ 0.00 - € 0.00	€ 0.00 - € 0.00	€ 0.028 - € 0.035
C20.17	Manufacture of synthetic rubber in primary forms	€ 0.011 - € 0.009	€ 0.00 - € 0.00	€ 0.00 - € 0.00	€ 0.009 - € 0.011
	Total	**€ 0.046 - € 0.037**	**€ 0.00 - € 0.00**	**€ 0.00 - € 0.00**	**€ 0.037 - € 0.046**

Source: Study team.

Table 4-4 presents the baseline costs of ill health for workers (M1 and M2), employers and public authorities associated with the three health endpoints modelled for PAH. These figures represent the cost prior to any intervention being put in place to reduce exposure to PAH and reduce the number of resulting cases.

Table 4-4 Baseline costs of ill health for workers (M1 and M2), employers and public administrations (€ millions)

Sector	Workers and families (M1)	Workers and families (M2)	Employers	Public Authorities	Grand total (M1)	Grand total (M2)
C19.20 Manufacture of refined petroleum products	€ 0.035	€ 0.028	€ 0.00	€ 0.00	€ 0.035	€ 0.028
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.011	€ 0.009	€ 0.00	€ 0.00	€ 0.011	€ 0.009
Total	**€ 0.046**	**€ 0.037**	**€ 0.00**	**€ 0.00**	**€ 0.046**	**€ 0.037**

Source: Study team.
Notes: Values for workers and values are calculated using two different methodologies (M1-M2), for more information on the differences between these methods, please see the methodological note. Grand total (M1) is the sum value of Workers & Families (M1), Employers, and Public Authorities. Grand total (M2) is the sum value of Workers & Families (M2), Employers, and Public Authorities

4.9.2 Legacy burden of disease

Previous OEL studies have not included the calculation of future burden of disease from legacy exposure. The reason is that this burden of disease would not be affected by the assessed policy options and just be added to all scenarios and will make differences in the scenarios less prominent.

A mean latency period of 18 years is assumed for liver cancer. This means that exposure before 2023 may lead to cancer cases for a period of 18 years i.e. from 2024-2041. The total number of cases are calculated in the same way as described for the current burden of disease where the total burden for each year due to exposure during the period 1985-2023 is calculated using the past trends in workforce and exposure concentrations as described in section 3.12.1.

For the non-cancer endpoints, the latency time is assumed to be zero years and past exposure would not lead to future cases.

The future burden of disease from past exposure is reported in Table 4-5, but is not presented with the policy options.

Table 4-5 Legacy burden of disease that will occur in the next 40 years due to exposure in the last 40 years

Endpoint	Number of cases over 40 years
Liver cancer	0.1
Degeneration of olfactory epithelium	0
Degeneration of spinal cord white matter	0

Source: Study team

4.10 Summary of the baseline scenario

Table 4-6 Baseline scenario over 40 years for isoprene

Item	Detail
Chemical agent	Isoprene
Classification	Flam. Liq. 1 Muta. 2 Carc. 1B Aquatic Chronic. 3
Sectors	Manufacture of refined petroleum products Manufacture of synthetic rubber in primary forms
Period for estimation	40 years
Types of cancer caused	Liver
Other adverse health effects	Degeneration of olfactory epithelium Degeneration of spinal cord white matter Reduced birthweight
No. of exp. workers	10,539
Change exp. level	0%
Change no. of exp. workers	6% decrease for petroleum products manufacturing 7% increase for synthetic rubber manufacturing
Current disease burden (CDB) - no. of cancer cases/year (2023)	0.007
Future disease burden (FDB) - no. of cancer cases/year over 40 years	0.03
CBD - no. of non-cancer enpoint cases (2023)	0 (degeneration of olfactory epithelium and spinal cord white matter)
FDB - no. of non-cancer cases over 40 years	0 (degeneration of olfactory epithelium and spinal cord white matter)
Estimated deaths due to FDB cancer over 40 years	0
Estimated deaths due to FDB from non-cancer en-points over 40 years	0
Monetary value FDB cancer over 40 years	€ 0.05 (M1) - € 0.04 (M2) million
Monetary value FDB other adverse health effects over 40 years	€ 0

Source: Study team summary on basis of the information presented in this chapter.

Table 4-7 Estimated number of exposed workers, expected number of cancers and other hazardous diseases cases and related health costs in case no action is taken (baseline scenario), over a 40 year period

Carcinogen	No. of exposed workers	Expected no. of cancer cases	Expected no. of cases of other adverse health effects	Estimated health costs, (€ million) M1-M2
Isoprene	10,539	0.03	0.0	€ 0.05 – € 0.04

Source: Study team summary on basis of the information presented in this chapter.

5 POLICY OPTIONS

The ACSH has in its "Opinion on limit value setting for non-threshold carcinogens, a Risk-Based Approach" agreed on the on the following regarding the levels of OELs:

- *"In the future, limit values for non-threshold substances will be set in between the predetermined "upper risk level" and the "lower risk level". It is agreed that the upper risk is 4:1,000 (corresponding to 4 predicted cancer cases in 1,000 employees) and the lower risk level is 4:100,000. This assumes exposure occurs over 8 hours per day, 5 days a week and 40 years of working life."* (ACSH, 2022)

A risk estimate based on an ERR for isoprene was not presented by RAC due to a lack of available human data and the complexities of transposing data from animal studies. As such the RAC opinion was derived based on a methodology set out by the German DFG relating to setting the limit value within the natural variation of human endogenous formation of isoprene.

Since the formation of the RAC opinion however, the study team have been able to derive a suitable ERR to be used in the case of isoprene exposure. As such the derived risk values are shown in the table below (see further description of the ERR in sections 2.2).

Table 5-1 Risk estimate based on the ERR for isoprene derived by study team

Risk estimate	Isoprene concentration (mg/m³, isoprene fraction, long-term mean value, 40 years of workplace exposure)
Risk 4:1,000	129.4
Risk 4:10,000	12.9
Risk 4:100,000	1.3

Source: Study team

Following derivation of these values a number of policy options were derived ranging between the upper bound 4:1,000 excess risk and the lower bound 4:100,000 excess risk levels. These policy options and their reason for inclusion within the study are highlighted in the table below.

Table 5-2 Policy options acting as reference points for this study for Isoprene (see comments in the body text)

Level, mg/m³	Reason for inclusion
1.3	This value corresponds to the lowest 4:100,000 excess cancer risk level and is therefore included for assessment as the lower bound.
8.5	This value corresponds to that of the RAC opinion and thus presents a value believed to be relatively in alignment with the natural variation of isoprene produced endogenously in humans.
40.0	This value is included as it is currently the median value for existing national OELs within the EU.
129.4	This value corresponds to the lowest 4:1,000 excess cancer risk level and is therefore included for assessment as the upper bound.

Source: Study team

These policy options will form the basis of the cost benefits analysis in the following sections of this report. Via consultation early in the project with industry associations, the majority of industrial stakeholders support the 8.5 mg/m^3 policy option. This is based on their own risk assessment carried out as part of the registration process which was used to help support RAC in the derivation of their opinion.

6 BENEFITS OF THE MEASURES UNDER CONSIDERATION

This chapter comprises the following sections:

- Section 6.1: Summary of the assessment framework;
- Section 6.2: Improved welfare, assumptions and avoided cases of ill health;
- Section 6.3: Benefits to workers & families;
- Section 6.4: Benefits to employers;
- Section 6.5: Benefits to the public sector; and
- Section 6.6: Summary of the benefits of the measures.

6.1 Summary of the assessment framework

6.1.1 Summary of the key features of the model

The model developed to estimate the benefits in terms of reduced costs takes into account the cost categories set out in Table 6-1 below. More details are presented in the methodology report.

Table 6-1 The benefits framework

Category		Benefits	Notes
Direct	Improved welfare	Reduced healthcare costs	Avoided cost of medical treatment, including hospitalisation, surgery, consultations, radiation therapy, chemotherapy/immunotherapy, etc. Avoided private direct and indirect medical costs and rehabilitation costs.
		Reduced informal care costs[8]	Avoided opportunity cost of unpaid care (i.e. the monetary value of the working and/or leisure time that relatives or friends provide to those with ill health).
		Reduced cost for employers	E.g. avoided costs due to insurance payments and absence from work.
		Safety	Covered in first two health benefits.
		Direct economic benefits	Not sure there are any direct economic benefits as they all result indirectly from health benefit. OR are the reduced costs for employers?
		Environment	See section 9, not monetised (included in next report).
	Improved market efficiency	Cost savings	Include higher economic productivity, improved allocation of resources, removal of regulatory or market failures or cost savings.
		Improved information	Includes improved information availability

[8] A decision has been taken to include informal care costs in this analysis even though some elements of these costs may also have been included in individuals' willingness to pay values to avoid a future case of ill health. This decision may result in an overestimate of the benefits as generated by this study.

Category		Benefits	Notes
		Wider range of products/services	Enhanced product and service variety and quality for end consumers.
Indirect	Indirect compliance benefits	Reduced mortality – productivity loss	Avoided costs to society due to premature death.
		Reduced morbidity – lost working days	Avoided earnings and output due to absence from work due to illness or treatment.
		Other indirect benefits to workers and families	
		Indirect benefits to administrations	Avoided tax revenue losses. Avoided administrative and legal costs. Avoided costs linked to the process of defining a national OEL.
	Wider economic benefits	Including higher GDP, productivity enhancements, greater employment rates, improved job quality etc.	Employment may increase as a result of industry 'clean up' due to better perception of workplaces and increased acceptability of risks.
	Other, non-monetary benefits	Protection of fundamental rights, social cohesion, reduced gender discrimination, international and national stability	
Intangible	Improved welfare	Approach 1 WTP[9]: Mortality	A monetary value of the impact on quality of life of affected workers. Avoided moral pain and suffering. Avoided loss of present and future income. Avoided cost of time claiming benefits, waiting for treatment etc. Reduction in insurance contributions.
		Approach 1 WTP: Morbidity	
		Approach 2 DALY[10]: Mortality	
		Approach 2 DALY: Morbidity	

Source: Study team

The total avoided cost of ill health is calculated using the following two methods:

$$\text{Method 1: } Ctotal = Ch+Ci+Ce+Cp+Cvsl+Cvsm$$

$$\text{Method 2: } Ctotal = Ch+Ci+Ce+Cp+Cl+Cdaly$$

Cl is not considered under Method 1 since Cvsm may already include these costs.

The abbreviations are explained in Table 6-2 below.

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9 Willingness to Pay: The maximum sum an individual is willing to pay for a service/goods in order to avoid loss, in this case, in terms of health treatment.

10 DALY = Disability Adjusted Life Year. DALY is whereby one year of health is lost. It is used to calculate the gap between current health status and the ideal health situation (WHO, accessed Feb 2018).

6.2 Improved welfare, assumptions and avoided cases of ill health

6.2.1 Benefits categories for improved welfare

The cost savings (benefits) that have been estimated for each substance are summarised below.

Table 6-2 Overview of benefits categories for improved welfare

Category	Code	Cost to be avoided
Direct	*Ch*	Healthcare
	Ci	Informal care
	Ce	Total cost to an employer
Indirect	*Cp*	Productivity loss due to mortality
	Cl	Lost earnings due to morbidity
Intangible	*Cvsl*	Value of statistical life
	Cvsm	Value of cancer morbidity/value of statistical morbidity
	Cdaly	Value of DALYs

Source: Study team.

The benefit model provides the following two outputs:

- The number of new cases for each health endpoint assigned to a specific year in the 40-year assessment period; and
- The Present Value (PV) of the direct, indirect, and intangible costs of each case.

A detailed overview of the key features of the model for the estimation of the benefits and the assumptions underpinning it are set out in the methodology report.

6.2.2 Relevant health endpoints for isoprene

The relevant health points for isoprene include one cancer endpoint and three non-cancer endpoints:

- Liver cancer;
- Degeneration of olfactory epithelium;
- Degeneration of spinal cord white matter; and
- Reduced birthweight.

The degeneration of spinal cord white matter can lead to neurodegenerative diseases, e.g., multiple sclerosis, amyotrophic lateral sclerosis, and Parkinson's disease. These are serious diseases that usually occur at an advanced age, have complex developmental processes, or can be caused by various triggers. Compared to neurodegenerative diseases, the observed effect on spinal cord white matter in mice exposed to isoprene is not as severe and thus, this effect is assigned to a milder form of neurodegenerative disorders for the current assessment. Hence, a mild form of Parkinson's disease was used as a proxy for this non-cancer endpoint.

The modelling for reduced birthweight has not been undertaken. This is because the reported DNEL of 44.6 mg/m^3 means that three out of four policy options will have no cases. At the highest OEL of 129.4 mg/m^3, the number of cases is extremely low (Table 6-3, see Section 2.2.3.5 for further information on DRR). In addition, these exposure concentration levels are unlikely to be realised based on the exposure concentration levels observed in this study (see Section 3.3) resulting in no estimated cases. Should a case also be identified, then the impact of reduced birthweight is not fully understood. In many cases, lower birthweight may actually result in limited/no health impacts as the extent of the birthweight reduction is hard to estimate and may not be large enough to produce any adverse health effects. In addition to this, birthweights of infants will have natural variation and, if reduction in birthweight is small, this may still fall under the natural variation which would not pose any risk to infants health or development. Due to the sum of the above reasons and uncertainties, this endpoint has not been further investigated in this report.

Table 6-3 Estimated number cases of reduced birthweight for OEL 129.4 mg/m^3.

Sector	Number of pregnancies	Incidence (129.4 mg/m^3), %	Number of cases
C19.20 Manufacture of refined petroleum products	4	0.054	0.002
C20.17 Manufacture of synthetic rubber in primary forms	2	0.054	0.001

Source: Study team, Eurostat

6.2.3 Summary of the key assumptions for isoprene

6.2.3.1 Onset of the disease

The time required for the endpoints to develop over an average working life takes into account the minimum and maximum time required to develop the condition (MinEx and MaxEx) and the distribution of new cases between these two points in time, combined with the latency period with which the effects are diagnosed. As no information on the exposure duration of workers exposed to isoprene is available, the MinEx of one day (zero years) and MaxEx of one year is assumed for two non-cancer endpoints to include a full pregnancy period. For cancer endpoints, the MaxEx is typically a full working life, i.e., 40 years.

Table 6-4 Minimum & maximum exposure duration to develop a condition (MinEx & MaxEx)

Endpoint	MinEx (years)	MaxEx (years)
Liver cancer	0	40
Degeneration of olfactory epithelium	0	1
Degeneration of spinal cord white matter	0	1

Source: Study team.

According to Rushton *et al*. (2012), all solid tumours are expected to have a latency of 10-50 years, meaning that the average latency is 30 years. However, the latency for liver cancer is lower with a range of 10-25 years (Bevan *et al*., 2012), giving an approximate average latency of 18 years (Table 6-5). The assumed latency period for the non-cancer endpoints in this study is zero years as there is limited evidence for latency of the relevant non-cancer conditions.

Table 6-5 Latency by endpoint

Endpoint	Latency (years)
Liver cancer	18
Degeneration of olfactory epithelium	0
Degeneration of spinal cord white matter	0

Source: Study team.

6.2.3.2 The effects of the disease

The primary adverse health effects for liver cancer and two non-cancer endpoints are presented in Table 6-6.

Table 6-6 Primary ill-health effects for each endpoint

Endpoint	Primary ill-health effects
Liver cancer	Mortality, lethargy, loss of appetite/weight loss, feeling tired/unwell.
Degeneration of olfactory epithelium	Loss of smell.
Degeneration of spinal cord white matter	Mild tremors, sleep problems, loss of smell.

Source: Study team.

6.2.3.3 Treatment period and years lived with the disease

The table below presents treatment periods for all endpoints.

Table 6-7 Treatment period

Type of illness	Treatment period (years)
Liver cancer	5
Degeneration of olfactory epithelium	1
Degeneration of spinal cord white matter	1

Source: See Methodological note for more details.

The average disease duration after treatment is given in the table below. According to Gelband *et al.* (2015), liver cancer mortality rates are roughly equivalent to incidence rates, and the number of years lived with disability is very small. Accordingly, years lived with liver cancer has been set at five.

The degradation of olfactory epithelium causes irreversible damage that results in partial or complete loss of smell. This condition cannot be successfully treated as the olfactory epithelium is replaced with respiratory epithelium. Therefore, workers are expected to live with the condition for the rest of their lives. Similarly, degeneration of spinal cord white matter is also irreversible, and the years lived with disability/disease has been set at 30.

Table 6-8 Years lived with disability/disease (YLD)

Type of illness	YLD
Liver cancer	5
Degeneration of olfactory epithelium	30
Degeneration of spinal cord white matter	30

Source: See Methodological note for more details.

6.2.3.4 Mortality rate and additional life expectancy at death

The mortality rates for all endpoints are presented in Table 6-9. The prognosis for liver cancer is usually unfavourable. Diagnosis of hepatocellular carcinoma mostly happens at an advanced stage of cancer, when curative treatments are no longer an option, and the majority of patients do not live more than one year after the diagnosis. However, an earlier diagnosis, when curative treatment is available, can increase a five-year survival rate to 50%–70% (Cullen *et al*., 2023). For these reasons, the mortality rate for liver cancer has been set to 90%. The two non-cancer endpoints are not fatal; hence the mortality rate has been set at zero.

Table 6-9 Fatality rates (MoR)

Type of illness	MoR (years)
Liver cancer	0.9
Degeneration of olfactory epithelium	0
Degeneration of spinal cord white matter	0

Source: See Methodological note for more details.

Table 6-10 presents additional life expectancy at death. The average life expectancy used for the calculations in the model is 82 years. In the absence of other information and taking into account the age distribution of cancer deaths, it is assumed that a typical cancer death occurs at the age of 60 and the number of years lost is thus 22. However, as the latency period for liver cancer is much shorter compared with the average latency of other cancers, as explained in section 6.2.3.1, the additional life expectancy at death for liver cancer has been increased to 35 years. For the two non-fatal non-cancer endpoints, the additional life expectancy at death has been set to zero.

Table 6-10 Additional life expectancy at death

Type of illness	Additional life expectancy at death (years)
Liver cancer	35
Degeneration of olfactory epithelium	0
Degeneration of spinal cord white matter	0

Source: See Methodological note for more details.

6.2.3.5 Cost of treatment

The median cost of hepatocellular carcinoma per patient over two years was £9,065 in the UK (Cullen *et al*., 2023). Hence, one-year costs inflated to 2020 (from 2016) and converted to Euros would be approximately €5,500.

As no treatment is available for degeneration of olfactory epithelium, the cost of treatment has been set to €500 to only reflect visits to doctors for diagnosis.

A mild Parkinson's disease is used as a proxy for degeneration of spinal cord white matter. According to Weir *et al*. (2018), mean costs attributable to Parkinson's disease rose steadily from £2,471 per patient in the first year following diagnosis up to £4,004 per patient in year ten. As the first year of Parkinson's disease is considered mild, the healthcare costs attributable to this period are used for costs associated with degeneration of spinal cord white matter, which, inflated to 2020 (from 2013) and converted to Euros, would be approximately €3,100.

Table 6-11 Cost of healthcare treatment

Type of illness	Unit cost in €
Liver cancer	5,500
Degeneration of olfactory epithelium	500
Degeneration of spinal cord white matter	3,100

Source: See Methodological note for more details.

6.2.3.6 Willingness to Pay (WTP) values

The WTP for a statistical life is presented in the table below. The method for deriving this value for cancer endpoints is described in the methodology report. As non-cancer endpoints do not lead to death, WTP for these endpoints has been set to zero.

Table 6-12 WTP: value of a statistical life (VSL)

Type of illness	WTP, €	Comment
Liver cancer	4,710,000	
Degeneration of olfactory epithelium	0	Not fatal and as such no VSL
Degeneration of spinal cord white matter	0	Not fatal and as such no VSL

Source: See Methodological note for more details.

The WTP for statistical morbidity is presented in the table below. The method for deriving this value for cancer endpoints is described in the methodology report. For degeneration of olfactory epithelium, the value has been set at €32,000. This value is based on the fact that a person irreversibly loses, partially or completely, one of the senses, which can result in adverse psychological and social impacts. According to Schäfer *et al*. (2021), potential consequences of impairment include ingestion related problems and reduced enjoyment of food, increased worrying about hazard avoidance, enhances insecurities in social situations, reduction in well-being and quality of life, and depression.

The WTP for degeneration of spinal cord white matter is based on a WTP per QALY for Parkinson's disease in the Netherlands. According to Sturkenboom *et al*. (2015), the illness burden of this disease in the Netherlands is 0.497. As the WTP per QALY is nearly €40,000 for this disease at the disability weight of 0.497, it has been assumed that the WTP for a mild Parkinson's disease at the disability weight of 0.01 could be approximately €1,000.

Table 6-13 WTP: value of statistical morbidity (VSM)

Type of illness	WTP, €	Comment
Liver cancer	455,000	
Degeneration of olfactory epithelium	32,000	Estimated based on psychological and social impacts.
Degeneration of spinal cord white matter	1,000	Based on QALY for mild Parkinson's disease.

Source: See Methodological note for more details.

6.2.3.7 Disability weights

Disability weights for all endpoints are presented in the table below. The disability weights for liver cancer and mild Parkinson's disease have been taken from the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease study 2019 (IHME, 2020). Disability weight for degeneration of olfactory epithelium has not been published in the literature and was derived based on other similar conditions affecting nasal cavity.

Table 6-14 Disability weights

Type of illness	During treatment	After treatment
Liver cancer	0.45	0.049
Degeneration of olfactory epithelium	0.01	0.01
Degeneration of spinal cord white matter	0.01	0.01

Source: See Methodological Note for more details.

6.2.3.8 Summary

The table below summarises all direct, indirect and intangible costs used in the benefits assessment: these are explained in more detail in the Methodological Note.

Table 6-15 Unit costs used for the benefits assessment

Category	Code	Cost type	Cost, €/case		
			Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter
Direct	*Ch*	Healthcare	5,500	500	3,100
	Ci	Informal care	3,000	0	1,000
	Ce	Cost for employers	13,200	0	5,000
Indirect	*Cp*	Mortality – productivity loss due to mortality	5,000	0	0
	Cl	Morbidity – lost working days due to morbidity	1,000	0	1,000
Intangible	*Cvsl*	Approach 1 WTP: Value of statistical life	4,710,000	0	0
	Cvsm	Approach 1 WTP: Value of cancer morbidity/value of statistical morbidity	455,000	32,000	1,000
	Cdaly	Approach 2 DALY: Value of DALYs	100,000	100,000	100,000

Source: Study team and Methodological Note.

6.2.4 Avoided cases of ill health (cancer and non-cancer)

The table below presents cases over 40 years for each policy option at current exposure levels. The estimated number of liver cancer cases will not reach a full case, and the number will not change over this period compared to the baseline due to current exposure levels being lower than the strictest policy option. No cases have been estimated for the two non-cancer endpoints.

Table 6-16 Cases over 40 years for each policy option

Policy option	Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter
Baseline	0.03	0	0
1.3 mg/m³	0.03	0	0
8.5 mg/m³	0.03	0	0
40.0 mg/m³	0.03	0	0
129.4 mg/m³	0.03	0	0

Source: Study team.

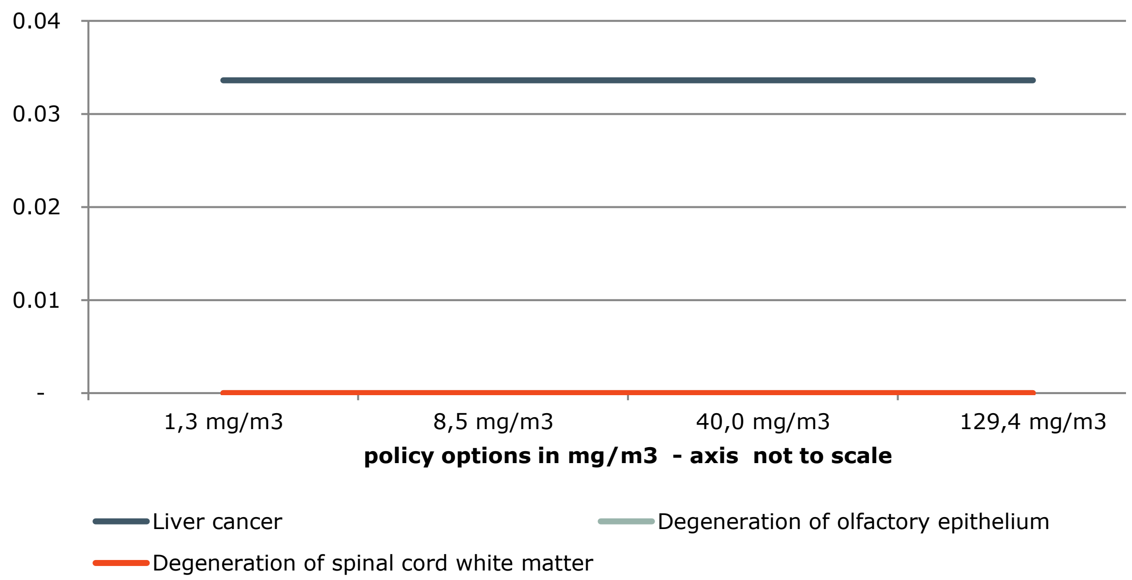

Figure 6-1 Cases over 40 years due in relation to different policy options

Source: Study team

As shown in
Table 6-17, no cases will be avoided over 40 years at all policy options due to current exposure levels being lower than the strictest policy option.

Table 6-17 Avoided cases over 40 years for each policy option

Policy option	Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter
1.3 mg/m³	0	0	0
8.5 mg/m³	0	0	0

Policy option	Liver cancer	Degeneration of olfac-tory epithelium	Degeneration of spinal cord white matter
40.0 mg/m³	0	0	0
129.4 mg/m³	0	0	0

Source: Study team.

6.3 Benefits to workers & families

6.3.1 Avoided costs of ill health

The benefits that will be realised by exposed workers and their families are, first of all, intangible benefits of reduced mortality rates. All the categories are presented in the table below.

Table 6-18 Benefits for workers and their families (avoided cost of ill health)

Stakeholder group	Costs	Method of summation
Workers/family	Ci, Cl, Cvsl, Cvcm, Cdaly	Method 1: *CtotalWorker&Family=Ci+Cvsl+Cvcm* Method 2: *CtotalWorker&Family=Ci+Cl+Cdaly*

Source: See Methodological note for more details.

The benefits of each policy option (relative to the baseline) are summarised below. Method 1 relies on WTP values for morbidity, with the resulting estimates given in Table 6-19.

Table 6-19 METHOD 1: Benefits to WORKERS & FAMILIES (relative to the baseline) (€ millions)

Policy option (Inhalable)	Liver cancer	Degeneration of olfactory epithe-lium	Degeneration of spinal cord white matter	Total
1.3 mg/m³	€ 0	€ 0	€ 0	€ 0
8.5 mg/m³	€ 0	€ 0	€ 0	€ 0
40.0 mg/m³	€ 0	€ 0	€ 0	€ 0
129.4 mg/m³	€ 0	€ 0	€ 0	€ 0

Note: Workforce turnover 5% per year

Source: Study team.

Method 2 relies on monetised DALYs, with the estimates given in Table 6-20.

Table 6-20 METHOD 2: Benefits to WORKERS & FAMLILIES (policy options, relative to the baseline) (€ millions)

Policy option	Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter	Total
1.3 mg/m³	€ 0	€ 0	€ 0	€ 0
8.5 mg/m³	€ 0	€ 0	€ 0	€ 0
40.0 mg/m³	€ 0	€ 0	€ 0	€ 0
129.4 mg/m³	€ 0	€ 0	€ 0	€ 0

Note: Workforce turnover 5% per year

Source: Study team.

The estimations performed by both methods show no benefits for workers and families at all policy options.

6.3.2 Other benefits to workers and families

No other benefits have been identified at this stage of the project.

6.4 Benefits to employers

6.4.1 Avoided costs of ill health

The benefits (avoided costs of ill health relative to the baseline) accrued by employers are calculated using the method summarised below.

Table 6-21 Benefits to EMPLOYERS (avoided cost of ill health)

Stakeholder group	Costs	Method of summation
Employers	Ce, Cp	*CtotalEmployer=Ce+0.8*Cp*

Source: Study team.

The benefits of each policy option are summarised below in Table 6-22. The workforce turnover is 5% per year and a static discount rate of 3% is used. The estimates show no benefits for employers at all policy options.

Table 6-22 Benefits to EMPLOYERS (policy options, relative to the baseline) (€ millions)

Policy option (Inhalable)	Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter	Total
1.3 mg/m³	€ 0	€ 0	€ 0	€ 0
8.5 mg/m³	€ 0	€ 0	€ 0	€ 0
40.0 mg/m³	€ 0	€ 0	€ 0	€ 0
129.4 mg/m³	€ 0	€ 0	€ 0	€ 0

Source: Study team.

6.4.1.1 Better company image, public perception

The introduction of an OEL will not have an effect on companies' image or public perception, because businesses already achieve levels of exposure that are lower than the strictest policy option. As such, no changes would be implemented which may improve company image.

6.4.1.2 Level playing field

A harmonisation of the OEL leads to a level playing field, as all companies across all Member States follow a more symmetric requirement. The level-playing field increases slightly with the stringency of OEL. However, as companies already meet exposure levels lower that the lowest OEL, the introduction of the EU level OEL may not have a significant impact on the level playing field in the EU.

6.4.1.3 One set of limit values across all Member States

The harmonisation of OEL would make it easier for companies working in more than one EU Member State, because only one set of limit value would have to be followed. Companies could achieve savings in research and design costs, as well as expect an administrative simplification. If there is a single OEL across the EU, the company can have a centralised group of people dealing with the OEL, which would likely be more efficient. However, as companies already achieve low levels of exposure, the introduction of a single OEL in the EU may not be seen as a benefit compared to the baseline.

6.4.1.4 Moving away from RPE can be cheaper over a long period

The industries covered in this study already use full enclosure systems in their processes, and changes in these processes are not foreseen. Employees use RPE regardless, and this will not change with an introduction of any of the policy option OELs.

6.5 Benefits to public administrations

6.5.1 Avoided costs of ill health

The benefits (avoided costs of ill health, relative to the baseline) for the public administrations are calculated using the method summarised Table 6-23. These costs include healthcare treatment costs, which assume that the costs are borne by the public administrations. These costs do not include informal care costs, which are costs for workers and families covered in section 6.3. The workforce turnover is 5% per year and a static discount rate of 3% is used.

Table 6-23 Benefits to the PUBLIC ADMINISTRATIONS (avoided cost of ill health)

Stakeholder group	Costs	Method of summation
Governments	Ch, part of Cp (loss of tax revenue), part of Cl (loss of tax revenue)	*CtotalGov=Ch+0.2(Cp+Cl) (Note 1)*

Note: 1 Assumes 20% tax
Source: Study team.

The benefits of each policy option (relative to the baseline) are summarised in Table 6-24 below. The estimates show no benefits for public administrations at all policy options.

Table 6-24 Benefits to the PUBLIC ADMINISTRATIONS (policy option, relative to the baseline) (€ millions)

Policy option (Inhalable)	Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter	Total
1.3 mg/m³	€ 0	€ 0	€ 0	€ 0
8.5 mg/m³	€ 0	€ 0	€ 0	€ 0
40.0 mg/m³	€ 0	€ 0	€ 0	€ 0
129.4 mg/m³	€ 0	€ 0	€ 0	€ 0

Source: Study team.

6.5.2 Other benefits to public administrations

6.5.2.1 Avoided costs for Member State Authorities of defining national OEL levels

Table 6-25 below indicates indirect benefits that may be gained by Member States not having to define their own national OEL as a result of the introduction of an EU OEL. Defining a national OEL has associated costs for Member States public administrations to carry out impact assessments and define a suitable level of avoided risk. The data inputted are based on the assumption that all Member States without a national OEL would want to implement one and that all Member States with an existing OEL would want to revise them to ensure higher degrees of worker protection. In reality this situation may not be accurate given that isoprene is not often considered a high priority substance of concern. In addition, as indicated in Table 3-24, not all Member States have enterprises with exposed workers to isoprene, so these Member States may not be inclined to set up a national OEL. As such the indirect benefits stated below are likely an overestimate of the true value of avoided costs from establishing an EU OEL as opposed to multiple national OELs.

Table 6-25 Avoided costs of implementing Policy Options for Member State Authorities, € millions

Member State situation	Number of Member States	Avoided cost per Member State, €	Total cost across the EU (€ millions)
1.3 mg/m³			
Member States with no OEL	22	€ 100,000	€ 2.2
Member States with an OEL above this policy option	5	€ 50,000	€ 0.25
Total			**€ 2.45**
8.5 mg/m³			
Member States with no OEL	22	€ 100,000	€ 2.2
Member States with an OEL above this policy option	4	€ 50,000	€ 0.2
Total			**€ 2.4**
40.0 mg/m³			
Member States with no OEL	22	€ 100,000	€ 2.2
Member States with an OEL above this policy option	1	€ 50,000	€ 0.05
Total			**€ 2.25**
129.4 mg/m³			
Member States with no OEL	22	€ 100,000	€ 2.2
Member States with an OEL above this policy option	0	€ 50,000	€ 0
Total			**€ 2.2**

Source: Study team.

6.6 Summary of the benefits of the measures

6.6.1 Benefits from avoided ill health

Method 1 relies on WTP values for morbidity, with the resulting estimates given in Table 6-26. The estimates by Method 1 show no benefits from avoided ill health at all policy options.

Table 6-26 METHOD 1: Benefits from avoided ill health (policy options, relative to the baseline) (€ millions)

Policy option	Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter	Total
1.3 mg/m³	€ 0	€ 0	€ 0	€ 0
8.5 mg/m³	€ 0	€ 0	€ 0	€ 0
40.0 mg/m³	€ 0	€ 0	€ 0	€ 0
129.4 mg/m³	€ 0	€ 0	€ 0	€ 0

Source: Study team.

The Method 1 benefits at different policy options, split by sector are presented in Table 6-27. No benefits have been estimated for both sectors at all policy options.

Table 6-27 METHOD 1: Benefits from avoided ill health by sector by policy options, relative to the baseline (€ millions)

Sector	Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter	Total
1.3 mg/m³				
C19.20 Manufacture of refined petroleum products	€ 0	€ 0	€ 0	€ 0
C20.17 Manufacture of synthetic rubber in primary forms	€ 0	€ 0	€ 0	€ 0
8.5 mg/m³				
C19.20 Manufacture of refined petroleum products	€ 0	€ 0	€ 0	€ 0
C20.17 Manufacture of synthetic rubber in primary forms	€ 0	€ 0	€ 0	€ 0
40.0 mg/m³				
C19.20 Manufacture of refined petroleum products	€ 0	€ 0	€ 0	€ 0
C20.17 Manufacture of synthetic rubber in primary forms	€ 0	€ 0	€ 0	€ 0
129.4 mg/m³				

Sector	Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter	Total
C19.20 Manufacture of refined petroleum products	€ 0	€ 0	€ 0	€ 0
C20.17 Manufacture of synthetic rubber in primary forms	€ 0	€ 0	€ 0	€ 0

Source: Study team.

Method 2 relies on monetised DALYs, with the results presented in Table 6-28 below. The total net benefits are calculated on the basis of Method 2. The workforce turnover is 5% per year and a static discount rate of 3% is used. The estimates by Method 2 show no benefits from avoided ill health at policy options.

Table 6-28 METHOD 2: Benefits from avoided ill health (policy options, relative to the baseline) (€ millions)

Policy option	Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter	Total
1.3 mg/m³	€ 0	€ 0	€ 0	€ 0
8.5 mg/m³	€ 0	€ 0	€ 0	€ 0
40.0 mg/m³	€ 0	€ 0	€ 0	€ 0
129.4 mg/m³	€ 0	€ 0	€ 0	€ 0

Source: Study team.

The Method 2 benefits at different policy options, split by sector are presented in Table 6-29. No benefits have been estimated for both sectors at all policy options.

Table 6-29 METHOD 2: Benefits from avoided ill health by sector by policy options, relative to the baseline (€ millions)

Sector	Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter	Total
1.3 mg/m³				
C19.20 Manufacture of refined petroleum products	€ 0	€ 0	€ 0	€ 0
C20.17 Manufacture of synthetic rubber in primary forms	€ 0	€ 0	€ 0	€ 0
8.5 mg/m³				

Sector	Liver cancer	Degeneration of olfactory epithelium	Degeneration of spinal cord white matter	Total
C19.20 Manufacture of refined petroleum products	€ 0	€ 0	€ 0	€ 0
C20.17 Manufacture of synthetic rubber in primary forms	€ 0	€ 0	€ 0	€ 0
40.0 mg/m³				
C19.20 Manufacture of refined petroleum products	€ 0	€ 0	€ 0	€ 0
C20.17 Manufacture of synthetic rubber in primary forms	€ 0	€ 0	€ 0	€ 0
129.4 mg/m³				
C19.20 Manufacture of refined petroleum products	€ 0	€ 0	€ 0	€ 0
C20.17 Manufacture of synthetic rubber in primary forms	€ 0	€ 0	€ 0	€ 0

Source: Study team.

At current exposure levels, all policy options show no benefits for workers and families, employers and public administrations (Table 6-30).

Table 6-30 Overview of benefits (total for all provisions), € over 40 years (without transition measures) (€ millions)

Description	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³	Comments
Avoided costs for workers & families (method 1)	€ 0	€ 0	€ 0	€ 0	No avoided costs for workers and families have been estimated.
Avoided costs for workers & families (method 2)	€ 0	€ 0	€ 0	€ 0	No avoided costs for workers and families have been estimated.
Avoided costs for employers	€ 0	€ 0	€ 0	€ 0	No avoided costs for employers have been estimated.
Avoided costs for public administrations	€ 0	€ 0	€ 0	€ 0	No avoided costs for public administrations have been estimated.

Source: Study team.

Note: Estimates are relative to the baseline as a whole (i.e. the impact of individual actions/obligations of the preferred option are aggregated together).

6.6.2 Other benefits

No other benefits have been identified.

6.6.3 Total benefits

Overall, at current exposure levels, all policy options show no benefits for workers and families, employers and public administrations. No other benefits have been identified.

Table 6-31 Overview of benefits (total for all provisions), € over 40 years (without transition measures) (€ millions)

Description		**Total costs of policy options, € millions**			
		1.3 mg/m³	**8.5 mg/m³**	**40.0 mg/m³**	**129.4 mg/m³**
Health and safety	Avoided costs for workers & families M1	€ 0	€ 0	€ 0	€ 0
	Avoided costs for workers & families M2	€ 0	€ 0	€ 0	€ 0
	Avoided costs for employers	€ 0	€ 0	€ 0	€ 0
	Avoided costs for public administrations	€ 0	€ 0	€ 0	€ 0

Note: Estimates are relative to the baseline as a whole (i.e. the impact of individual actions/obligations of the preferred option are aggregated together).

Source: Study team.

7 COSTS OF THE MEASURES UNDER CONSIDERATION

This chapter comprises the following sections:

- Section 7.1: The cost framework;
- Section 7.2: Direct compliance costs for companies;
- Section 7.3: Indirect costs for companies;
- Section 7.4: Costs for public administrations;
- Section 7.5: Impact of transitional periods on costs; and
- Section 7.6: Summary of the costs of the measures.

7.1 The cost framework

The costs assessed in this section, together with an indication of which stakeholders are likely to be affected, are presented Table 7-1 below.

Table 7-1 Impact of costs on different stakeholders

Type of cost		Citizens	Con-sumers	Work-ers	Busi-ness	Public admini-stra-tions
Direct costs						
Direct compliance costs	Adjustment costs - First year (RMMs) - Recurrent (RMMs) - Discontinuations - Air Monitoring - Biomonitoring and health sur-veillance				✓	
	Administrative costs Relating to air monitoring and biomonitoring and health sur-veillance				✓	
	Charges					
Enforcement costs	Transposition					✓
	Information & monitoring (Inspections by enforcement agencies)				✓	✓
	Inspections and sanctions				✓	✓
	Complaint handling				✓	✓
	Adjudication/litigation				✓	✓

Type of cost		Citizens	Con-sumers	Work-ers	Busi-ness	Public admini-stra-tions
Hassle costs					✓	✓
Indirect costs						
Indirect compliance costs			✓		✓	
Other indirect costs	Offsetting/substitution effects		✓		✓	
	Transaction costs		✓		✓	
	Opportunity costs		✓		✓	
	Reduced competition		✓		✓	
	Reduced market access		✓		✓	
	Reduced investment/innovation		✓		✓	

Source: Study team on the basis of the Better Regulation Toolbox (European Commission, 2021).

Notes: ✓= key cost, quantified where possible, ✓ = minor cost, covered qualitatively where possible

7.2 Direct adjustment costs to companies

7.2.1 Introduction

This section will present key features of the adjustment cost model as well as inputs to the model. It will also present the outcome of the stakeholder consultation on adjustment costs, estimations of adjustment costs, monitoring costs and related administrative burden costs for companies, administrative burden costs for Member State authorities and aggregated costs for companies by sector.

7.2.2 Summary of the key features of the adjustment cost model

The cost model is described in the methodology report accompanying this report. The cost model takes several inputs and calculates the predicted costs incurred for a range of policy options. There are eleven types of inputs:

- Limit value options, see Section 5;
- Number of small, medium and large enterprises at each of the current exposure concentrations for each sector, see Section 7.2.3;
- Estimated breakdown of primary risk management measures (RMMs) used by enterprises for each sector, see Section 7.2.4;
- Characteristics of isoprene and type of work, see Section 7.2.7;
- Effectiveness of RMMs, see the methodological note;
- Cost of RMMs, see the methodological note;

- Discount rates, see the methodological note;
- Level of compliance with the policy option, see the methodological note;
- Discontinuation costs per sector;
- Estimated average number of exposed workers per company, see Section 7.2.5; and
- Estimated average number of workstations exposed to PAH in small, medium and large enterprises, see Section 7.2.6.

The output is the cost of implementing the OEL, split by:

- Sector;
- Company size: small, medium and large; and
- Capital expenditure (first year), operating expenditure (recurrent).

7.2.3 Number of enterprises at current exposure levels

The key parameter in the cost model is the distribution of companies across different exposure levels. The cost model is based on small, medium and large enterprises, and the number of companies and their distribution across different size bands is taken as a proxy in the model.

The exposure data for isoprene have been collected through questionnaires, CSRs, and literature review, as discussed in section 3.3. The exposure data have been analysed to provide estimated percentile values (50th or median, 75th, 90th, 95th and 100th). To obtain a cost estimate for each sector, the numbers of small, medium and large companies affected by isoprene at different exposure levels are entered into the model for each policy option. These numbers are based upon the analysis described in section 3.3.8, and particularly the exposure levels in Table 3-10, adjusted according to Table 3-11. Table 7-2 contains numbers of companies allocated to each exposure level.

Table 7-2 Number of enterprises with workers exposed to isoprene at current exposure levels by size of enterprise by sector

Sector & exposure levels mg/m³	Small	Medium	Large	Total
C19.20	**0**	**0**	**18**	**18**
0.11	0	0	9	9
0.17	0	0	5	5
0.34	0	0	3	3
0.55	0	0	1	1
0.94	0	0	1	1
C20.17	**53**	**7**	**2**	**62**
0.21	27	4	1	31

Sector & exposure levels mg/m³	Small	Medium	Large	Total
0.26	13	2	1	16
0.37	8	1	0	9
0.48	3	0	0	3
0.63	3	0	0	3
Total	**53**	**7**	**20**	**80**

Source: Study team

Note: Totals may not be the sum of all sectors due to rounding

7.2.4 Estimated breakdown of RMMs used by enterprises

The model requires a profile of the primary risk management measure used by enterprises in each sector. This is based upon the information in section 3.5, which has been obtained through stakeholder consultation and literature review. It is difficult to define the primary risk management measure as most companies use several RMMs, but generally, the primary is taken to be the highest level of RMM upon which the company depends.

Table 7-3 Percentage breakdown of primary RMMs currently used by enterprises by sector

Sector/	Full enclosure	Partial enclosure	Open hood	Pressurised or sealed cabin	Simple enclosed cabin	Breathing apparatus	HEPA filter	Simple mask	Organisational measures	General dilution ventilation	No ventilation	Total
C19.20 Manufacture of refined petroleum products	100 %	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100 %
C20.17 Manufacture of synthetic rubber in primary forms	100 %	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100 %

Source: Study team

7.2.5 Estimated average number of exposed workers per enterprise

The model requires an estimate of the average number of exposed workers per enterprise by size of enterprise in each sector. These estimates made by the study team are based upon the information in Table 3-17, and data in Table 3-22 split by size of enterprise according to Eurostat data about employees and the size of enterprise for which they work.

Table 7-4 Estimated average number of exposed workers per enterprise by size of enterprise by sector

Sector name	Number of exposed workers per company		
	Small	Medium	Large
C19.20 Manufacture of refined petroleum products	0	0	570
C20.17 Manufacture of synthetic rubber in primary forms	0.5	8	94

Source: Study team

7.2.6 Estimated average number of workstations per enterprise

The model requires an estimate of the average number of workstations per enterprise by size of enterprise in each sector. These estimates made by the study team are based upon the information in

Table 7-4 and the assumption that there will be five exposed employees per workstation; the numbers are rounded to the nearest integer and all values of 0.5 or lower are set to 0.5.

Table 7-5 Estimated average number of workstations per enterprise by size of enterprise by sector

Sector	Number of workstations per enterprises		
	Small	Medium	Large
C19.20 Manufacture of refined petroleum products	0	0	114
C20.17 Manufacture of synthetic rubber in primary forms	0.5	2	19

Source: Study team

7.2.7 Characteristics of isoprene and type of work

The use of isoprene in each sector identified in section 3.2 has certain characteristics and certain types of work during which exposure occurs. This information helps to determine the type of risk and management measures that are suitable. These characteristics are split into three groups:

- Duration of exposure over one day;
- Form of isoprene to which workers are exposed; and
- Extent to which isoprene disperse or spread when emitted.

The amount of exposure is split into work where the worker is exposed to isoprene for less than an hour a day and for more than an hour a day. This also equates to exposure for more or less than 2.5 days/month.

The form of substance to which workers are exposed varies considerably from dust and fibres to vapour, fumes, gas, mist, and aerosol. The form of a substance has a direct bearing on the types of RMM that are suitable. For this analysis, the substance form is split into two types: dust, which also includes fibres, and gas which includes all the other types.

The extent of the spread is the final characteristic that affects the choice of RMM, and this is split into three types: local, diffuse and peripheral. Local means the dust or gas is created around a specific machine and often means that highly targeted ventilation can effectively remove the chemical. Other processes spread the substance over a wider area, which is known as diffuse. In this case, dilution ventilation, workers enclosures or full enclosures are more suitable, the choice depending upon the decrease in exposure required. Peripheral means that the substance spreads more widely and cause exposure to workers beyond the area where the isoprene is being used. This means that administrators, managers and sales staff may also be exposed.

In Table 7-6 below, the percentage split for each characteristic used in the analysis is given for each sector. These values were built into the cost model.

Table 7-6 Isoprene: amount of exposure, form of isoprene and extent of spread by sector

Sector	Amount		Form		Spread		
	<1h	>1h	Dust	Gas	Local	Diffuse	Periph-eral
C19.20 Manufacture of re-fined petroleum products	100%	0%	0%	100%	100%	0%	0%
C20.17 Manufacture of syn-thetic rubber in primary forms	100%	0%	0%	100%	100%	0%	0%

Source: Study team

Note: Dust = dust and fibres, Gas = vapour, fumes, gas, mist and aerosol

7.2.8 Survey and stakeholder consultation data on adjustment costs

7.2.8.1 Survey - RMMs needed to achieve compliance

Table 7-7 outlines the percentage of companies currently using each RMM, and the RMM to which they would change if each of the policy option was implemented. Both sectors have chosen same RMMs as currently used in their processes. These include cleaning, creating a culture of safety, measures for personal hygiene of workers, provision of separate storage facilities for work clothing, training and education, face covers such as screens, shields or visors, goggles, gloves, half and full facemasks (negative pressure respirators), self-contained breathing apparatus or airline respirators, closed systems, general ventilation, and pressurised or sealed control cabs. The only additional RMM chosen by C20.17 sector was open hoods over equipment or local extraction ventilation. In the scenario where an OEL is introduced, C19.20 sector mostly indicated 'other' followed by 'no action required as OEL is already achieved' for all policy options. Those that chose 'other' mentioned PPE which is self-resurrecting or masks with filter. Sector C20.17 foresaw no action required for all policy options, although couple of respondents also indicated that training and education would be required.

Table 7-7 Current RMMs and RMMs needed to achieve compliance for different policy options (values = count & percentage)

RMMs required / **Sector (n)** **OEL: mg/ m³**	**No action required as OEL already achieved**	**Cleaning**	**Continuous measurement of air concentrations to detect unusual exposures**	**Continuous measurement to detect unusual exposures**	**Creating a culture of safety**	**Formal/external RPE cleaning and filter changing regime**	**Measures for workers' personal hygiene (e.g. daily cleaning of work clothing, oblig-**	**Provision of separate storage facilities for work clothes**	**Training and education**	**Other**	**Disposable respirators (FFP masks)**	**Face screens, face shields, visors**	**Gloves**	**Goggles**	**Half and full facemasks (negative pressure respirators)**	**Powered air-purifying respirators**	**PPE is essential regardless of the OEL**	**Self-contained breathing apparatus (with bottled air) or airline respirators (air sup-**	**Redesign of work processes**	**Reducing the amount of substance used**	**Reducing the number of workers exposed**	**Rotating the workers exposed**	**Discontinuation of process using the substance**	**Partial substitution of Isoprene used in this activity in the past**	**Substitution of substance**	**Closed systems**	**General ventilation**	**Open hoods over equipment or local extraction ventilation**	**Partial hood enclosures**	**Pressurised or sealed control cabs**	**Simple enclosed control cabs**
C19.20 Manufacture of refined petroleum products (7)																															
Current		71% (5)			71% (5)		71% (5)	71% (5)	71% (5)	14% (1)		43% (3)	71% (5)	71% (5)	71% (5)		71% (5)	71% (5)					14% (1)			86% (6)	71% (5)			57% (4)	
129.4	14% (1)									57% (4)																					
40.0	14% (1)									57% (4)																					
8.5	29% (2)									57% (4)																					
1.3	14% (1)									57% (4)																					
C20.17 Manufacture of synthetic rubber in primary forms (5)																															
Current		60% (3)			60% (3)		60% (3)	100% (5)	100% (5)	60% (3)		40% (2)	100% (5)	60% (3)	40% (2)		60% (3)	40% (2)					60% (3)			60% (3)	80% (4)	40% (2)		20% (1)	
129.4	100% (5)																														
40.0	100% (5)																														

RMMs required / **Sector (n)** / **OEL: mg/ m³**	**No action required as OEL already achieved**	**Cleaning**	**Continuous measurement of air concentrations to detect unusual exposures**	**Continuous measurement to detect unusual exposures**	**Creating a culture of safety**	**Formal/external RPE cleaning and filter changing regime**	**Measures for workers' personal hygiene (e.g. daily cleaning of work clothing, oblig-**	**Provision of separate storage facilities for work clothes**	**Training and education**	**Other**	**Disposable respirators (FFP masks)**	**Face screens, face shields, visors**	**Gloves**	**Goggles**	**Half and full facemasks (negative pressure respirators)**	**Powered air-purifying respirators**	**PPE is essential regardless of the OEL**	**Self-contained breathing apparatus (with bottled air) or airline respirators (air sup-**	**Redesign of work processes**	**Reducing the amount of substance used**	**Reducing the number of workers exposed**	**Rotating the workers exposed**	**Discontinuation of process using the substance**	**Partial substitution of Isoprene used in this activity in the past**	**Substitution of substance**	**Closed systems**	**General ventilation**	**Open hoods over equipment or local extraction ventilation**	**Partial hood enclosures**	**Pressurised or sealed control cabs**	**Simple enclosed control cabs**
8.5	100% (5)																														
1.3	100% (5)								40% (2)																						

Source: Consultation survey.

7.2.8.2 Survey - Companies' estimated costs of adjustment

Table 7-8 provides initial investment costs anticipated by companies for implementing RMMs required to achieve policy options. As shown in this table, for all policy options, no additional costs or costs below €10,000 have been anticipated by companies in C19.20 sector and no costs have been anticipated by companies in C20.17 sector. This corresponds with the fact that the current exposure levels are below the lowest policy option, hence the businesses would not need to adjust their RMMs. The costs indicated by respondents in the survey refer to monitoring costs for instrumental confirmation of compliance with OEL.

Table 7-9 provides annual recurrent costs anticipated by companies for implementing RMMs required to achieve policy options. As shown in this table, for all policy options, no additional costs or costs ranging between €1,000 and €10,000 have been anticipated by companies in C19.20 sector and no costs have been anticipated by companies in C20.17 sector. As with the initial investment costs, these costs refer to environmental monitoring.

Table 7-8 Companies anticipated cost range for RMM initial investment costs required to achieve policy options, by company size (values = count & percentage)

Sector	< €10,000			€10,000–€100,000			€100,000–€1 million			€1–10 million			> € 10 million			No additional cost			Number of responses per sector		
	S	M	L	S	M	L	S	M	L	S	M	L	S	M	L	S	M	L	S	M	L
129.4 mg/m³																					
C19.20 Manufacture of refined petroleum products			67 % (2)															33 % (1)			3
C20.17 Manufacture of synthetic rubber in primary forms																		100 % (2)			2
40.0 mg/m³																					
C19.20 Manufacture of refined petroleum products			67 % (2)															33 % (1)			3
C20.17 Manufacture of synthetic rubber in primary forms																		100 % (2)			2
8.5 mg/m³																					
C19.20 Manufacture of refined petroleum products			50 % (2)															50 % (2)			4
C20.17 Manufacture of synthetic rubber in primary forms																		100 % (2)			2
1.3 mg/m³																					
C19.20 Manufacture of refined petroleum products			67 % (2)															33 % (1)			3
C20.17 Manufacture of synthetic rubber in primary forms																		100 % (2)			2

Source: Consultation survey.

Table 7-9 Companies anticipated cost range for RMM annual recurrent costs required to achieve OEL/BLV options, by company size (values = count & percentage)

Sector	< €1,000			€1,000–€10,000			€10,000–€100,000			> €100,000			No additional costs			Number of re-sponses per sector		
	S	M	L	S	M	L	S	M	L	S	M	L	S	M	L	S	M	L
129.4 mg/m³																		
C19.20 Manufacture of refined petroleum products						67% (2)									33% (1)			3
C20.17 Manufacture of synthetic rubber in primary forms															100 % (2)			2
40.0 mg/m³																		
C19.20 Manufacture of refined petroleum products						67% (2)									33% (1)			3
C20.17 Manufacture of synthetic rubber in primary forms															100 % (2)			2
8.5 mg/m³																		
C19.20 Manufacture of refined petroleum products						50% (2)									50% (2)			4
C20.17 Manufacture of synthetic rubber in primary forms															100 % (2)			2
1.3 mg/m³																		
C19.20 Manufacture of refined petroleum products						67% (2)									33% (1)			3
C20.17 Manufacture of synthetic rubber in primary forms															100 % (2)			2

Source: Consultation survey.

7.2.8.3 Survey - Lowest technically possible and economically feasible option

As part of the survey, respondents were asked for their views on the lowest technically and economically feasible policy option for their company. Table 7-10 provides an overview of the responses.

Only one respondent from each sector replied to this question and only a technically feasible option had been proposed. For sector C19.20, the lowest proposed technically feasible exposure concentration is 9.1 mg/m^3, whereas for C20.17 sector – 1.5 mg/m^3, with an average of 5.3 mg/m^3. However, the questionnaire results indicate that both sectors are achieving exposure levels much lower than these values, as presented in section 3.3.4.

Table 7-10 Lowest technically and economically feasible 8-hour TWA

Sector	Technically feasible 8-hour TWA, average (min-max), mg/m3	Economically feasible 8-hour TWA, average (min-max), mg/m3
C19.20 Manufacture of refined petroleum products	9.1	
C20.17 Manufacture of synthetic rubber in primary forms	1.5	
Grand Total	5.3 (1.5 – 9.1)	

Source: Consultation survey

7.2.8.4 Survey - EU Member State Authorities

A total of 22 questionnaire responses were received from Member State Authorities. Seven to ten respondents answered questions covering impacts of the policy options for isoprene on costs for companies, costs for public authorities, competitiveness, SMEs, occupational health, and environment. The results are shown in Table 7-11.

The majority of respondents from Member State authorities thought that the impact on costs for companies would be moderately or significantly negative at the three most restrictive policy options, whereas at the least restrictive policy option, only a third of respondents thought that impact would be negative with half of respondents foreseeing no impact. Regarding costs to public authorities, half of respondents indicated no impact at the two most restrictive policy options, and the majority indicated no impact at the two least restrictive policy options.

More than a half of respondents thought that the introduction of one of the three most restrictive policy options would have a negative impact on competitiveness. However, at the highest policy option, respondents mostly foresaw no impact. Similarly, the majority of respondents indicated that the impact on SMEs would be moderately or significantly negative at the three most restrictive policy options but indicated less negative impact at the highest policy option.

The large majority of respondents noted that at the two most restrictive policy options, the impact on occupational health would be moderately or significantly positive, with less of such an impact at the two least restrictive policy options.

Finally, more than a half of all respondents thought that the impact on environment at all policy options would be moderately or significantly positive.

Table 7-11 Impact of the policy options for isoprene. Values = % (n)

Impact	OEL (mg/m^3)	Significant negative impact	Moderate negative impact	No impact	Moderate positive impact	Significant positive impact	No of responses (n)
Costs for companies	129.4	-	38%	50%	13%	-	8
	40	25%	38%	25%	13%	-	8
	8.5	50%	25%	13%	-	13%	8
	1.3	63%	13%	13%	-	13%	8
Costs for public authorities	129.4	-	25%	75%	-	-	8
	40	13%	25%	63%	-	-	8
	8.5	25%	25%	50%	-	-	8
	1.3	25%	25%	50%	-	-	8
Competitiveness	129.4	-	29%	71%	-	-	7
	40	29%	29%	29%	14%	-	7
	8.5	43%	14%	29%	14%	-	7
	1.3	43%	14%	29%	-	14%	7
SMEs	129.4	14%	29%	57%	-	-	7
	40	29%	43%	29%	-	-	7
	8.5	57%	29%	14%	-	-	7
	1.3	57%	29%	14%	-	-	7
Occupational health	129.4	10%	-	30%	50%	10%	10
	40	-	-	30%	50%	20%	10
	8.5	-	-	10%	30%	60%	10

Impact	OEL (mg/m^3)	Significant negative impact	Moderate negative impact	No impact	Moderate positive impact	Significant positive impact	No of responses (n)
	1.3	-	-	10%	20%	70%	10
Environment	129.4	-	-	43%	43%	14%	7
	40	-	-	43%	29%	29%	7
	8.5	-	-	29%	43%	29%	7
	1.3	-	-	29%	43%	29%	7

Source: Consultation survey

7.2.8.5 Surveys undertaken by Industry Organisations

No surveys were undertaken by the industry organisations.

7.2.9 Estimated adjustment costs

The cost model considers companies using each type of RMM and works out which new RMM is required to achieve the policy option. The model calculates the first year and recurrent costs of the new RMM. It also calculates the recurrent cost of the old RMM and the first year costs of the old RMM that would have been expected at 20 and 40 years: these are deducted from the costs for the new RMMs as the company was already expecting to pay for these.

The estimated adjustment costs over 40 years (first year and recurrent) that are incremental to the baseline, together with the combined present value over 40 years for the key sectors are summarised in

Table 7-12, Table 7-13, Table 7-14 and Table 7-15 below. The estimated combined adjustment costs over 40 years split by company size and sector are shown in Table 7-17 and Table 7-18, and these adjustment costs per company are shown in Table 7-19. Table 7-17 shows discontinuation costs as a percentage of compliance costs over 40 years.

As current exposure levels in both sectors are below the strictest policy option, no first year or recurrent adjustment costs or discontinuation costs have been estimated over 40 years for all policy options.

Table 7-12 Total PV adjustment costs over 40 years for the different policy options by sector, excluding monitoring and administrative costs

Sector	Total PV cost by policy option (€ million)			
	1.3 mg/m^3	8.5 mg/m^3	40.0 mg/m^3	129.4 mg/m^3
C19.20 Manufacture of refined petroleum products	€ 0	€ 0	€ 0	€ 0

Sector	Total PV cost by policy option (€ million)			
	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
C20.17 Manufacture of synthetic rubber in primary forms	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**

The total costs presented in

Table 7-12 include discontinuation costs. The percentage of discontinuation costs in the total PV40 adjustment costs are estimated below.

First year adjustment costs in Table 7-13 include the first year costs of purchasing/installing alternative RMMs, plus associated operating cost in the first year, minus the first year cost of operating existing RMMs which are being replaced.

Table 7-13 First year PV adjustment costs over 40 years by policy options, sector and company size (excluding the costs of monitoring and associated administrative burden)

Sector	€ million			
	Small	Medium	Large	Total
1.3 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
8.5 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
40 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
129.4 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**

Table 7-14 Discontinuation PV adjustment costs over 40 years by policy options, sector and company size

Sector	€ million			
	Small	Medium	Large	Total
1.3 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
8.5 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
40 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
129.4 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**

Source: Study team.

Table 7-15 Recurrent PV adjustment costs over 40 years by policy options, sector and company size (excluding the costs of monitoring and associated administrative burden)

Sector	€ million			
	Small	Medium	Large	Total
1.3 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
8.5 mg/m³				

Sector	€ million			
	Small	Medium	Large	Total
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
40 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
129.4 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**

Table 7-16 illustrates the combined first year, recurrent, and discontinuation costs for all sectors, split by company size.

Table 7-16 Total PV adjustment costs over 40 years by policy options, sector and company size (excluding the costs of monitoring and associated administrative burden)

Sector	€ million			
	Small	Medium	Large	Total
1.3 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
8.5 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
40 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0

Sector	€ million			
	Small	Medium	Large	Total
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**
129.4 mg/m³				
C19.20	€ 0	€ 0	€ 0	€ 0
C20.17	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**

Table 7-17 PV Discontinuation adjustment costs over 40 years as a percentage of total PV compliance costs, by policy options, sector and company size

Sector name	%			
	Small	Medium	Large	Total
1.3 mg/m³				
C19.2	0%	0%	0%	0%
C20.17	0%	0%	0%	0%
8.5 mg/m³				
C19.2	0%	0%	0%	0%
C20.17	0%	0%	0%	0%
40 mg/m³				
C19.2	0%	0%	0%	0%
C20.17	0%	0%	0%	0%
129.4 mg/m³				
C19.2	0%	0%	0%	0%
C20.17	0%	0%	0%	0%

Source: Study team.

Table 7-18 Total PV adjustment costs over 40 years by policy options and company size (excluding the costs of monitoring and associated administrative burden)

Enterprise size	€ millions			
	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Small	€ 0	€ 0	€ 0	€ 0
Medium	€ 0	€ 0	€ 0	€ 0
Large	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**

Source: Study team.

Table 7-19 Total PV adjustment costs per company over 40 years by policy options and company size (excluding the costs of monitoring and associated administrative burden)

Enterprise size	€ millions			
	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Small	€ 0	€ 0	€ 0	€ 0
Medium	€ 0	€ 0	€ 0	€ 0
Large	€ 0	€ 0	€ 0	€ 0
Total	**€ 0**	**€ 0**	**€ 0**	**€ 0**

Source: Study team.

7.2.10 Costs of air monitoring, biomonitoring and health surveillance

7.2.10.1 Air monitoring costs

7.2.10.1.1 Air monitoring campaigns

A significant number of the companies are expected to measure exposure concentration to refine their risk assessment and possibly to demonstrate compliance with the new OEL. The costs are based on the following overall considerations:

- Additional monitoring would not be needed in Member States where the OEL is already at the level of the policy option or lower;
- Larger companies in general undertake monitoring more often than smaller companies;
- The percentage of companies which would need to monitor increases as the OEL decreases (the larger the difference between the new OEL and current exposure concentrations);
- Not all companies would need additional monitoring - some companies already undertake monitoring and some companies, in particular smaller companies, would install additional RMMs without monitoring;

- Companies that only implement better RPE would not need an additional monitoring campaign to demonstrate efficiency of the RMM; and
- Companies in all sectors would have low monitoring levels.

It is assumed that those companies that monitor would need either one or two monitoring campaigns:

- For all companies that monitor at all, one monitoring campaign before the new RMMs are introduced to establish which RMMs are required; and
- For some of the companies, one further monitoring campaign after the introduction of the RMMs to demonstrate compliance if there is uncertainty as to whether the new RMMs will achieve compliance.

Further detail about the assumptions and calculations behind the modelling of air monitoring are provided in the Methodological Note.

7.2.10.1.2 Companies with exposed workers operating above each policy option

Percentage of companies in the EU with exposed workers that would not need additional monitoring because they already need to meet an OEL at the same or lower level is shown in Table 7-20. The input for the calculation is Table 3-1 with national OELs in section 16.4 and Table 16-15 with number of companies by sector and Member State in section 3.10.5.

Table 7-20 Percentage of companies in the EU with exposed workers that would not need additional monitoring because they already need to meet an OEL at same or lower level

Policy option	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
C19.20	0%	13%	13%	33%
C20.17	0%	12%	12%	16%

7.2.10.1.3 Costs of air monitoring

The total costs of air monitoring per size of the company and based on two campaigns are presented in Table 7-21. At the lowest policy option, large companies in C19.20 sector would be paying almost three times more for air monitoring than for the next policy option. The cost for air monitoring for all other policy options would be lower, with the costs at the least strict policy option of 129.4 mg/m^3 being 1.5 times lower than at the policy option of 8.5 mg/m^3. Similar situation is observed in C20.17 sector, where companies would be paying almost three times higher costs for air monitoring at the strictest policy option compared to the next strictest option. However, the difference in the cost at policy options of 8.5, 40 and 129.4 mg/m^3 is very little.

Table 7-21 Estimated costs of air monitoring over 40 years, based on two campaigns, € millions

Sector	Total costs, € million (based on two campaigns)			
	Small	Medium	Large	Total
1.3 mg/m³				
C19.20	n/a	n/a	€ 0.32	€ 0.32
C20.17	€ 0.06	€ 0.08	€ 0.04	€ 0.18
Total	**€ 0.06**	**€ 0.08**	**€ 0.36**	**€ 0.50**
8.5 mg/m³				
C19.20	n/a	n/a	€ 0.12	€ 0.12
C20.17	€ 0.02	€ 0.03	€ 0.01	€ 0.07
Total	**€ 0.02**	**€ 0.03**	**€ 0.13**	**€ 0.19**
40 mg/m³				
C19.20	n/a	n/a	€ 0.09	€ 0.09
C20.17	€ 0.01	€ 0.03	€ 0.01	€ 0.05
Total	**€ 0.01**	**€ 0.03**	**€ 0.10**	**€ 0.14**
129.4 mg/m³				
C19.20	n/a	n/a	€ 0.08	€ 0.06
C20.17	€ 0.01	€ 0.02	€ 0.01	€ 0.05
Total	**€ 0.01**	**€ 0.02**	**€ 0.07**	**€ 0.11**

Source: Study team.

7.2.10.2 Biomonitoring and health surveillance costs

Biomonitoring and health surveillance costs are not relevant for isoprene (see section 2).

7.2.11 Cost to companies of administrative burden relating to air monitoring

7.2.11.1 Air monitoring administration burden

The administrative burden costs for air monitoring per company by size are shown below, together with the days assumed to be required by companies by size to set up the monitoring each year. As in the previous calculations of cost of the monitoring, the cost of a worker or manager is assumed to be €500/day.

Table 7-22 Costs per company of administrative burden to manage first and second campaigns for air monitoring, by size of enterprise, discounted as appropriate over 40 years

	Small	Medium	Large
Days to administrate monitoring one campaign	1	3	6
Campaign 1 costs	€ 500	€ 1,500	€ 3,000
Campaign 2 costs (discounted)	€ 458	€ 1,373	€ 2,745

Source: Study team.

The cost of the administrative burden of running air monitoring for companies is shown below, by sector and size of a company for each policy option. For companies in C19.20 sector, the costs would be three times higher at the most restrictive policy option compared with the least restrictive policy option, whereas for companies in C20.17 sector, these costs would be two times higher. Most of the air monitoring costs would be borne by large enterprises in C19.20 sector at all policy options.

Table 7-23 Estimated costs of administrative burden of air monitoring by sector and policy option discounted as appropriate over 40 years, € millions

Sector	Total costs, € million (based on two campaigns)			
	Small	Medium	Large	Total
1.3 mg/m³				
C19.20	n/a	n/a	€ 0.10	€ 0.10
C20.17	€ 0.01	€ 0.02	€ 0.01	€ 0.04
Total	**€ 0.01**	**€ 0.02**	**€ 0.11**	**€ 0.15**
8.5 mg/m³				
C19.20	n/a	n/a	€ 0.08	€ 0.08
C20.17	€ 0.01	€ 0.01	€ 0.01	€ 0.03
Total	**€ 0.01**	**€ 0.01**	**€ 0.09**	**€ 0.11**
40 mg/m³				
C19.20	n/a	n/a	€ 0.06	€ 0.06
C20.17	€ 0.00	€ 0.01	€ 0.01	€ 0.02
Total	**€ 0.00**	**€ 0.01**	**€ 0.07**	**€ 0.08**
129.4 mg/m³				
C19.20	n/a	n/a	€ 0.03	€ 0.03
C20.17	€ 0.00	€ 0.01	€ 0.01	€ 0.02

Sector	Total costs, € million (based on two campaigns)			
	Small	Medium	Large	Total
Total	**€ 0.00**	**€ 0.01**	**€ 0.04**	**€ 0.05**

Source: Study team.

7.2.12 Cost to Member State authorities of administrative burden

Member State authorities incur admin costs if, for example, more reporting back to the EU is required or there are other additional administrative burdens. No additional reporting is anticipated and any other administrative burdens for Member State authorities cannot be identified or quantified.

7.2.13 Aggregated costs for companies by sector

The aggregated costs of adjustment, air monitoring and administrative burden for companies by sector are shown in Table 7-24; by sector and size of a company in Table 7-25; by size of a company in Table 7-26; and as costs per company by size of a company in Table 7-28. The total aggregated costs of adjustment, air monitoring and administrative burden for businesses and social costs from employment changes for workers and families are shown in Table 7-30. Table 7-27 presents annualised compliance, air monitoring and administrative costs by company size and Table 7-29 shows annualised compliance, air monitoring and administrative burden costs per company by company size for all policy options.

Table 7-24 Total PV compliance costs (RMMs, monitoring and administrative burden) discounted over 40 years by policy options and sector

Sector	Total costs policy options, € millions			
	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
C19.20 Manufacture of refined petroleum products	€ 0.42	€ 0.19	€ 0.15	€ 0.10
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.22	€ 0.11	€ 0.07	€ 0.06
Total	**€ 0.65**	**€ 0.30**	**€ 0.22**	**€ 0.16**

Source: Study team.

Table 7-25 Total PV compliance costs (RMMs, monitoring and administrative burden) discounted over 40 years by policy options, sector and company size

Sector	Aggregated costs of PV compliance, monitoring, and administrative burden over 40 years, size of enterprise, by sector and policy option, € millions			
	Small	Medium	Large	Total
1.3 mg/m³				
C19.20 Manufacture of refined petroleum products	n/a	n/a	€ 0.42	€ 0.42
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.07	€ 0.10	€ 0.05	€ 0.22
Total	**€ 0.07**	**€ 0.10**	**€ 0.47**	**€ 0.65**
8.5 mg/m³				
C19.20 Manufacture of refined petroleum products	n/a	n/a	€ 0.19	€ 0.19
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.03	€ 0.05	€ 0.02	€ 0.11
Total	**€ 0.03**	**€ 0.05**	**€ 0.22**	**€ 0.30**
40.0 mg/m³				
C19.20 Manufacture of refined petroleum products	n/a	n/a	€ 0.15	€ 0.15
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.02	€ 0.04	€ 0.02	€ 0.07
Total	**€ 0.02**	**€ 0.04**	**€ 0.16**	**€ 0.22**
129.4 mg/m³				
C19.20 Manufacture of refined petroleum products	n/a	n/a	€ 0.10	€ 0.10
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.02	€ 0.03	€ 0.01	€ 0.06
Total	**€ 0.02**	**€ 0.03**	**€ 0.11**	**€ 0.16**

Source: Study team.

Table 7-26 Total PV compliance costs (RMMs, monitoring and administrative burden) discounted over 40 years by policy options and company size, € millions

Sector	Policy options [mg/m³]			
	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Small	€ 0.07	€ 0.03	€ 0.02	€ 0.02
Medium	€ 0.10	€ 0.05	€ 0.04	€ 0.03
Large	€ 0.47	€ 0.22	€ 0.16	€ 0.11
Total	**€ 0.65**	**€ 0.30**	**€ 0.22**	**€ 0.16**

Source: Study team.

Table 7-27 Annual PV compliance costs (RMMs, monitoring and administrative burden) by policy options and company size, € millions

Sector	Policy options [mg/m³]			
	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m3
Small	€ 0.002	€ 0.001	€ 0.000	€ 0.000
Medium	€ 0.003	€ 0.001	€ 0.001	€ 0.001
Large	€ 0.012	€ 0.005	€ 0.004	€ 0.003
Total	**€ 0.016**	**€ 0.007**	**€ 0.005**	**€ 0.004**

Source: Study team.

Table 7-28 Total PV compliance costs (RMMs, monitoring and administrative burden) <u>per company</u> discounted over 40 years by policy options and company size, € millions

Sector	Policy options [mg/m³]			
	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Small	€ 0.001	€ 0.001	€ 0.000	€ 0.000
Medium	€ 0.015	€ 0.007	€ 0.005	€ 0.004
Large	€ 0.023	€ 0.011	€ 0.008	€ 0.006
Total	**€ 0.008**	**€ 0.004**	**€ 0.003**	**€ 0.002**

Source: Study team.

Table 7-29 Annual PV compliance costs (RMMs, monitoring and administrative burden) per company by policy options and company size, € millions

Sector	Policy options [mg/m³]			
	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Small	€ 0.0000	€ 0.0000	€ 0.0000	€ 0.0000
Medium	€ 0.0004	€ 0.0002	€ 0.0001	€ 0.0001
Large	€ 0.0006	€ 0.0003	€ 0.0002	€ 0.0001
Total	**€ 0.0002**	**€ 0.0001**	**€ 0.0001**	**€ 0.0001**

Source: Study team.

Overall, it was estimated that the lowest policy option would generate total direct costs four times higher than the least strict policy option (Table 7-30). Most of the costs would be generated by air monitoring, followed by administrative burden for running air monitoring campaigns.

Table 7-30 Total PV compliance costs (RMMs, monitoring and administrative burden), single-market costs, and social costs, discounted over 40 years, by sector, by policy options

Description	Stakeholders affected	Total costs of policy options, € millions			
		1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Adjustment costs (first year)	Business	€ 0.00	€ 0.00	€ 0.00	€ 0.00
Adjustment costs (recur-rent)	Business	€ 0.00	€ 0.00	€ 0.00	€ 0.00
Air monitoring costs	Business	€ 0.50	€ 0.19	€ 0.14	€ 0.11
Administrative burden costs	Business	€ 0.15	€ 0.11	€ 0.08	€ 0.05
Total across all sec-tors/companies/stake-holders		**€ 0.65**	**€ 0.30**	**€ 0.22**	**€ 0.16**

Source: Study team.

7.2.14 Regulatory charges

No regulatory charges are foreseen due to the introduction of an EU level OEL.

7.2.15 Comparison of costs estimates

The main costs that will be incurred by businesses if any of the policy option is introduced are monitoring and administrative costs, which would be higher for the lowest policy option. Based on the stakeholder consultation, companies are not expecting initial investment costs or annual recur-rent costs due to introduction of new RMMs because they already achieve exposure levels lower than the strictest policy option, but a few companies are anticipating additional annual costs for monitoring, which in large enterprises range between €1,000 and €10,000 (Consultation survey, 2023).

7.3 Indirect costs for companies

Indirect costs could arise in terms of the availability of products, the choice and quality of products, as well as possible ripple effects through the value chain; these types of costs are also discussed in more detail in Section 8 on Market Effects.

7.4 Costs for public administrations

Costs for Member State public authorities consist of costs that would be required to transpose the OEL into national legislation and costs of enforcement. These are discussed in sections below.

7.4.1 Costs of transposition

Member States incur costs for transposing the relevant changes into national legislation. In practice, the exact costs depend on the specific changes agreed in the final version of the Directive and the regulatory model used in each country to implement the Directive (i.e., the number of departments involved in transposition or implementing the Directive). These costs vary significantly between Member States (for example, some Member States are obliged to carry out an impact assessment on new EU legislation).

Of the 27 EU Member States, five countries already have an OEL for isoprene, see Table 16-15. These include Bulgaria, Germany, Latvia, Lithuania, and Poland. There is no information about OELs for isoprene in the remaining 22 Member States. It is thus assumed that these 22 Member States would incur higher costs for transposing an OEL than those with existing OELs.

This study assumes €50,000 per Member State as an approximation of the general order of magnitude of the transposition costs in Member States that do not currently have an OEL. Those Member States that have an OEL and need to change to a lower value are assumed to entail a lower cost of €30,000. The method for deriving these values is described in the methodological note.

Member States that already have an OEL at or lower than a policy option do not incur a cost.

The table below shows estimated transposition costs for public administrations in Member States for each policy option. As there are no Member States that have an OEL of 1.3 mg/m^3 or below, this policy option would generate the highest transposition costs.

Table 7-31 Transposition costs for Member State public administrations, € millions

Member States: Situation	Number of Member States	Transposition cost per Member State, €	Total cost across the EU, € million
1.3 mg/m^3			
No OEL: AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PT, RO, SE, SI, SK	22	€ 50,000	€ 1.10
Has an OEL above 1.3 mg/m^3: BG, DE, LT, LV, PL	5	€ 30,000	€ 0.15
Has an OEL at or below 1.3 mg/m^3:	0	€ 0	€ 0
Total cost			**€ 1.25**

Member States: Situation	Number of Member States	Transposition cost per Member State, €	Total cost across the EU, € million
8.5 mg/m^3			
No OEL: AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PT, RO, SE, SI, SK	22	€ 50,000	€ 1.10
Has an OEL above 8.5 mg/m^3: BG, LT, LV, PL	4	€ 30,000	€ 0.12
Has an OEL at or below 8.5 mg/m^3: DE	1	€ 0	€ 0
Total cost			**€ 1.22**
40 mg/m^3			
No OEL: AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PT, RO, SE, SI, SK	22	€ 50,000	€ 1.10
Has an OEL above 40 mg/m^3: PL	1	€ 30,000	€ 0.03
Has an OEL at or below 40 mg/m^3: BG, DE, LT, LV	4	€ 0	€ 0
Total cost			**€ 1.13**
129.4 mg/m^3			
No OEL: AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PT, RO, SE, SI, SK	22	€ 50,000	€ 1.10
Has an OEL above 129.4 mg/m^3:	0	€ 30,000	€ 0
Has an OEL at or below 129.4 mg/m^3: BG, DE, LT, LV, PL	5	€ 0	€ 0
Total cost			**€ 1.10**

Source: Study team.

If Member States introduce multiple OELs at the same time, the costs of transposition may be less than if each OEL is introduced individually. However, the study team does not know which, if any, OELs will be introduced and when, and therefore this factor cannot be incorporated into the cost of transposition.

7.4.2 Enforcement costs

The enforcement, monitoring and adjudication costs depend on the number of companies that will be covered by the policy option. In principle, national authorities are supposed to inspect companies already as they have the general obligation to protect workers. The enforcement costs depend on the inspection regime in each Member State. However, such costs for each Member State are unknown (and by extent are not estimated in this study). Despite this, limited costs are expected for some Member States' authorities.

7.5 Impact of transitional periods on costs

As there are no adjustment costs foreseen for the industry due to the introduction of the EU level OEL, the impact of transitional periods on costs is not relevant.

7.6 Summary of costs of the measures [incl. previous Aggregated costs]

The overall costs for each policy option are presented in Table 7-32. Regarding costs to businesses, no adjustment costs are foreseen as companies already achieve exposure levels lower than the most restrictive policy option. However, businesses would incur monitoring and administrative costs, which are around four times higher for the most restrictive policy option compared to the least restrictive option, although when annualised, these costs are extremely low, as shown in Table 7-29.

The highest costs will be incurred by public administrations, ranging from €1.10 million for the least restrictive policy option to €1.25 for the most restrictive policy option. No social costs are foreseen for any of the policy options, as there would be no discontinuations due to the introduction of an OEL at any level.

Table 7-32 Overview of costs over 40 years (without transition measures) (€ millions)

Description	Stakeholders affected	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Adjustment costs (first year)	Business	€ 0.00	€ 0.00	€ 0.00	€ 0.0
Adjustment costs (recurrent)	Business	€ 0.00	€ 0.00	€ 0.00	€ 0.0
Monitoring costs	Business	€ 0.50	€ 0.19	€ 0.14	€ 0.11
Administrative costs	Business	€ 0.15	€ 0.11	€ 0.08	€ 0.05
Transposition costs	Public administrations	€ 1.25	€ 1.22	€ 1.13	€ 1.10
Total across all sectors /companies /stakeholders		**€ 1.90**	**€ 1.51**	**€ 1.35**	**€ 1.26**

Note: Estimates are relative to the baseline as a whole (i.e. the impact of individual actions/obligations of the preferred option are aggregated together).

Source: Study team.

Overall, the total costs across all sectors, companies and stakeholders range from €1.26 million at the OEL of 129.4 mg/m^3 to €1.90 million at the OEL of 1.3 mg/m^3 and largely depend on transposition costs to public authorities as currently only five countries have existing OELs, and no country has an OEL at the most restrictive policy option.

8 MARKET EFFECTS

This chapter comprises the following sections:

- Section 8.1: Overall impact;
- Section 8.2: Research and innovation;
- Section 8.3: Single market;
- Section 8.4: Competitiveness of EU businesses;
- Section 8.5: Employment; and
- Section 8.6: Summary of the market effects.

8.1 Overall impact

Overall, market impacts (in terms of the effect on the single market, Research and Development (R&D), competitiveness of EU businesses and employment) are strongly influenced by two key drivers: the extent to which costs are incurred to comply with the OEL and the feasibility of meeting the required air concentrations. In extreme cases, companies will be forced out of business if they are unable to meet the OEL at a cost that maintains profitability.

The likely costs that would be incurred at each of the policy option considered in this study are set out in section 7 above. These have then been modelled to predict the likely number of companies (or business units) that would discontinue operations.

Table 8-1 provides estimates of the compliance costs that are estimated to be incurred on a per company basis (discounted at 3% over 40 years) including the cost of discontinuations. The remaining tables in this section present estimates of the compliance costs per company at different OEL levels (Table 8-2), compliance costs as a percentage of turnover (Table 8-5) and as a percentage of gross operating surplus (Table 8-6), first year compliance costs (Table 8-7) and first year compliance costs as a percentage of annual turnover (Table 8-8) and as a percentage of annual gross operating surplus (Table 8-9).

As seen in the table below, companies will experience minor compliance costs over 40 years at all policy options, ranging from €2,000 at the least restrictive policy option to €8,000 at the most restrictive policy option. There would be no costs in relation to the introduction of RMMs, and the costs incurred would only be due to air monitoring and administrative burden.

As shown in Table 8-2, large companies would experience higher costs at all policy options compared to small and medium enterprises. However, these costs would be higher for small and medium businesses as a percentage of the turnover (Table 8-5) and as a percentage of gross operating surplus (Table 8-6) compared to large enterprises. Still, these costs are minor and present only a small proportion of turnover and gross operating surplus for all companies.

Table 8-1 Total PV compliance costs (RMMs, discontinuations, monitoring and administrative burden) per company discounted over 40 years by policy options and sector) (€ millions)

Sector	Compliance cost per company, OEL in [mg/m³]			
	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
C19.20	€ 0.02	€ 0.01	€ 0.008	€ 0.005
C20.17	€ 0.004	€ 0.002	€ 0.001	€ 0.001
Total	**€ 0.008**	**€ 0.004**	**€ 0.003**	**€ 0.002**

Source: Study team.

Note: Total cost per company is much smaller due to the fact that 53 out of 80 companies are small enterprises.

Table 8-2 Total PV compliance costs (RMMs, discontinuations, monitoring and administrative burden) per company discounted over 40 years by policy options, sector and company size (€ millions)

Sector	Compliance cost per business, OEL in [mg/m³], by size		
	Small	Medium	Large
1.3 mg/m³			
C19.20	n/a	n/a	€ 0.023
C20.17	€ 0.001	€ 0.015	€ 0.023
Total	**€ 0.001**	**€ 0.015**	**€ 0.023**
8.5 mg/m³			
C19.20	n/a	n/a	€ 0.011
C20.17	€ 0.001	€ 0.007	€ 0.011
Total	**€ 0.001**	**€ 0.007**	**€ 0.011**
40.0 mg/m³			
C19.20	n/a	n/a	€ 0.008
C20.17	€ 0.000	€ 0.005	€ 0.008
Total	**€ 0.000**	**€ 0.005**	**€ 0.008**
129.4 mg/m³			
C19.20	n/a	n/a	€ 0.005

Sector	Compliance cost per business, OEL in [mg/m³], by size		
	Small	Medium	Large
C20.17	€ 0.000	€ 0.004	€ 0.007
Total	**€ 0.000**	**€ 0.004**	**€ 0.006**

Source: Study team.

The annual turnover and gross operating surplus, by sector and size of companies, are presented below. Further analysis below compares the total compliance costs over the 40-year period with turnover and gross operating surplus of the same 40-year period.

Table 8-3 Average annual turnover per company based on Eurostat figures, by size and sector (€ millions)

Sector	Small	Medium	Large
C19.20 Manufacture of refined petroleum products	€ 2.92	€ 73.54	€ 4,042.99
C20.17 Manufacture of synthetic rubber in primary forms	€ 1.32	€ 31.85	€ 429.43

Source: Study team.

Table 8-4 Average annual gross operating surplus per company based on Eurostat figures, by size and sector (€ millions)

Sector	Small	Medium	Large
C19.20 Manufacture of refined petroleum products	€ 0.04	€ 1.06	€ 58.11
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.07	€ 1.78	€ 24.04

Source: Study team.

Based on the estimated number of small, medium, and large companies, as well as Eurostat data on the turnover and gross operating surplus of companies in different size classes and sectors where exposure to isoprene can occur, the likely significance of the compliance costs modelled in Section 7 is estimated in Table 8-5. The average annual turnover of companies (which is presented in Table 8-3) has been used to calculate PV40 costs, additional to the baseline, as a percentage of 40 years (discounted) turnover.

The comparison of total compliance costs (adjustment costs, such as additional first year and recurrent RMMs, discontinuations, and air monitoring, plus administrative costs) to turnover and gross operating surplus is an indicator of the overall impact to the sector over time. The discontinuation costs are sometimes a reflection of the high cost of measures that need to be implemented, where the model is insufficiently sensitive to describe and categorise them.

Table 8-5 Total PV compliance costs (RMMs, discontinuations, monitoring and administrative burden) as percentage of turnover discounted over 40 years, by policy options, sector and company size and proportion of companies discontinuing at least a part of their business

Sector	Compliance costs as a percentage of turnover, per company			Percentage of companies discontinuing
	Small	Medium	Large	
1.3 mg/m³				
C19.2 Manufacture of refined petroleum products	n/a	n/a	0.00002%	0%
C20.17 Manufacture of synthetic rubber in primary forms	0.004%	0.002%	0.0002%	0%
8.5 mg/m³				0%
C19.2 Manufacture of refined petroleum products	n/a	n/a	0.00001%	0%
C20.17 Manufacture of synthetic rubber in primary forms	0.002%	0.001%	0.0001%	0%
40.0 mg/m³				
C19.2 Manufacture of refined petroleum products	n/a	n/a	0.00001%	0%
C20.17 Manufacture of synthetic rubber in primary forms	0.001%	0.001%	0.0001%	0%
129.4 mg/m³				
C19.2 Manufacture of refined petroleum products	n/a	n/a	0.00001%	0%
C20.17 Manufacture of synthetic rubber in primary forms	0.001%	0.001%	0.0001%	0%

Source: Study team.

Table 8-6 Total PV compliance costs (RMMs, compliance, monitoring and administrative burden) as percentage of gross operating surplus discounted over 40 years, by policy options, sector and company size and proportion of companies discontinuing at least a part of their business

Sector	Compliance costs as a percentage of gross operating surplus, per company			Percentage of companies discontinuing
	Small	Medium	Large	
1.3 mg/m³				
C19.2 Manufacture of refined petroleum products	n/a	n/a	0.002%	0%
C20.17 Manufacture of synthetic rubber in primary forms	0.08%	0.03%	0.004%	0%
8.5 mg/m³				

Sector	Compliance costs as a percentage of gross operating surplus, per company			Percentage of companies discontinuing
	Small	Medium	Large	
C19.2 Manufacture of refined petroleum products	n/a	n/a	0.001%	0%
C20.17 Manufacture of synthetic rubber in primary forms	0.03%	0.02%	0.002%	0%
40.0 mg/m³				
C19.2 Manufacture of refined petroleum products	n/a	n/a	0.001%	0%
C20.17 Manufacture of synthetic rubber in primary forms	0.02%	0.01%	0.001%	0%
129.4 mg/m³				
C19.2 Manufacture of refined petroleum products	n/a	n/a	0.0004%	0%
C20.17 Manufacture of synthetic rubber in primary forms	0.02%	0.01%	0.001%	0%

Source: Study team.

Companies would experience some compliance costs in the first year of the introduction of an OEL at all policy options (Table 8-7). These costs would solely be incurred due to monitoring and related administrative burden, as no need for new RMMs is foreseen. These costs would make a fraction of an annual turnover for all companies, although they would be significantly lower for large companies compared to small companies (Table 8-8). First year costs as a percentage of annual gross operating surplus would also be higher for smaller enterprises, reaching 1% at the most restrictive policy option (Table 8-9).

Table 8-7 First year compliance costs (RMMs, monitoring and administrative burden), by policy options, sector and company size (minus discontinuations) (€ million)

Sector	Aggregated first year PV compliance costs			
	Small	Medium	Large	Total
1.3 mg/m³				
C19.2 Manufacture of refined petroleum products			€ 0.22	€ 0.22
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.04	€ 0.06	€ 0.02	€ 0.12
Total	**€ 0.04**	**€ 0.06**	**€ 0.25**	**€ 0.34**
8.5 mg/m³				
C19.2 Manufacture of refined petroleum products			€ 0.11	€ 0.11
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.01	€ 0.03	€ 0.01	€ 0.05

Sector	Aggregated first year PV compliance costs			
	Small	Medium	Large	Total
Total	**€ 0.01**	**€ 0.03**	**€ 0.12**	**€ 0.16**
40.0 mg/m³				
C19.2 Manufacture of refined petroleum products			€ 0.08	€ 0.08
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.01	€ 0.02	€ 0.01	€ 0.04
Total	**€ 0.01**	**€ 0.02**	**€ 0.09**	**€ 0.12**
129.4 mg/m³				
C19.2 Manufacture of refined petroleum products			€ 0.05	€ 0.05
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.01	€ 0.02	€ 0.01	€ 0.03
Total	**€ 0.01**	**€ 0.02**	**€ 0.06**	**€ 0.09**

Source: Study team.

Table 8-8 First year costs (compliance costs (RMMs, monitoring and administrative burden) minus discontinuation costs) as percentage of annual turnover, by policy options, sector and company size, and the proportion of companies expected to continue operations

Sector	First year costs % of annual turnover (incurred by % of companies continuing)			% of companies continuing
	Small	Medium	Large	
1.3 mg/m³				
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.0003%	100%
C20.17 Manufacture of synthetic rubber in primary forms	0.05%	0.03%	0.003%	100%
8.5 mg/m³				
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.0001%	100%
C20.17 Manufacture of synthetic rubber in primary forms	0.02%	0.01%	0.001%	100%
40.0 mg/m³				

Sector	First year costs % of annual turnover (incurred by % of companies continuing)			% of companies continuing
	Small	Medium	Large	
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.0001%	100%
C20.17 Manufacture of synthetic rubber in primary forms	0.01%	0.01%	0.001%	100%
129.4 mg/m³				
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.0001%	100%
C20.17 Manufacture of synthetic rubber in primary forms	0.01%	0.008%	0.001%	100%

Source: Study team.

Table 8-9 First year (compliance costs (RMMs, monitoring and administrative burden) minus discontinuation) as a percentage of annual gross operating surplus, by policy options, sector and company size, and the proportion of companies expected to continue operations

Sector	First year costs % of gross operating surplus (incurred by % of companies continuing)			% of companies continuing
	S	M	L	
1.3 mg/m³				
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.02%	100%
C20.17 Manufacture of synthetic rubber in primary forms	1.0%	0.5%	0.05%	100%
8.5 mg/m³				
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.01%	100%
C20.17 Manufacture of synthetic rubber in primary forms	0.4%	0.2%	0.03%	100%
40.0 mg/m³				
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.01%	100%
C20.17 Manufacture of synthetic rubber in primary forms	0.3%	0.2%	0.02%	100%
129.4 mg/m³				
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.01%	100%

Sector	First year costs % of gross operating surplus (incurred by % of companies continuing)			% of companies continuing
	S	M	L	
C20.17 Manufacture of synthetic rubber in primary forms	0.2%	0.1%	0.02%	100%

Source: Study team.

8.2 Research and innovation

Research and development (R&D) are key activities in an industry's capacity to develop new products and produce existing ones more efficiently and sustainably, in a way that protects the safety of workers. The ability of the different sectors to engage in R&D activities is likely to be affected by:

- The availability of financial resources to invest in R&D;
- The availability of human resources to conduct R&D activities; and
- The regulatory environment and whether it is conducive to invest in R&D activities.

Table 8-10 provides estimates of average R&D expenditures for small, medium and large companies in the sectors with workers exposed to isoprene, based on Eurostat data. Clearly significant investment is being made in large enterprises across the two sectors.

Table 8-10 Average annual R&D expenditure per company, by company size, by sector (€ millions)

Sector	Average annual R&D expenditure per company (€ millions)		
	Small	Medium	Large
C19.20 Manufacture of refined petroleum products	€ 0.05	€ 1.29	€ 70.65
C20.17 Manufacture of synthetic rubber in primary forms	€ 0.02	€ 0.56	€ 7.50

Source: Eurostat (2018)

Note: 1. In most cases, R&D expenditure is not available at the level of the specific subsector in Eurostat. In these cases, the next level where data was available has been taken as a proxy for the sub-sector using isoprene, and so may be under- or over-estimated.

2. Data gaps exist for some Member States. In these cases, the most recent data was used.

3. Data in Eurostat is not presented by company size. It is assumed that share of R&D expenditure between different sized companies is the same as the share for turnover (based on 2018 data)

Table 8-11 PV adjustment costs (additional to the baseline) for businesses implementing RMMs as a percentage of R&D expenditure (over 40 years, discounted by 3% annually), per company, by size

Sector	PV adjustment costs as a percentage of R&D expenditure, per company		
	Small	Medium	Large
1.3 mg/m³			
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.00%
C20.17 Manufacture of synthetic rubber in primary forms	0.00%	0.00%	0.00%
8.5 mg/m³			
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.00%
C20.17 Manufacture of synthetic rubber in primary forms	0.00%	0.00%	0.00%
40.0 mg/m³			
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.00%
C20.17 Manufacture of synthetic rubber in primary forms	0.00%	0.00%	0.00%
129.4 mg/m³			
C19.20 Manufacture of refined petroleum products	n/a	n/a	0.00%
C20.17 Manufacture of synthetic rubber in primary forms	0.00%	0.00%	0.00%

Source: Study team on the basis of calculations performed in the study and Eurostat.

No adjustment costs for implementing RMMs are foreseen for the two sectors. Therefore, there would be no costs for businesses that would need to be diverted away from R&D.

8.3 Single market

8.3.1 Competition

Table 8-12 below includes the initial screening of impacts on competition in order to focus the analysis on those impacts likely to be the most significant. However, no significant impacts have been identified that would have an effect on competition.

The answers in the table are the overall assessment following a more sector specific considerations.

Table 8-12 Screening of competition impacts

Impacts	Key questions	Yes/No
Existing firms	Additional costs?	No
	Scale of costs significant?	No

Impacts	Key questions	Yes/No
	Old firms affected more than new?	No
	Location influences?	No
	Some firms will exit the market?	No
	Are competitors limited in growth potential?	No
	Increased collusion likely?	No
New entrants	Restrict entry?	No
Prices	Increased prices for consumers	No
Non-price impacts	Product quality/variety affected?	No
	Impact on innovation	No
Upstream and downstream market	Will OELs affect vertically integrated companies more or less than non-integrated ones?	No
	Will OELs encourage greater integration and market barriers?	No
	Will OELs affect bargaining power of buyers or suppliers?	No

Source: Study team.

8.3.1.1 Existing firms

The analysis presented indicates that the number of firms likely to exit the market in two sectors identified as using isoprene is very low and most companies will continue their operations. This is because many organisations are already operating at exposure levels lower than the strictest policy option.

8.3.1.2 Firms leaving the market (discontinuations)

Discontinuations are not foreseen for any policy scenario as indicated in Table 8-13 and Table 8-14.

Table 8-13 Estimated companies or business units that will discontinue operation under different policy options, by sector and size of enterprise (values = number of discontinuations (percentage of sector discontinuing))

Sector	1.3 mg/m³			8.5 mg/m³			40.0 mg/m³			129.4 mg/m³		
	S	M	L	S	M	L	S	M	L	S	M	L
C19.20 Manufacture of refined petroleum products	0	0	0	0	0	0	0	0	0	0	0	0
C20.17 Manufacture of synthetic rubber in primary forms	0	0	0	0	0	0	0	0	0	0	0	0

Source: Study team.

Table 8-14 Companies discontinuing at different policy options by sector

Sector	Number of enterprises in EU (Eurostat)	Estimated enterprise with exposed workers in EU	No. of discontinuations	Discontinuations as a % of enterprises	Discontinuations as a % of enterprises with exposed workers
1.3 mg/m³					
C19.20 Manufacture of refined petroleum products	821	18	0	0.0%	0.0%
C20.17 Manufacture of synthetic rubber in primary forms	179	62	0	0.0%	0.0%
8.5 mg/m³					
C19.20 Manufacture of refined petroleum products	821	18	0	0.0%	0.0%
C20.17 Manufacture of synthetic rubber in primary forms	179	62	0	0.0%	0.0%
40.0 mg/m3					
C19.20 Manufacture of refined petroleum products	821	18	0	0.0%	0.0%
C20.17 Manufacture of synthetic rubber in primary forms	179	62	0	0.0%	0.0%
129.4 mg/m3					
C19.20 Manufacture of refined petroleum products	821	18	0	0.0%	0.0%
C20.17 Manufacture of synthetic rubber in primary forms	179	62	0	0.0%	0.0%

Source: Study team.

8.3.1.3 New entrants

Significant capital expenditures are often incurred by new start-ups when entering the market. When entering the market companies are required to monitor exposure and so costs of running monitoring campaigns cannot be attributed to the introduction of OELs. However, as OELs become lower more precise and more expensive monitoring techniques are required, potentially increasing the costs of monitoring and making entry to the market more challenging. In the case of isoprene, the additional investments (as a proportion of turnover) foreseen for businesses in both sectors for all OEL scenarios is minor, as shown in section 8.1. It is not envisaged that the introduction of OELs at any level will have a significant impact on new entrants compared with existing firms. In addition, the costs of RMM's would most likely be insignificant compared to the huge capital investment needed to enter these two sectors.

8.3.2 Consumers

Consumers are not likely to be affected by the implementation of any policy option, because businesses already achieve exposure levels below the lowest policy option. Hence, no changes in processes or substitutions that may increase the costs of products are anticipated.

8.3.3 Internal market

Currently, five EU Member States have the existing limit values for isoprene. Table 8-15 shows that the majority of Member States that have an OEL operate at the level that represents the third policy option of 40 mg/m^3, with only Germany operating at a lower OEL of 8.5 mg/m^3. None of the countries operate at the lowest policy option.

Although current exposure levels are lower than the most restrictive policy option, the introduction of an OEL at the EU level are likely to have a positive impact on the simplification of the existing rules and the creation of a more level playing field in the internal market. The establishment of the EU OEL should reduce the diversity of national OELs, and the resulting simplification would be beneficial to companies that operate in more than one Member State. For instance, some larger companies that manufacture refined petroleum products have refineries in several Member States, although this could not be confirmed for businesses in C20.17 sector due to limitation of data. However, according to the estimations based on Eurostat data, the majority of companies in C20.17 sector are small enterprises (see Table 3-23), and it is unlikely that these companies are operating in multiple Member States.

Table 8-15 Simplification/level playing field

Policy option	Number of MS currently above the policy option
1.3 mg/m^3	0
8.5 mg/m^3	1
40.0 mg/m^3	4
129.4 mg/m^3	5
Baseline	5

Source: Study team.

8.4 Competitiveness of EU businesses

The analysis revealed that with current exposure levels, the introduction of even the lowest policy option would not results in additional costs for implementing new RMMs, because businesses already achieve exposure levels lower than the lowest policy option of 1.3 mg/m^3 and use full enclosure systems in their processes. Hence, the introduction of harmonised OEL will have no impact on companies' cost competitiveness. This has also been confirmed by the stakeholder survey, where all respondents (7) said that the level of costs incurred to comply with an OEL of 1.3 mg/m^3 would have no or limited effect on the competitiveness of their companies both inside and outside of the EU (Consultation survey, 2023).

8.4.1 Sectors affected

None of the two sectors would be adversely affected due to the introduction of any of the policy options.

8.4.2 SME competitiveness

Although the introduction of any policy option will not result in any adjustment costs for companies for implementing RMMs, all companies will incur some costs for monitoring and related administrative burden. The latter costs are lower for small and medium enterprises as presented in Table 7-29; however, for SMEs, these costs are higher as a percentage of the annual turnover compared to large companies, which are more capable to absorb such costs. Nevertheless, these costs still remain relatively low and should not affect the competitiveness of small and medium enterprises.

8.4.3 Cost competitiveness

The introduction of the harmonised OEL would have no impact on cost competitiveness of companies, because even with the lowest policy option, businesses would not incur any additional costs due to the need to implement more or better RMMs in order to comply with the OEL.

8.4.4 Capacity to innovate

No impacts on capacity to innovate are expected due to introduction of any OEL, because, as seen in Table 8-11, there would be no adjustment costs for businesses that would need to be diverted away from R&D.

8.4.5 International competitiveness

Only a few non-EU countries presented in Table 8-16 have existing OELs. However, due to exposure levels in two relevant sectors being below the lowest proposed OEL, the introduction of any policy option should not adversely affect businesses in the EU and their international competitiveness.

Table 8-16 below draws on information provided in Table 16-15 in section 16.4.

Table 8-16 OELs in selected non-EU countries

Country	OEL [mg/m^3]	Specification of OEL	STEL [mg/m^3]	Specification of STEL
Australia	-		-	
Canada	-		-	
China	-		-	
India	-		-	
Japan	8.4	- Carc	-	
Norway	-		-	
Russia	40 (V)		-	
South Korea	-		-	
Switzerland	8.5	- Carc	68	- Carc
Turkey	-		-	

Country	OEL [mg/m³]	Specification of OEL	STEL [mg/m³]	Specification of STEL
UK	-		-	
USA, ACGIH	-		-	
USA, NIOSH	-		-	
USA, OSHA	-		-	

Source: Information presented in section 3.1.

8.5 Employment

There will be no unemployment resulting from discontinuations, hence no social costs.

8.6 Summary of market effects

No effects on research and innovation, competitiveness inside and outside the EU, employment, consumers, existing firms and new entrants are foreseen for the two sectors investigated in this study as they already achieve exposure levels that are lower than the most restrictive policy option, and no adjustment costs are expected for the implementation of new RMMs. As a result, no discontinuations are foreseen due to the introduction of an OEL at all policy options (Table 8-17). Nevertheless, SMEs may experience higher monitoring and administrative costs as a percentage of turnover and gross operating surplus, although these costs are still relatively low and are not expected to have an impact on competitiveness of SMEs.

Table 8-17 Summary of market effects

Sector	1.3 mg/m³			8.5 mg/m³			40.0 mg/m³			129.4 mg/m³		
	S	M	L	S	M	L	S	M	L	S	M	L
Discontinuations	0	0	0	0	0	0	0	0	0	0	0	0
Number of MS currently at or above the policy option	0			1			4			5		

Source: Study team.

9 ENVIRONMENTAL IMPACTS

This chapter comprises the following sections:

- Section 9.1: Potential environmental impacts;
- Section 9.2: Current environmental exposure to the substance;
- Section 9.3: Direct impact on the environment;
- Section 9.4: Indirect impacts on the environment and environmental legislation; and
- Section 9.5: Summary of environmental impacts.

9.1 Potential environmental impacts

The overall approach to the assessment of the environmental impacts, based on the Better Regulation (BR) Toolbox for environmental impacts (BR Tool #36) is described in the Methodological note. Initially the key questions listed in section 3.3. of the BR Tool #36 have been screened in order to identify which questions is relevant for the introduction of an OEL and should be answered in the impact assessment. From this screening the following potential environmental impacts are included in the assessment for isoprene:

- Issues relating to the implementation and enforcement of existing environmental legislation – section 9.4;
- Climate change including impacts on climate neutrality objectives – section 9.4;
- Air, Water, Biodiversity and Soil – section 9.3;
- Waste – section 9.4;
- Zero pollution and toxicity – section 9.3;
- Efficient use of resources – section 9.4;
- Circular economy – section 9.4; and
- International environmental effects – section 9.4.

9.2 Current environmental exposure to the substance

9.2.1 Persistent, bio-accumulative, and toxic (PBT) screening

Table 9-1 outlines the persistent, bio-accumulative, and toxic (PBT) assessment status of isoprene. To be classified as PBT, all three criteria must be fulfilled. The following table outlines the PBT status and harmonised classification for isoprene in respect to the environment.

Table 9-1 PBT assessment and harmonised classification with regard to the environment for isoprene

Substance	P	B	T	PBT	Harmonised classification (environment)
Isoprene	No	No	Yes	Not PBT	Aquatic Chronic 3 (H412)

PBT: Persistent, Bio-accumulative and Toxic.

Sources: ECHA Registration Dossiers and CLP.

Under the PBT assessment conducted for isoprene as a part of the registration dossier, isoprene can be found to not meet the criteria for persistence or bioaccumulation set out in ECHA's Guidance on information requirements and chemical safety assessment (ECHA, 2017). This is based on evidence from biodegradation screening studies, isoprene's experimental Kow value and QSAR modelling which means the criteria for P/vP and B/vB are not met. In terms of toxicity the classification of T has been attributed based on the carcinogenicity and mutagenicity of isoprene.

9.2.2 Current environmental exposure

9.2.2.1 Sources

Isoprene is produced naturally via plants and mammals meaning atmospheric concentrations are largely attributed to natural releases. These natural emissions of isoprene have been quantified via modelling conducted by Guenther *et al*. (2006), at approximately 600 Tg per year globally, with tropical broadleaf trees highlighted as the major contributor. This report also highlights that over 90% of all atmospheric isoprene is sourced from terrestrial plants.

In addition to natural sources, there is potential for anthropogenic sources of isoprene. Anthropogenic sources of isoprene are largely tied to road traffic emissions with isoprene being released from the combustion of hydrocarbon fuels (Wagner and Kuttler, 2014). In addition, the findings of Wagner and Kuttler (2014) also stated that, in areas with a high density of people, isoprene emissions from human exhalation can be detected. These however are relatively small (0.54 ppb) and confined to densely populated locations meaning these would be unlikely to provide a major source of atmospheric isoprene. Wagner and Kuttler (2014) also note that, over the last 20 years decreases in road traffic, emissions throughout central Europe have resulted in 'substantially' decreased anthropogenic isoprene emissions.

Greve (2000) estimated isoprene emissions globally arising from the polyisoprene manufacturing industry at 0.8 Tg C per year. Based on the fact that this estimate was conducted in 2000 it is likely not accurate of the current situation where improvements in processes (Lynch, 2001) and closed systems have been better implemented resulting in this figure likely being an overestimate of current emissions despite market growth for polyisoprene. The majority of these emissions would also be expected to occur to air due to the volatility of the substance and safety data sheets requiring discharge to the environment and drains to be avoided (Parchem, 2015; Sigma-Aldrich, 2006).

9.2.2.2 Background exposure

Despite isoprene emissions being commonplace from both anthropogenic and biogenic sources, background exposure to isoprene is not expected to be in high concentrations. It is reported in the NTP Report on Carcinogens (NTP, 2021) that isoprene concentrations in the US ambient air range between 1 and 21 parts per billion carbon (ppbC). This data does indicate a relatively broad range as biogenic sources of isoprene are correlated to the photosynthesis rate meaning that diurnal patterns may be observed and fluctuations may occur as a result of varying light and temperature conditions (Wagner and Kuttler, 2014). Additionally, isoprene has a relatively short half-life in the atmosphere (1.2 h) due to photooxidation reactions which occur with hydroxy radicals (OECD, 2005). This has been found to be the dominant degradation process for isoprene in ambient air although other degradation routes have been stated resulting in a half-life of 0.5 h (nitric oxide) and 19 h (ozone) (NTP, 2021).

9.2.2.3 Environmental levels in relation to hazard data

Isoprene in the atmosphere from biogenic or anthropogenic sources is generally not expected to be present in concentrations which would relate in any adverse human health or environmental risks.

In the aquatic environment, Conte *et al*. (2020) have estimated a range of concentrations in marine water with variability tied to location, conditions and chlorophyll concentrations. This results in a range of natural marine isoprene concentrations of 1 to 200 pmol/l which equates to 4.45 $x10^{-7}$ to 8.9 $x10^{-5}$ mg/L. In freshwater, data have been gathered by Steinke *et al*. (2017) which indicates freshwater concentrations of isoprene between 8.1 $x10^{-5}$ and 3.2 $x10^{-4}$ mg/L in lake Constance in the Germany. These isoprene concentrations are large attributed to production naturally via micro and macro algae (Dawson *et al*., 2021). In terms of anthropogenic emissions to water, these should be avoided based on classification as aquatic chronic 3 however, once in water, isoprene is expected to mainly be removed by volatisation back to the air compartment (J-PRTR, N.D.). Degradation with hydroxy radicals is not expected in water however, isoprene can be considered readily biodegradable in water (ECHA, 2023a). Given the above data and the calculated PNEC values stated in the isoprene registration dossier of between 0.004-0.2 mg/L (ECHA, 2023a), no risk is expected to be realised for aquatic organisms based on environmental levels and releases to water are expected to result in biodegradation or volatisation into the atmosphere.

9.3 Direct impact on the environment

The table below indicates the potential alternative RMMs which may be implemented under each of the policy options and the potential impact this might have on environmental releases of harmful substances and energy consumption. For isoprene, as no changes are set to be made to the RMMs under any of the policy options, no direct environmental impacts are expected to occur as a result of implementing OELs for isoprene.

Table 9-2 Primary and alternative RMMs for each OEL and STEL option, together with the broad environmental impact

Primary RMM	**Alternative primary RMM for each policy option**				**Broad environmental impacts**
	1.3 mg/m³	**8.5 mg/m³**	**40.0 mg/m³**	**129.4 mg/m³**	
Closed systems	Not applicable	Not applicable	Not applicable	Not applicable	None
Self-contained breathing apparatus (oxygen fed)	Not applicable	Not applicable	Not applicable	Not applicable	None
Half and full facemasks (negative pressure respirators)	Not applicable	Not applicable	Not applicable	Not applicable	None

Source: Study team.

9.4 Indirect impacts on the environment and environmental legislation

9.4.1 EU Green Deal

In 2019 the European Commission announced the European Green Deal to encourage future policies to be developed in line with minimal adverse impacts on the environment and to support efforts to move to sustainable practices (European Commission, 2019). This section reviews the implementation of OELs for isoprene in the context of the key elements of the green deal. This is also in line with the approach described in chapter 36 of the better regulation toolbox.

Table 9-3 outlines the key elements put forward in the EU Green Deal and contains a short overview of the expected impact (positive or negative) of introducing OELs for isoprene on the progress towards each of these elements. A short explanation is given to indicate the justification for the expected impact.

Table 9-3 Potential for OELs to impact benefits of the EU Green Deal

Elements of the EU Green Deal	OELs impact (Yes/No)	Comment
Increasing the EU's climate ambition for 2030 and 2050	N/A	See 9.4.2 on the European Climate Law
Supplying clean affordable and secure energy	No	As the introduction of an OEL for isoprene will cause no changes in manufacturing processes, supply or demand of isoprene or isoprene rubber products, no impacts (positive or negative) are expected on any of the stated goals.
Mobilising industry for a clean and circular economy	No	
Building and renovating in an energy and resource efficient way	No	
Accelerating the shift to sustainable and smart mobility	No	
Designing a fair, healthy and environmentally-friendly food system	No	
Preserving and restoring ecosystems and biodiversity	No	
Zero pollution ambition for a toxic-free environment	No	

Source: Study team

9.4.2 European Climate Law

The European climate law was introduced in 2021 and sets out legally binding targets for emissions reductions proposed by the EU Green Deal. The main target proposed is to ensure that the European economy and society become climate neutral by 2050, with an intermediate goal to reduce greenhouse gas emissions 55% by 2030, compared to 1990 levels. It is therefore important that any implementation of OELs for isoprene should support the drive to climate neutrality and not contradict the objectives set out in this legislation.

In the case of isoprene, as no changes will be incurred by industry to meet any of the OEL policy options then it is not expected that the introduction of OELs will have any impact on the ability to meet climate goals.

9.4.3 Waste management and disposal

No impacts expected due to no changes implemented by industry.

9.4.4 Resource consumption and circular economy

No impacts expected due to no changes implemented by industry.

9.4.5 Global impacts

No impacts expected due to no changes implemented by industry.

9.4.6 Green initiatives

No impacts expected due to no changes implemented by industry.

9.5 Summary of environmental impacts

The environmental impacts of isoprene are relatively limited. This is because isoprene is mainly released to the environment from natural sources and so releases from anthropogenic emissions have a relatively small impact. Isoprene is classified as aquatic chronic 3 but is not PBT and so direct environmental impacts would largely be tied to accidental release into water (as airborne concentrations would not result in any risk to human or environmental health). Should proper handling of isoprene be followed as outlined in safety data sheets then this risk will be largely mitigated. Once in water, isoprene is readily biodegradable and will also re-release into air from the water surface so it will not pose long term risk.

Introducing OELs will not have any direct or indirect impacts on the environment or environmental legislation/targets. This is due to the fact that industry will not be required to take any action as a result of the proposed policy options and so no change would be observed from the baseline as described above.

10 OTHER IMPACTS

This chapter comprises the following sections:

- Section 10.1: Impacts on fundamental rights, including equality;
- Section 10.2: Subsidiarity and proportionality principles;
- Section 10.3: Impacts on digitalisation;
- Section 10.4: Contributions to the UN sustainable development goals; and
- Section 10.5: Summary of other impacts.

10.1 Impacts on EU Strategic Goals

In June 2019, the European Council agreed the EU's agenda for the next five years, setting out the priority areas for the European Council and establishing guidance for the work programmes of all parts of the EU (Council of the European Union, 2019).

It focuses on four priorities:

- Protecting citizens and freedoms;
- Developing a strong and vibrant economic base;
- Building a climate-neutral, green, fair and social Europe; and
- Promoting European interests and values on the global stage.

The introduction of any of the policy options as a binding OEL for isoprene is unlikely to impact any of the above points. This is due to the fact that none of the policy options require any real change in the current system and so citizen freedoms, economic stability, climate adaptability and wider European interests will not be impacted (positively or negatively) via the introduction of OELs for isoprene.

Additionally, consideration has been given to the EU Commission priority areas for 2019-2024. These are assessed in table 10-1 below.

Table 10-1 Potential for OELs to impact benefits of the EU Green Deal

EU Commission Priority Areas 2019-2024	OELs impact (Yes/No)	Comment
A European Green Deal	No	See section 9.4.1
A Europe Fit for the Digital Age	No	See section 10.3
An Economy that Works for People	No	The introduction of EU Binding OELs will have no disproportionate impacts on SMEs as no significant costs are expected to be incurred by any of the policy options.
A Stronger Europe in the World	Yes	The introduction of OELs will help to affirm the EU's reputation of delivering safe workplaces and respecting

EU Commission Priority Areas 2019-2024	OELs impact (Yes/No)	Comment
		the fundamental rights of EU workforce. If OELs are set at a disproportionately low level however this could compromise the attractiveness of EU to international business and so to meet this priority area a balance should be found. The policy options for isoprene would present very little change to industry or workplace safety and as such cannot be seen as disproportionately impacting one over the other.
Promoting our European Way of Life	Yes	The introduction of EU Binding OELs will mean all Member States are subject to the same regulation of hazardous substances set out in the CMRD. EU OELs therefore support an equal approach to chemical risk management and a united Europe when dealing with external markets.
A New Push for European Democracy	No	The introduction of OELs for isoprene does not impact the push for a maintained and renewed European democracy.

Source: Study team.

10.2 Impacts on fundamental rights, including equality

Article 31.1 of the Charter of Fundamental Rights of the European Union states that "*Every worker has the right to working conditions which respect his or her health, safety and dignity*" (European Commission, 2012). In the case of isoprene, none of the policy options lead to an improvement in air quality for European workers that are currently exposed to isoprene, although this is currently not believed to pose a health risk due to low exposure levels (see section 6.2). It should however be noted that the requirement of companies using isoprene to monitor for air concentration will improve the available data on workplace exposure and will ensure that worker conditions remain under safe conditions.

10.3 Impacts on digitalisation

The Commission has in its 2030 Digital Compass Communication (European Commission, 2023) set out a vision, targets and avenues for a successful digital transformation of Europe by 2030. To support this process, the Commission committed to assess how the options under consideration reflect the 'digital by default' principle and contribute to the digital transformation.

As before the impact of isoprene OELs will not result in any changes to wider European digitalisation plans either in a positive or negative way. Polyisoprene may be used in electronics (photoresists in semiconductor manufacturing (Fujifilm, 2023)) and so should wider regulatory action result in impacts to the polyisoprene sector, the electronics market may be impacted effecting digitalisation.

10.4 Contributions to the UN sustainable development goals

The third UN sustainable development goal (SDG) (UNDP, 2023), which calls for "*good health and wellbeing - improved worker and family health*" is directly relevant to the setting of limit values for isoprene. None of the policy options lead to an improvement in air quality for European workers that are currently exposed to isoprene, although this is currently not believed to pose a health risk due to low exposure levels (see section 6.2).

Additionally, policy option two would contribute towards SDG 8 which calls for "Decent work & economic growth" in particular towards the targets for:

- (8.2) Achieving higher levels of economic productivity through diversification, technological upgrading and innovation, including through a focus on high-value added and labour-intensive sectors.

- (8.8) Protecting labour rights and promoting safe and secure working environments for all workers, including migrant workers, in particular women migrants, and those in precarious employment.

Impacts of OELs for isoprene on wider UN sustainable development goals are not expected as the OEL policy options will not relate to any changes in the actions of industry. It should however be noted that the requirement of companies using isoprene to monitor for air concentration will improve the available data on workplace exposure and will ensure that worker conditions remain under safe conditions.

10.5 Summary of other impacts

Table 10-2 below gives a total summary of the other impacts expected to arise as a consequence of introducing OELs for isoprene. As stated throughout this section the policy options assessed will not result in any changes to industry (beyond a requirement for workplace monitoring of isoprene) and so the impacts of OELs being introduced are highly limited.

Table 10-2 Summary of other impacts

Other impacts	Impacts
EU Strategic goals	None
Fundamental rights	Increased monitoring will help to ensure that future exposures remain controlled and worker risk remains low.
Effectiveness, efficiency, and coherence	None
Digitalisation	None
UN Sustainable Development Goals – Goal 3	Increased monitoring will help to ensure that future exposures remain controlled and worker risk remains low.

11 DISTRIBUTION OF THE IMPACTS

The impacts identified under the previous tasks will be broken down by stakeholder type and a systematic analysis of who will bear the costs and accrue the benefits will be provided.

This chapter comprises the following sections:

- Section 11.1: Businesses;
- Section 11.2: SMEs;
- Section 11.3: Workers;
- Section 11.4: Consumers;
- Section 11.5: Taxpayers/public authorities;
- Section 11.6: Specific Member States/regions; and
- Section 11.7: Summary of distribution of the impacts.

11.1 Businesses

The costs and benefits for businesses (relative to the baseline) are summarised in Table 11-1 for the different policy options. As shown in the table, no benefits for employers due to avoided disruption have been estimated at all policy options. However, some monitoring and administrative costs are foreseen at all policy option, which range from around €2,000 per enterprise at the least restrictive policy option to approximately €8,000 at the most restrictive policy option.

Table 11-1 Costs and benefits to EMPLOYERS (PV over 40 years, policy options relative to the baseline) (€ millions)

	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Total benefits for employers (avoided disruption)	€ 0	€ 0	€ 0	€ 0
Total RMM adjustment, air monitoring, and administrative burden costs	€ 0.65	€ 0.30	€ 0.22	€ 0.16
Number of companies minus those discontinuing	80	80	80	80
Benefits (avoided disruption) per enterprise	€ 0	€ 0	€ 0	€ 0
Compliance, monitoring and admin costs per enterprise	€ 0.008	€ 0.004	€ 0.003	€ 0.002

Source: Study team.

11.2 SMEs

The assessment of the impact on SMEs are done following the principles of the SME test; see BR Tool #23. The SME test includes the following steps:

- Identification of affected business
- Consultation of SME stakeholders
- Assessment the impacts on SMEs
- Minimising the negative impacts on SMEs

Table 11-2 Summary of the SME test

SME test	Summary assessment
Identification of affected businesses	
	66% of the affected companies are small companies and 9% are medium sized companies.
	The share of SMEs is different between the two sectors in this analysis as no SMEs are associated with the C19.2 Manufacture of refined petroleum products sector.
Consultation with SME stakeholders	
	SMEs have been consulted as part of stakeholder consultation. The share of SME respondents is 33% in the stakeholder survey conducted for this study. While this share is lower than the share of SMEs in affected companies, SMEs are still well represented.
	SME stakeholders expressed no concern for any of the policy options, in relation to their competitiveness.
Assessing the impacts on SMEs	
	One indicator for assessing the impacts on SMEs is the share of first year costs in annual turnover. While there is no specific agreed benchmark for what significant impacts are, when the indicator is above 5%, then it will be considered significant in this study. The table presents how many sectors where the indicator is above 5% for small and medium companies. This indicates that it is only small companies that face more significant challenges for the lower OELs.

Policy option	Share of sectors where first year costs exceed 5% of annual turnover	
	Small sized companies	**Medium sized companies**
1.3 mg/m^3	0%	0%
8.5 mg/m^3	0%	0%
40 mg/m^3	0%	0%

SME test	Summary assessment		
	129.4 mg/m³	0%	0%
Minimising the negative impacts on SMEs			
	The option proposed by the ACSH will not have any major impacts on SMEs due to the fact that all companies are already in compliance with the policy options and would not need to invest significant funds to achieve compliance. The ACSH decision can therefore be seen as minimising negative impacts for SMEs.		

The numbers of small, medium and large enterprises likely to have workers exposed to isoprene in the EU are estimated in Table 3-23 of section 3.10.4.

The table below shows that, at all policy options, there will be no discontinuations for small and medium enterprises. In addition, companies will experience only very little costs as a percentage of their turnover, although proportion would be slightly higher for small enterprises. For large enterprises, costs would be insignificant at all policy options compared to their annual turnover. Hence, small companies would be slightly more impacted than medium or large companies, albeit only by a very small proportion.

Table 11-3 Costs for EMPLOYERS by size of company (PV over 40 years, constant discount rate, policy options relative to the baseline) (€ millions)

Sector	Small	Medium	Large
Number of companies	53	7	20
1.3 mg/m³			
Total RMM adjustment costs, monitoring costs, and administrative burden	€ 0.073	€ 0.104	€ 0.470
Cost per company	€ 0.001	€ 0.015	€ 0.023
Cost per company as a percentage of turnover	0.002%	0.001%	0.000%
Discontinuations	€ 0	€ 0	€ 0
8.5 mg/m³			
Total RMM adjustment costs, monitoring costs, and administrative burden	€ 0.028	€ 0.048	€ 0.215
Cost per company	€ 0.001	€ 0.007	€ 0.011
Cost per company as a percentage of turnover	0.001%	0.000%	0.000%
Discontinuations	€ 0	€ 0	€ 0

Sector	Small	Medium	Large
40.0 mg/m³			
Total RMM adjustment costs, monitoring costs, and administrative burden	€ 0.019	€ 0.036	€ 0.165
Cost per company	€ 0.000	€ 0.005	€ 0.008
Cost per company as a percentage of turnover	0.001%	0.000%	0.000%
Discontinuations	€ 0	€ 0	€ 0
129.4 mg/m³			
Total RMM adjustment costs, monitoring costs, and administrative burden	€ 0.018	€ 0.031	€ 0.112
Cost per company	€ 0.000	€ 0.004	€ 0.006
Cost per company as a percentage of turnover	0.001%	0.000%	0.000%
Discontinuations	€ 0	€ 0	€ 0

Source: Study team.

11.3 Workers

The costs and benefits for workers and their families (relative to the baseline) are summarised below for the different policy options. The benefits are the avoided costs of ill health. As shown in the table, there would be no benefits to workers and their families at all policy options.

Table 11-4 Comparison of the costs and benefits to WORKERS & THEIR FAMILIES (PV over 40 years, policy options, relative to the baseline) (€ millions)

Method	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Number of workers	10,539	10,539	10,539	10,539
Benefits (avoided ill health) (M1)	€ 0	€ 0	€ 0	€ 0
Benefits (avoided ill health) (M2)	€ 0	€ 0	€ 0	€ 0
Costs (unemployment distress)	€ 0	€ 0	€ 0	€ 0
Benefits (avoided ill health) per worker (M1)	€ 0	€ 0	€ 0	€ 0
Benefits (avoided ill health) per worker (M2)	€ 0	€ 0	€ 0	€ 0
Costs (unemployment distress) per worker	€ 0	€ 0	€ 0	€ 0

Notes: Only additional costs and benefits (i.e. relative to the baseline) are presented in this table.

Source: Study team.

11.4 Consumers

Consumers are not likely to be affected by the implementation of any policy option, because businesses already achieve exposure levels below the lowest policy option. Hence, no changes in processes or substitutions that may increase the costs of products are anticipated.

11.5 Taxpayers/public authorities

The costs and benefits for the public sector (relative to the baseline) are summarised in Table 11-5 for the different policy options. As shown in the table, there would be no avoided costs of healthcare and avoided loss of tax revenue at all policy options. However, Member State authorities would avoid costs for defining their own national OEL as a result of the introduction of an EU level OEL. These avoided costs would be highest for the lowest policy option as there are no Member State that has an OEL at this level or below. However, the indirect benefits stated below are likely an overestimate of the true value of avoided costs from establishing an EU OEL as opposed to multiple national OELs, as explained in section 6.5.2.

The table also shows costs for public authorities for transposing the OEL into national legislation. These costs are highest for the lowest policy option. However, these costs are twice as low as the avoided costs of setting a national OEL. Therefore, it would be more beneficial for Member States to transpose an EU level OEL than to set a national OEL. Nevertheless, the estimations of avoided costs of setting a national OEL are based on the assumption that all Member States without a national OEL would want to implement one and that all Member States with an existing OEL would want to revise it. In reality, this situation may not be accurate given that isoprene is not often considered a high priority substance of concern.

Table 11-5 Comparison of the costs and benefits to the PUBLIC SECTOR (PV over 40 years, policy options relative to the baseline) (€ millions)

Cost elements	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Benefits				
Avoided costs of healthcare and avoided loss of tax revenue	€ 0	€ 0	€ 0	€ 0
Avoided costs of setting OELs	€ 2.45	€ 2.40	€ 2.25	€ 2.20
Costs				
Transposition costs	€ 1.25	€ 1.22	€ 1.13	€ 1.10

Notes: Only additional costs and benefits (i.e. relative to the baseline) are presented in this table.

Source: Study team.

11.6 Specific Member States/regions

No detailed analysis of direct impacts on Member States can be derived from this assessment. This is because the distribution of companies using isoprene across EU Member States has been modelled based on Eurostat data and so may have a level of uncertainty relating to the true distribution. As such any analysis of impacts on specific Member States would pose a level of uncertainty and may lead to inaccurate conclusions.

The table below presents Member States that would need to introduce or alter legislation at different policy options. At the lowest policy option, all Member States would need to change their legislation, which would affect all companies producing isoprene in these countries, especially businesses in Germany, Spain, Italy and Slovakia, as they share more than a half of all companies in the EU with workers exposed to isoprene (see Table 3-24).

At an OEL of 8.5 mg/m^3, only Germany would not need to alter its legislation, and the highest impact would be felt by companies in few countries that share the highest proportion of enterprises with exposed workers, namely Italy, Slovakia and Spain. Similar situation would be observed at an OEL of 40 mg/m^3. Although more countries would not need to alter legislation, including Latvia, Lithuania, and Bulgaria, there are no companies in these Member States with workers exposed to isoprene that would be affected. It needs to be noted however that the numbers of enterprises with exposed workers per Member State were derived by using Eurostat data, hence may not be an entirely accurate representation of the current situation.

Table 11-6 Member States who would need to introduce or alter legislation

OEL (mg/m^3)	Member States who would need to introduce or alter legislation	% of MSs who would need to introduce or alter legislation	No of MS required to introduce or alter legislation	Notes
1.3	AU, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK	100%	27	
8.5	AU, BE, BG, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK	96%	26	Only Germany has an OEL at or below this policy option
40.0	AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PL, PT, RO, SE, SI, SK	85%	23	Bulgaria, Germany, Latvia and Lithuania have an OEL that equals or is below this policy option
129.4	AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PT, RO, SE, SI, SK	81%	22	Bulgaria, Germany, Latvia, Lithuania and Poland have an OEL that equals or is below this policy option

Source: Study team on the basis of information in section 3.1.

11.7 Summary of distribution of the impacts

The introduction of an OEL at any level will mostly impact public authorities due to transposition costs, as the majority of Member States do not have an existing OEL. Although businesses will incur monitoring and administrative costs, these are relatively low and range between approximately €2,000 for the least restrictive and €8,000 for the most restrictive policy option per enterprise over 40 years period (Table 11-1). These costs represent less than 1% of turnover for all enterprises, as shown in Table 11-3, and are only slightly higher for SMEs as a percentage of turnover compared to large companies.

No benefits are expected for employers, workers, and consumers, because the current exposure levels in two sectors already meet the most restrictive policy option. However, some avoided costs are foreseen for Member State public authorities at all policy options for not needing to set up a national OEL. Nevertheless, the estimations of avoided costs of setting a national OEL are based on the assumption that all Member States without a national OEL would want to implement one and that all Member States with an existing OEL would want to revise it. In reality, this situation may not be accurate given that isoprene is not often considered a high priority substance of concern.

The introduction of the lowest OEL will affect all Member States, whereas the introduction of the least restrictive policy option will impact 22 Member States. Countries that have higher number of enterprises with workers exposed to isoprene (e.g., Germany, Italy, Spain, Slovakia) would be more affected.

12 SUMMARY OF ECONOMIC, SOCIAL AND ENVIRONMENTAL IMPACTS

This chapter comprises the following sections:

- Section 12.1: Economic impacts;
- Section 12.2: Social impacts; and
- Section 12.3: Environmental impacts.

12.1 Economic impacts

The economic impacts relate to the direct and indirect costs that fall on companies that need to comply with the policy options are shown in Table 12-1.

Table 12-1 Aggregated PV costs and benefits for companies discounted over 40 years by policy options, € millions

Cost or benefit	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Cost	€ 0.65	€ 0.30	€ 0.22	€ 0.16
Benefit (avoided cost)	€ 0	€ 0	€ 0	€ 0

Source: Study team

Notes: M1= Method 1, a methodology that relies on "willingness to pay" values

M2= Method 2, a methodology that relies on monetised Disability Adjusted Life Years

The costs mentioned in the above table are attributed to the implementation of air monitoring to meet the requirements of the EU OEL. These costs however are low enough that this would not impact companies competitiveness in both internal and external markets regardless of company size. The model also indicates that no benefits from avoided ill health will occur as a result of the introduction of any of the policy options and so the costs of air monitoring are not offset by any benefits for companies.

These are the only economic impacts on companies as a result of the policy options and so wider economic implications such as effects on R&D, innovation or development and implementation of alternatives will also not be realised. As such the economic impacts of the introduction of any policy option are relatively limited.

12.2 Social impacts

The social impacts relating to the benefits and costs that fall on workers and public administrations, are shown in

Table 12-2.

Table 12-2 Aggregated PV costs and benefits for workers and public administrations discounted over 40 years by policy options, € millions

Cost or benefit	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Workers				
Cost	€ 0	€ 0	€ 0	€ 0
Benefit (avoided cost) M1	€ 0	€ 0	€ 0	€ 0
Benefit (avoided cost) M2	€ 0	€ 0	€ 0	€ 0
Public administrations				
Cost	€ 1.25	€ 1.22	€ 1.13	€ 1.10
Benefit (avoided cost)	€ 0	€ 0	€ 0	€ 0
Benefit (indirect)	€ 2.45	€ 2.40	€ 2.25	€ 2.20

Source: Study team

Notes: M1= Method 1, a methodology that relies on "willingness to pay" values

M2= Method 2, a methodology that relies on monetised Disability Adjusted Life Years

The social impacts relating to the implementation of any policy options for isoprene do not result in any significant costs or benefits to workers. This is because exposure levels are low enough that no cases of ill health will be realised over the next 40 years and as such there are no benefits to the implementation of any policy options. In terms of social costs relating to workers employment, the policy options would not cause any redundancies and so no costs to employees will occur.

When considering public administrations, who subsequently use funding to provide public services, low levels of both costs and benefits are estimated. These costs are incurred by the public administrations needing to spend money on transposing or introducing the EU OEL in national legislation. This results in increased costs at lower policy options as some Member States already have existing national OELs which would not need to be amended at higher policy options.

The indirect benefits which are listed in Table 12-2 relate to avoided costs of introducing a new national OEL as the background and scoping work would already have been conducted for the EU OEL. These costs would only be avoided in the case where a Member State is wanting to introduce a national OEL for isoprene. In this study, the assumption has been made that all Member States would want to introduce an OEL for isoprene.

No benefits to public administrations as a result of avoided costs of ill health would be realised under any policy option as exposures in the baseline will not result in any cases of ill health.

12.3 Environmental impacts

Given that none of the policy options result in any tangible changes for industry, no direct or indirect impacts on the environment and environmental legislation will occur under any of the policy options.

13 LIMITATIONS & SENSITIVITY ANALYSIS

This chapter presents the limitations and uncertainties of this study, and comprises the following sections:

- Section 13.1: Overview of limitations and uncertainties; and
- Section 13.2: Key limitations and uncertainties.

13.1 Overview of limitations and uncertainties

This section presents an overview of the limitations and uncertainties of this study and considers their potential impact on the conclusions. Table 13-1 provides a summarised overview of each element and assesses their significance for the results of this study. A more detailed assessment of some of these limitations and uncertainties is provided in section 13.2.

Table 13-1 Overview of the key limitations/uncertainties and their significance

Limitation or uncertainty	Explanation	Estimates in this study are likely U (underestimates) or O (overestimates)	
		Costs	Benefits
Uncertainties further assessed in section 13.2			
None			
Uncertainties not further assessed in section 13.2			
RMMs in place	Given that only little data was available on RMMs used in industry it has been assumed that all industry use similar RMMs to those stated in the consultation response and in literature. This is likely accurate for C19.20 refineries as these companies must also comply with other OELs in the same system such as benzene and so RMMs are likely standardised to meet this level. In the case of C20.17 polymer manufacturers however industry may have more variation of RMMs despite potential exposure to other harmful chemicals such as styrene and butadiene. Should companies be using less efficient RMMs than expected then exposure concentrations will likely be higher resulting in underestimates of both benefits and costs.	U	U
Positive biases in reported data	It is possible that there is some self-selection among companies that participated in the consultation for this study or provided data for the surveys of the industry associations. Worse-performing companies are less likely to report their exposure concentrations and are probably less likely to be member of an industry association. This may underestimate both costs and benefits and has not been further assessed.	U	U

Limitation or uncertainty	Explanation	Estimates in this study are likely U (underestimates) or O (overestimates)	
		Costs	Benefits
Exposed workforce	Given that very few responses and available data sources were available, the number of workers exposed to isoprene per company has been based on limited consultation data. As such there is a level of inaccuracy in the potential number of workers exposed. However, this uncertainty is not further assessed as impacts on the benefits are not expected. This is because the benefits are more reliant on the ERR and the exposure concentrations than the number of exposed workers.	No impacts	U
Slope of ERRs/DRRs	Whilst deriving the ERR and DRRs to determine the number of cases of ill health, data were transferred from animal studies to human studies. As humans and animals have different metabolism of isoprene there is uncertainty over the true correlation stated in the ERR and DRRs calculated. In many cases a conservative approach was used and as such these values, despite being low already, may be an overestimate of the number of cases resulting from isoprene exposure. This is not further explored as despite uncertainty in the translation to humans, other approaches would not be justifiable within the published literature.	No impacts	O

Source: Study team.

The uncertainties outlined in the above table have the potential to result in an underestimation of both the costs and benefits in this report. These uncertainties however are not further explored as cost/benefit data would not change unless exposure concentrations and ERR values change. ERR gradients and exposure concentrations are the primary factors responsible for no cases of ill health and no adjustment costs for industry. Whilst these factors are stated as having some uncertainty the study team is confident that the exposure concentrations used within the report are reflective of wider industry and that use of RMMs and RPE is consistent. Likewise, the ERR gradient has been well justified with available literature and so the study team does not believe this would realistically increase despite uncertainty.

Uncertainty around the number of workers or biases in the respondents to the consultation without changing exposure concentrations or ERR gradients would not result in any significant changes to the costs or benefits and therefore these uncertainties are not further explored.

Despite the low response rate and little publicly available literature, the study team remains relatively confident in the data that are available. This is because monitoring values from industry do align with expectations which have been gathered from known use of RMMs, changes in processes and conversations with industry members. Given this high level of coherence in the existing data, expectations and discussions with industry, the study team has a relatively high degree of confidence in the data despite limited datasets being available.

13.2 Key limitations and uncertainties

13.2.1 Cost estimates and sensitivity scenarios

Not further assessed in this report – see section 13.1

13.2.2 Benefit assessment and sensitivity scenarios

Not further assessed in this report – see section 13.1

13.2.3 Combined effect of alternative assumptions

Not further assessed in this report – see section 13.1

14 OVERVIEW OF THE IMPACTS

This chapter comprises the following sections:

- Section 14.1: Cost-benefit assessment (CBA);
- Section 14.2: Multi-criteria analysis (MCA);
- Section 14.3: Practical implications of establishing an OEL;
- Section 14.4: Compliance with the subsidiarity and proportionality principles;
- Section 14.5: Highlighted issues; and
- Section 14.6: Summary for the option suggested by the ACSH.

This chapter summarises the estimates presented in the previous chapters by means of a Cost-benefit assessment (CBA) and a Multi-criteria (MCA) analyses of the policy options. All the costs and benefits presented in this chapter are Present value (PV) over 40 years and additional to the baseline scenario.

14.1 Cost-benefit assessment (CBA)

14.1.1 Overview of the benefits for the policy options

The benefits (relative to the baseline) estimated in this report for the different policy options are summarised in the tables below. The benefits include the direct, the indirect and the intangible benefits as described in Section 6.1.1

Table 14-1 Overview of the benefits (PV cost savings due to reduced ill health and avoided costs) per policy option (€ million)

Impact	Stakeholders affected	Policy options			
		1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Direct benefits – improved well-being – health					
Reduced cases of ill health (Liver cancer)	Workers & families	€ 0	€ 0	€ 0	€ 0
Reduced cases of ill health (Degeneration of olfactory epithelium)	Workers & families	€ 0	€ 0	€ 0	€ 0
Reduced cases of ill health (Degeneration of spinal cord white matter)	Workers & families	€ 0	€ 0	€ 0	€ 0
Ill health avoided, incl. intangible costs (M1 to M2)	Workers & families	€ 0	€ 0	€ 0	€ 0
Avoided costs	Companies	€ 0.00 - € 0.00	€ 0.00 - € 0.00	€ 0.00 - € 0.00	€ 0.00 - € 0.00
Avoided costs	Public sector	€ 0	€ 0	€ 0	€ 0
EU policy agenda	All	Minor improvements in workers fundamental rights and contribution towards Green Deal: Chemical Strategy towards a toxic-free environment			
Direct benefits – improved well-being – environmental					
Environmental releases	All	No direct or indirect impacts on the environment and environmental legislation will occur under any of the policy options.			
Direct benefits – market efficiency					
Level playing field	Companies	A harmonised OEL at EU level would help to ensure a level playing field between companies operating in different EU Member States.			

Impact	Stakeholders affected	Policy options			
		1.3 mg/m³	**8.5 mg/m³**	**40.0 mg/m³**	**129.4 mg/m³**
Indirect benefits					
Administrative simplification	Companies	Should all Member States have a harmonised OEL this would reduce the administrative burden for companies with operations across multiple Member States. This reduction in administrative burden however would be less likely to have significant impacts in the case of isoprene due to the estimation that all companies already have relatively consistent operating processes which would not be influenced by the implementation of any of the policy options.			
Synergy	Companies	Synergistic reduction of risk to other chemicals via regulation of isoprene is not expected because no changes in RMMs or operating procedures would be introduced as a result of implementing any of the policy options. Isoprene risk was previously reduced via synergies from the implementation of the benzene OEL.			
Corporate Social Responsibility	Companies	No major impacts are expected on the perception of companies via meeting expectations around corporate social responsibility. This is due to the fact that if OELs for isoprene were to be implemented in the EU then companies would likely not introduce any new measures due to existing compliance. As such any wider benefits of building a good corporate reputation would not be applicable.			
Avoided cost of setting OEL	Public sector	€ 2.50	€ 2.40	€ 2.30	€ 2.20

Notes: May not sum to total due to rounding.

Source: Study team.

14.1.2 Overview of the costs for the policy options

The estimated direct and indirect costs are presented in Table 14-2. The costs are for the present value (PV) over 40 years with a static discount rate of 3%.

Table 14-2 Overview of the costs (incremental to the baseline, PV in € million over 40 years)

Impact	Stakeholders affected	Policy options			
		1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Direct costs – adjustment					
Risk management measures (first year and recurrent) and discontinuation costs	Companies	€ 0	€ 0	€ 0	€ 0
Air monitoring (sampling and analysis)	Companies	€ 0.50	€ 0.19	€ 0.14	€ 0.11
Transposition costs	Public sector	€ 1.30	€ 1.20	€ 1.10	€ 1.10
Direct costs – administrative					
Air monitoring	Companies	€ 0.15	€ 0.11	€ 0.08	€ 0.05
Direct compliance costs – total					
Adjustment, monitoring and administrative burden costs per company	Companies	**€ 0.65**	**€ 0.30**	**€ 0.22**	**€ 0.16**
Direct costs - enforcement costs					
Enforcement costs except transposition	Public sector	Enforcement costs may arise as a result of ensuring compliance with new OELs however these costs are not estimated as they are specific to Member States individual inspection regime.			
Indirect costs – other					
Firms exiting the market - No. of company closures	Companies	0	0	0	0
Employment – Jobs lost	Workers & families	0	0	0	0
Employment – Social cost	Workers & families	€ 0	€ 0	€ 0	€ 0

Impact	Stakeholders affected	Policy options			
		1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
International competitiveness	Companies	None of the introduced policy options are expected to have any impacts on international competitiveness of EU based business.			
Consumers	Consumers	None of the introduced policy options are expected to have any impacts on consumers.			
Internal market Lowest to highest OEL	Companies	1 : 1	1 : 1	1 : 4.7	1 : 15.2
Specific MSs/regions - MSs that would have to change OELs	Public sector	27 Member States: AU, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK	26 Member States: AU, BE, BG, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK	23 Member States: AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PL, PT, RO, SE, SI, SK	22 Member States: AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PT, RO, SE, SI, SK
Regulation	Companies	No impacts as no other regulations are expected to be introduced alongside the OEL.			

Notes: May not sum to total due to rounding.

Source: Study team.

14.1.3 Impact of different timescales for costs and benefits

In the case of isoprene, as costs and benefits are relatively negligible the impact of when these costs may occur is also negligible. As such this section is not further elaborated on within this report.

14.1.4 CBA for the policy options

The overall costs and benefits of the policy options investigated are shown in Table 14-3.

Table 14-3 Summary of monetised costs and benefits (static discount rate, additional to the baseline) (millions)

Policy option	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Total benefits M1	€ 0.00	€ 0.00	€ 0.00	€ 0.00
Total benefits M2	€ 0.00	€ 0.00	€ 0.00	€ 0.00
Total costs (€ millions)	€ 1.90	€ 1.50	€ 1.40	€ 1.30
Cost benefit ratio M1	1.90/0	1.50/0	1.40/0	1.30/0
Cost benefit ratio M2	1.90/0	1.50/0	1.40/0	1.30/0

*Notes: *Values relate to method 1 - method 2.*

Notes: May not sum to total due to rounding.

Source: Study team.

The data presented reflect the findings of the previous sections of the report in which no observable cases of ill health are currently expected in the event of isoprene exposure. This is on account of the already low exposure concentrations present in the two sectors investigated, namely in the manufacture of isoprene via steam cracking and refining and the polymerisation of isoprene into polymeric rubber products. Across these two sectors the estimated costs of ill health could therefore be calculated at €0.04 – €0.05 million euros (attributable to a proportion of a single liver cancer case). Based on this situation the introduction of any of the assessed OEL policy options would result in no benefits as no cases would be avoided as a result of regulatory intervention, hence no benefits are shown via either method in Table 14-3.

In contrast the costs stated are above zero. Indeed, if an OEL were to be introduced at EU level Member States public administrations would incur transposition costs whilst industry would also incur monitoring costs. The cost figures shown in this table are therefore a summation of both industry and public administrations costs that would be realised in order to introduce the different policy option OELs. The higher costs for lower policy options are largely driven by the transposition costs as Member States with existing OELs would need to spend money transposing their existing national OELs to a lower level. At the higher policy options this has lower costs across Member States public administrations as at these levels more Member States will already have existing national OELs below this level and as such would not incur costs of transposition as a result of new EU OEL introduction.

As a part of the cost benefit analysis, the cost benefit ratios derived in relation to method 1 and method 2 are highlighted. In this case, an exact ratio cannot be given as the benefits under both methods are zero meaning a ratio in the true sense cannot be derived. In place of these ratios the cost data represent the outcomes of the cost benefit analysis.

14.2 Multi-criteria analysis (MCA)

Table 14-4 summarises both the monetised and qualitative impacts. The MCA includes the monetised health benefits and the quantifying compliance costs. Other effects including market effects are described only qualitatively but included in the table for wider consideration.

The sensitivity assessment presented in the section 13 indicates the uncertainty related to the following monetised and quantified values. The sensitivity assessment indicates that, if anything, the benefits and costs could both be underestimates of the true values should industry not be consistently using closed systems and RPE in their operations. This situation is however not expected to be likely based on the study teams previous experience of industrial operations and the sectors in question.

In total, the MCA determines that quantitatively the benefits of the policy options (attributed to indirect benefits of avoided costs of establishing a national OEL) outweigh the costs of introduction of the policy options (attributed to industry compulsory air monitoring and public authority transposition costs). All values however do not exceed €5 million in present value over the next 40 years and so the costs/benefits of any policy option would have low impacts throughout the EU.

Table 14-4 Multi-criteria analysis (all impacts over 40 years and additional to the baseline) per policy option

Impact	Stakeholders affected	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Direct costs – adjustment					
Risk management measures – first year	Companies	€ 0	€ 0	€ 0	€ 0
Risk management measures – recurrent	Companies	€ 0	€ 0	€ 0	€ 0
Risk management measures - discontinuation	Companies	€ 0	€ 0	€ 0	€ 0
Risk management measures – total	Companies	€ 0	€ 0	€ 0	€ 0
Risk management measures – total per company	Companies	€ 0	€ 0	€ 0	€ 0
Monitoring (sampling and analysis)	Companies	€ 0.50 million	€ 0.19 million	€ 0.14 million	€ 0.11 million
Transposition costs	Public sector	€ 1.30 million	€ 1.20 million	€ 1.10 million	€ 1.10 million
Direct costs – administrative					
Company cost of administration burden	Companies	€ 0.15 million	€ 0.11 million	€ 0.08 million	€ 0.05 million
Direct costs – total compliance					
Adjustment, monitoring and administration burden costs	Companies	€ 0.65 million	€ 0.30 million	€ 0.22 million	€ 0.16 million
Adjustment, monitoring and administration burden costs per company	Companies	€ 0.008 million	€ 0.004 million	€ 0.003 million	€ 0.002 million
Direct costs - enforcement costs					
Enforcement costs except transposition	Public sector	Enforcement costs may arise as a result of ensuring compliance with new OELs however these costs are not estimated as they are specific to Member States individual inspection regime.			
Indirect costs – other					
Firms discontinuing at least a part of their business - No. of company closures	Companies	0	0	0	0

Impact	Stakeholders affected	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Firms discontinuing at least a part of their business - %	Companies	0	0	0	0
Total compliance costs as % of turnover over 40 years (including discontinuations)	Companies	Up to 0.004% (Synthetic rubber manufacture – small companies)	Up to 0.002% (Synthetic rubber manufacture – small companies)	Up to 0.001% (Synthetic rubber manufacture – small/medium companies)	Up to 0.001% (Synthetic rubber manufacture – small/medium companies)
First year compliance costs as % of turnover over 40 years (excluding discontinuations)	Companies	Same as above	Same as above	Same as above	Same as above
Employment – Jobs lost	Workers & families	0	0	0	0
Employment – Social cost	Workers & families	€ 0	€ 0	€ 0	€ 0
International competitiveness	Companies	No impact	No impact	No impact	No impact
Consumers	Consumers	No impact	No impact	No impact	No impact
Internal market Lowest to highest OEL*	Companies	1 : 1	1 : 1	1 : 4.7	1 : 15.2
Specific MSs/regions - MSs that would have to change OELs	Public sector	All	AU, BE, BG, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, LT, LV, MT, NL, PL, PT, RO, SE, SI, SK	AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PL, PT, RO, SE, SI, SK	AU, BE, CY, CZ, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LU, MT, NL, PT, RO, SE, SI, SK
Regulation	Companies	€ 0	€ 0	€ 0	€ 0
Direct benefits – improved well-being - health					
Reduced cases of ill health – liver cancer	Workers & families	0	0	0	0
Reduced cases of ill health – degeneration of olfactory epithelium	Workers & families	0	0	0	0
Reduced cases of ill health – degeneration of spinal cord white matter	Workers & families	0	0	0	0

Impact	Stakeholders affected	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Ill health avoided, incl. intangible costs (M1 to M2)	Workers & families	€ 0	€ 0	€ 0	€ 0
Direct benefits – improved well-being - safety					
Avoided costs	Companies	€ 0	€ 0	€ 0	€ 0
Avoided costs	Public sector	€ 0	€ 0	€ 0	€ 0
EU policy agenda	All	Contribution to the EU Green Deal: Chemical Strategy towards a toxic-free environment.			
Direct benefits – improved well-being - environmental					
Environmental releases	All	No direct or indirect impacts on the environment and environmental legislation will occur under any of the policy options.			
Direct benefits – market efficiency					
Level playing field	Companies	A harmonised OEL at EU level would help to ensure a level playing field between companies operating in different EU Member States. See row on 'internal market' for how harmonisation would occur at each policy option.			
Indirect benefits					
Administrative simplification	Companies	Should all Member States have a harmonised OEL this would reduce the administrative burden for companies with operations across multiple Member States. This reduction in administrative burden however would be less likely to have significant impacts in the case of isoprene due to the estimation that all companies already have relatively consistent operating processes which would not be influenced by the implementation of any of the policy options.			
Synergy	Companies	Synergistic reduction of risk to other chemicals via regulation of isoprene is not expected because no changes in RMMs or operating procedures would be introduced as a result of implementing any of the policy options. Isoprene risk was previously reduced via synergies from the implementation of the benzene OEL.			
Corporate Social Responsibility	Companies	No major impacts are expected on the perception of companies via meeting expectations around corporate social responsibility. This is due to the fact that if OELs for isoprene were to be implemented in the EU then companies would likely not introduce any new measures due to existing compliance. As such any wider benefits of building a good corporate reputation would not be applicable.			

Impact	Stakeholders affected	1.3 mg/m³	8.5 mg/m³	40.0 mg/m³	129.4 mg/m³
Avoided cost of setting OEL	Public sector	€ 2.50 million	€ 2.40 million	€ 2.30 million	€ 2.20 million
Other impacts					
Recycling – loss of business	Recycling companies	No impacts are expected to be felt by recycling companies as a result of any of the policy options.			
Impacts on fundamental rights	All	Compulsory monitoring of isoprene levels will help to ensure that the fundamental right of workers to workplace environments which respect human health is reliably enforced.			
Impacts on digitalisation	Companies	No impacts on digitalisation are expected.			
Contributions to the UN sustainable development goals	All	In relation to the third sustainable development goal – *"good health and wellbeing - improved worker and family health"* – the above comment for impacts on fundamental rights also applies.			

*Notes: * This row indicates the ratio between the lowest national EU OEL and the OEL that would be introduced at each policy option, therefore describing the ratio of harmonisation of OELs for isoprene in the EU.*

Notes: May not sum to total due to rounding.

Source: Study team.

14.3 Practical implications of establishing an OEL

The following table highlights practical considerations for citizens/consumers, businesses and administrations which should be considered under the introduction of an EU OEL for isoprene.

Table 14-5 Practical implications of establishing an OEL for isoprene

Citizens/Consumers	Businesses	Administrations
Workers have the duty to comply with the dispositions provided by the employers as regards the use of preventive and protective measures necessary to comply with OSH legislation (e.g. the newly established OEL).	Employers must comply with the whole set of OSH national legislation provisions. Given the nature of the proposed amendment, this would mainly be: - implementation of the necessary risk management measures (RMMs) (e.g. closed systems, local exhaust ventilation, improved valves and flanges, limitation of number of workers exposed, personal protection equipment) in order to comply with the new OEL; - implementation of a sampling strategy and airborne concentrations measurement programme for the chemical agents with a new OEL, as part of the risk assessment process and effectiveness check of the existing measures;	Member States must transpose the amended Directive into national legislation: - assessment of the national scenario and potential impacts; - tripartite consultation of the proposal (workers, employers, authorities); - facilitate implementation of the national legislation by providing, among other measures, technical guidance to employers. These costs are minor in comparison to the overall costs of functioning incurred by the enforcement.

Citizens/Consumers	Businesses	Administrations
	- ensure that isoprene be managed in line with the provisions of the carcinogens and mutagens national legislation; - ensure compliance with other provisions in the legislation (specific information and training to workers as regards the new working methods if such is the need in order to comply with the new OEL, collection of records, information to competent authorities, etc.).	

Source: Study team.

14.4 Compliance with subsidiarity and proportionality principles

Article 5.3 of the Treaty of Europe says "*Under the principle of subsidiarity, in areas which do not fall within its exclusive competence, the Union shall act only if and in so far as the objectives of the proposed action cannot be sufficiently achieved by the Member States, either at central level or at regional and local level, but can rather, by reason of the scale or effects of the proposed action, be better achieved at Union level.*" https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:115:0013:0045:en:PDF

Whilst Member States can and set their own limit values, the analysis and decision making are more efficient and effective if the process of setting limit values is undertaken at the Union level. The introduction of limit values at Union level also ensures that there is not divergence of risk within industry operating across the Union. For these reasons, the introduction of EU wide limit values can be seen as compliant with the principle of subsidiary.

Article 5.3 of the Treaty of Europe says "*Under the principle of proportionality, the content and form of Union action shall not exceed what is necessary to achieve the objectives of the Treaties."* https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:115:0013:0045:en:PDF It is often described as "not using a sledgehammer to crack a nut".

For control of exposure to CMR substances, it has been established that the inclusion in the CMRD and the subsequent introduction of limit values is an appropriate method of controlling exposure. Isoprene is already covered by the CMRD, therefore the Member States have already agreed that setting limit values through the process managed by the Advisory Committee for Safety and Health at Work (ACSH), Working Party on Chemicals (WPC) and DG EMPL is the appropriate and proportionate manner. By definition, Member States are obliged under the CMRD to continually work to reduce the exposure to the isoprene and this study provides all of the impacts, including the costs and benefits to the ACSH, WPC and DG EMPL enabling them to specify acceptable limit values. Given the structure and previous establishment of the above process, the introduction of EU wide limit values can be seen as compliant with the principle of proportionality.

14.5 Highlighted issues

In general, the findings of this report for the introduction of OELs for isoprene do not have many associated issues. The majority of findings indicate that very low impacts will be experienced as a result of OELs introduction and there are only low levels of uncertainty around these values.

However, during the consultation, a major trade association for industrial isoprene users highlighted that industry members support and are confident in their ability to meet the RAC opinion level of 8.5 mg/m^3 whilst they also believed that investigating below this limit is not scientifically accurate. This is grounded in the fact that the RAC opinion value was not derived via an ERR but instead by the endogenous isoprene concentrations which are naturally occurrent in humans. As such, the industry association argued that extrapolation downwards of this value to 1.3 mg/m^3 would not be scientifically accurate. Given however that isoprene is a non-threshold carcinogen it can be argued that any additional exposure above that of endogenous production will correlate to (albeit small) increases in risk.

In the current study, the study team were able to use the same data sources as those stated in the RAC opinion to derive an ERR for isoprene which in turn would allow extrapolation down to the 1.3 mg/m^3 value. There is some uncertainty in the gradient of the calculated ERR due to metabolic differences between tested animals and humans meaning that, in some cases, conservative assumptions were made and, as such, the benefits of this study may be slightly overestimated despite resulting in no cases of ill health.

Given this dispute, it should be acknowledged that whilst the findings of this study indicate no impacts across any of the policy options, industry would be most in favour of the 8.5 mg/m^3 level.

14.6 Summary for the option agreed by the ACSH

The ACSH opinion on BOEL values for isoprene was adopted on 22 September 2023. The opinion notes that isoprene is recognised as a non-threshold carcinogen and therefore exposure to workers should be controlled by intervention at the EU level. In discussions, the following three points were agreed upon:

- Isoprene is classified as Carc. 1B and Muta. 2 under the CLP regulation and is produced endogenously via biological pathways in humans;
- RAC proposed a limit value based on the naturally occurring endogenous isoprene levels. This value is 8.5 mg/m^3;
- The OEL should be set at this value (8.5 mg/m^3) and can enter into force without any transitional measures.

In the discussions leading to the above points, consideration was also given to the differences in approach between this impact assessment and the RAC opinion. The ACSH opinion acknowledges that based on currently available data and the approach taken in the current impact assessment, a BOELV of 1.3 mg/m^3 would also be achievable by industry. Despite this, the opinion of the ACSH remains at 8.5 mg/m^3, a level which would ensure a high degree of protection of workers and a level playing field for industry. Annex 2 in Section 0 of this report provides an overview of the impacts of the chosen option.

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16 ANNEXES

16.1 Annex 1 - Summary of Consultation

This section provides a summary of the stakeholder consultation exercises undertaken as part of this study ('Study on collecting the most recent information on substances to analyse health, socio-economic and environmental impacts in connection with possible amendments of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work').

16.1.1 Outline of consultation strategy

The primary aim of the consultation activities is to identify information not available via desk-based research. For example, although information on current OELs, STELs, BLVs and notations is available, there is limited information on the specific concrete risk management measures already in place, as well as those that would need to be implemented, should the proposed measures be introduced into the CMRD. There may also, for example, be complications regarding the specificities of different sites and environments in which workers may be exposed. Consultation activities therefore formed a valuable part of this study.

The consultation activities conducted to date have included:

- Targeted questionnaires, these included: substance specific questionnaires, Member State Authorities, OSH Experts, Trade Unions and a further short questionnaire for welding[11];
- Interviews;
- Site visits; and
- Conversations (these consisted of email exchanges and online calls).

The study team have consulted a range of organisations whose activities are relevant to the five substances[12] being analysed as part of this study. Information collected via consultation included the sectors and processes in which the relevant substances are used, the size of companies that would be impacted, estimates of numbers of workers exposed currently, current air concentrations of substances concerned (both 8-hour time weighted averages (8-h TWA) and 15-minute reference periods), current biological limit values, as well as risk management measures currently in place, and risk management measures that would need to be implemented should the limits be introduced and the associated costs.

Consultation activities have been conducted by those with expertise; substance experts (those writing the substance-specific reports) and national experts (with knowledge of the situation in their Member State and native language competence) conducted the interviews with stakeholders. The substance and national experts in turn were also supported by experts in cost-benefit analysis and consultation via a consortium led by RPA which has worked on all five previous OELs studies.

[11] Questionnaires for MSA, Trade Unions and the further welding questionnaire were often accompanied by interviews. The aim of these interviews was to fill in the questionnaire and this formed the basis of the interview questions.

[12] Cobalt and inorganic cobalt compounds, isoprene, polycyclic aromatic hydrocarbons, welding fume and 1,4-dioxane

Any contact made with stakeholders was logged so that progress can be monitored, and interview guides have been prepared for those conducting interviews to ensure that the approach to collecting data was thorough and consistent. These guides include information clarifying the objectives of the study, the study approach and provide detailed information on the measures being assessed. They also include information on the role of the national experts and the specific data that needs to be collected via consultation, as well as the privacy statement and the confidentiality options.

The following important aspects of the consultation exercise should be mentioned:

- There has been no public consultation conducted as part of this work, although the survey has – through its submission strategy – aimed to reach out widely;
- The consultation focused on generating *evidence* to directly support the analyses. Views and opinions have also been provided and are presented here as well, but the approach towards this has not been as systematic; and
- Much of the evidence gathered is of a confidential nature and is thus not presented here, however it has been used to support the calculations and assessments that result from the analyses.

The table below summarises the stakeholder groups targeted and the tools, interests and strategies applied:

Table 16-1 Consultation tools and strategies

Stakeholder type	Interests represented	Main consultation tools	Strategy
EU Associations and REACH Consortia	Industry	Online interviews Email requests	Our previous work demonstrated that EU Associations are the best instrument for reaching out to manufacturers/users. Upon our request, the EU associations thus forwarded the questionnaires to national associations and companies. Supplementary information e.g. on number of companies, numbers of workers exposed, market situation, etc. was collected through email requests and online interviews with the associations and REACH consortia and statistics from Eurostat.
Member State Authorities	Member State authorities	Questionnaires Online interviews	Member State authorities were contacted with a questionnaire and responses were followed up with online interviews, where possible. Experience from supporting the OELs 3, OELs 4 and OELs 5 studies demonstrated that this is the most effective way of collecting the specific information across all Member States.
Manufacturers/users	Industry	Questionnaires Online interviews Email requests	Based on the experience from OELs 3, OELs 4 and OELs 5, questionnaires for manufacturers/users were mainly distributed via EU associations. The EU associations forwarded the questionnaire directly to companies or forwarded it to national industry associations which then forwarded it to their member companies. This strategy was deemed the most sensible as

Stakeholder type	Interests represented	Main consultation tools	Strategy
			experience from the previous OELs studies shows that only a few companies answer the questionnaire unless encouraged to do so by either their relevant EU association or their national industry associations. To increase the number of responses, questionnaires were refined and kept as short as possible, and focused on providing data on existing RMMs as well as RMMs (and costs) needed to comply with the various reference limits (options) Questionnaire responses were then, where possible/ necessary, followed up by interviews and site visits. Some companies have been also contacted directly (i.e. not via the associations) by phone by national experts who encouraged and assisted the companies in filling out the questionnaire and/or undertook telephone interviews. This additional approach was selected to ensure that answers are provided by companies situated in as many Member States as possible.
National industry associations	Industry	Online interviews Email requests	National industry associations were primarily contacted via the EU associations. Some national associations were contacted directly by phone by national experts and interviewed to collect information supplementary to the information from EU associations, and identify relevant national companies to be approached by the national experts.
Trade Unions	Workers	Online interviews Email requests WPC	Based on previous experience, this study focused on obtaining a few more targeted telephone interviews and email correspondence, as well as collecting information from worker association representatives of the WPC.
Occupational Health & Safety Professionals	Contacted to obtain scientific information	Questionnaire Online interviews	Occupational health and safety professionals were contacted with a questionnaire. This is considered the most efficient way to collect specific information across all Member States.
Working Party on Chemicals (WPC)	Industry Workers Member State Authorities	Participation in workshop	The study team presented draft results to the Working Party on Chemicals in May 2023. Previously, this has proved to be an effective means of receiving feedback from representatives of industry, employers' associations, workers' organisations and Member State authorities.
Laboratories	In communication to obtain	Online interviews	In the study supporting OELs 3, a large number of laboratories were contacted via email

Stakeholder type	Interests represented	Main consultation tools	Strategy
	information on sampling and analysis	Email requests	requests. Limited information was obtained, and it was only obtained when the email requests were combined with telephone contact. For previous OELs studies and this study, the approach has been to contact a small number of laboratories by phone and email using direct contacts, and to dedicate efforts to following-up on these, to obtain detailed information on methods applied, standards, limits of quantification and prices.

Source: Analysis by RPA Ltd and COWI.

Some stakeholders could not be reached. Substance experts wanted to contact specific national welding institutes, companies and trade unions. Efforts were made to contact these stakeholders but there was no response.

16.1.2 Documentation of formal consultation activity

The questionnaires for isoprene and stakeholder groups can be found in the following annexes.

- Isoprene Questionnaire: Annex 3;
- MSA Questionnaire: Methodological Note Annex 2;
- OSH Questionnaire: Methodological Note Annex 3; and
- Trade Union Questionnaire: Methodological Note Annex 4.

16.1.3 Methodologies and tools to process data

The online questionnaires for this report were gathered using EU Survey. EU Survey allows for full control over the creation and design of the questionnaire and allows translations to be edited through the website tools. Once completed, the survey data was exported from EU Survey into Excel and cleaned to ensure that only genuine responses were analysed. Any test answers or irrelevant responses were removed. This was then provided to substance experts for their analysis to combine with information that had been obtained through internet research, interviews and other means.

A stakeholder log was also created to monitor and record contact with stakeholders. This included contact information, contact method, and survey completion.

Experts responsible for each substance were provided with all the information relevant for their substance (questionnaire responses, interview minutes, site visit reports, position papers, etc.). All information was analysed by the specific substance expert and, where considered robust and relevant, used as the basis for the substance-specific analyses in conjunction with information obtained via desk-based research.

16.1.4 Results of consultation activities

The consultation activities being conducted as part of this study are explained in greater detail in the subsections below.

16.1.4.1 Targeted online survey

The online targeted survey opened on 23 January 2023 and ran until 27 March 2023. The deadline was extended twice to allow for a broader range of stakeholders to respond and address low response rates for certain substances.

Stakeholders were initially contacted via email. The email provided an overview of the study and a link to the RPA webpage explaining the consultation activities, with links to each of the questionnaires, the privacy statement, and an introductory letter from the Commission. A link rather than an attachment was used to decrease the size of the email and reduce the number of emails automatically directed to junk folders. Five separate questionnaires were created for each of the substances for companies, three for the different stakeholder groups and an additional welding questionnaire. Those relevant for isoprene were:

- Companies - isoprene;
- Member State Authorities;
- Occupational Safety and Health Experts; and
- Trade Unions.

The questionnaires for companies were available as a link to EU Survey. The questionnaire for Member State authorities and occupational safety and health experts was available as a Word document which could be downloaded and sent to the study team using the designated OELs 6 email address. Trade Unions and specific welding stakeholders were also contacted by national experts and invited to interview for the questionnaire.

The questionnaires aimed to collect information on processes during which worker exposure to the substances in question is likely to occur, risk management measures that are already in place, current exposure concentrations, risk management measures that would need to be implemented should the limit be lowered, and any other impacts that could result from the introduction of EU-level limits. As mentioned above, the questionnaires were targeted, focusing on the evidence needed for the analyses. In that regard, particular focus was placed on risk management measures, as only limited information on these is available in the literature.

Translations of each of the substance questionnaires were available in German, French, Italian, Polish and Spanish and respondents also had the option to ask the study team for the questionnaire in a language of their choice. Translations were initially requested through EU Survey and were then checked and edited by the National Experts.

At the end of the questionnaire, respondents were given the opportunity to add any further comments and were asked if they were willing for a substance expert to ask potential follow-up questions and whether they would be willing to host a site visit. Follow-up interviews were very useful when there were gaps in a stakeholder’s response and questions could be asked further to fill in missing information. Other consultation methods were used to probe further into respondents’ answers and gain a more in-depth understanding of the topic and potential impacts.

National experts were used to contact MSAs for countries where the study team did not have a response from that country.

The Commission and the WPC were provided the opportunity to comment on the drafts of each questionnaire before they were launched, to ensure that they were relevant and user-friendly.

Some stakeholders however expressed difficulty in responding to the questionnaire due to the complexity of the study – this was particularly the case for welding fume. Discussions were held with key industry associations and these stakeholders were provided with the opportunity to respond to the questionnaire via interview, where explanation could be provided for each question. The study team also received responses from industry organisations.

It should also be noted that some industry associations had already carried out their own surveys or had contributed to discussions on the relevant occupational exposure limits prior to this study, which may have resulted in consultation fatigue for some substances.

Around **691** stakeholders were invited to take part in the questionnaire across all five substances. Many of the stakeholders contacted were relevant for multiple substances. However, the true number of stakeholders that were contacted is likely to be higher as many industry and EU associations were contacted and asked to distribute the survey to their members. Based on experience from previous studies, this has been a useful method to ensure a high response rate from companies. Efforts were also made during calls with industry associations to encourage their members to respond. Stakeholders were selected from the sectors that were identified as being relevant for each of the substances. The tables below provide a summary of the responses according to stakeholder type.

Table 16-2 Summary of numbers of stakeholders directly contacted by questionnaire type

Stakeholder type		Number contacted
Companies	Companies	15.91% (110 out of 691)
	Industry associations	61.07% (422 out of 691)
Member State Authorities		20.69% (143 out of 691)
Occupational Health and Safety Experts		2.32% (16 out of 691)
Trade Unions*		3 contacted
Welding (short interviews)*		20 contacted

*Source: Consultation. *These were accompanied by an interview and were undertaken in addition to the main questionnaires and thus are not included in the total number.*

Four reminders were sent out to stakeholders to prompt them to respond and update them on the extension to the survey deadline. Stakeholders that had completed the survey or indicated to the study team that the substance was not relevant to them were removed from the mailing list.

Table 16-3 Breakdown of number of stakeholders directly contacted by questionnaire type

Stakeholder type	Number contacted
Company	15.63% (108 out of 691)

Education and Training	0.14% (1 out 691)
Industry associations	59.62% (412 out of 691)
Laboratories	0.14% (1 out of 691)
Public authority	20.69% (143 out of 691)
NGO	1.45% (10 out of 691)
OSH Professional	2.32% (16 out of 691)
Trade Unions	0% (0 out of 691)

Source: Consultation.

The table below provides an overview of the number of responses received to the questionnaires from those contacted. This number includes the number of responses that were able to be analysed after the initial cleaning process. Most responses came from companies as this was the stakeholder group where there was the most engagement and requests for responses. At least one contact was approached for each Member State, however not all Member States provided a response to the targeted questionnaire. The study team used the national experts to conduct interviews with the Member State authorities that have not responded to the questionnaire, these were often accompanied by an interview based on the questions in the survey. National experts were also tasked with contacting and getting responses from trade unions.

Table 16-4 Responses per questionnaire

Stakeholder type	Number of responses
Companies	52.94% (9 out of 17)
Member State Authorities	47.06% (8 out of 17)
Occupational Health and Safety Experts	0 responses
Trade Unions	2 responses
Total	**17**

Source: Consultation.

A large number of responses were received for substances that are used in a wide variety of industries however the response rate for isoprene was relatively low. Nine responses were received to the isoprene questionnaire. A breakdown of the questionnaire responses by company size is presented in the table below.

Table 16-5 Number of responses submitted by companies, by substance questionnaire, and size of company

Company size (employees)	Isoprene
Micro (<10)	0

Company size (employees)	Isoprene
Small (10-49)	0
Medium (50-249)	3
Large (250<)	6
Total	**9**

Source: Consultation.

16.1.4.2Online interviews

Online interviews were conducted with stakeholders whose activities are relevant to the five substances. The aim of these interviews was to build upon the information provided in response to the questionnaires, to fill any information gaps. The study team aimed to obtain detailed information on processes, to pinpoint exactly where exposure is likely to occur, to investigate what types of risk management measures are already in place and how effective they are, as well as what risk management measures would be required if limits were lowered and other potential ramifications for the company, etc.

Interviews were obtained a variety of ways. At the end of the questionnaire, respondents were asked if they would be willing to take part in an interview. However, some online interviews were arranged through making direct contact with key industry associations.

Consultees were given the opportunity to respond in their native language. In cases where this was required, the interview was carried out by the national expert.

Each online interview lasted approximately one hour. At the end of the telephone interview, we ensured that the organisations/individuals are satisfied with the minutes of the interview. This either involves sending them the minutes by email and receiving confirmation or, if the interviewee was happy with this, a sign-off process at the end of the interview.

National experts and substance specific experts conducted interviews with relevant stakeholders. Some of the interviews were based on the responses to the questionnaire. The meeting notes were shared with the company after the interview, and that occasion was also used to ensure mutual agreement on the level of confidentiality required.

Four interviews were conducted relating to the use of isoprene in the EU. A summary of the number of isoprene interviews carried out by stakeholder type is presented in the table below.

Table 16-6 Breakdown of interviews per stakeholder type

Stakeholder type	Interviews conducted
Laboratories	0% (0 out of 4)
EU industry association	25% (1 out of 4)
Companies	75% (3 out of 4)

Stakeholder type	Interviews conducted
Member State Authorities	0% (0 out of 4)
Trade Unions	0% (0 out of 4)
Occupational health and safety experts	0% (0 out of 4)
Other	0% (0 out of 4)
Total	**4**

Source: Consultation.

16.1.4.3 Conversations

Email requests have also been used to collect information for the study. The purpose of email requests is similar to the interviews, with stakeholders being asked for further detail on their answers to the questionnaire, as well as making requests for additional information such as industry statistics.

Isoprene. For isoprene, constructive conversations have been carried out via email with the following stakeholders:

- Cefic;
- ERCA;
- Company, US;
- The Polymer Processing Society (PPS);
- FEICA;
- European Oleochemicals & Allied products Group (APAG);
- Company, Netherlands;
- Company, US;
- Company, Italy;
- Company, US;
- Company, Japan;
- BASF;
- OSHA;
- Company, US;
- Company, US;
- Company, Germany; and
- Industry Association, UK.

16.1.4.4 Site visits

Companies whose activities are likely to be affected by the potential modifications to the CMRD were also asked whether they would be willing to welcome members of the study team for a site visit. Companies to be visited were identified via the questionnaire or via contact established via industry associations.

The purpose of the site visits was to gain a more operational understanding of the risk management measures currently in place to protect against exposure to the substances concerned, as well as of the risk management measures that would be needed should the CMRD be modified.

Detailed notes from each site visit were drafted and sent back to the company to ensure that the information recorded is accurate. This process enabled the company to add more detail and information to the study, where possible, and to confirm the level of confidentiality accorded to the information.

Site visits were undertaken during Spring and Summer 2023, once significant progress had been made with data collection. This ensured that site visits added more nuance to the data already collected and helped to fill remaining information gaps.

For isoprene no site visits were conducted.

16.1.4.5 Consultation results by substance

Specific information obtained from the stakeholder consultation on exposure levels, exposed workforce, applied RMMs, costs of compliance with reference OELs, etc. is included in the substance-specific reports.

16.1.4.6 Summary of consultation statistics

The following tables provide breakdowns of the questionnaire responses, interviews and site visits carried out by company size, stakeholder type and substance.

The breakdown of questionnaire responses, interviews and site visits for isoprene by company size are provided below. They show that the majority of the responses were received from large or medium-sized enterprises, with fewer responses from small and very small enterprises.

Table 16-7 Breakdown of questionnaire responses, interviews and site visits per company size (only for consulted companies and laboratories)

Company size (employees)	Questionnaire responses	Interviews	Site visits
Micro (<10)	0% (0 out of 9)	0% (0 out of 3)	No site visits were conducted
Small (10-49)	0% (0 out of 9)	0% (0 out of 3)	
Medium (50-249)	33.33% (3 out of 9)	0% (0 out of 3)	
Large (250<)	66.66% (6 out of 9)	100% (3 out of 3)	

Source: Consultation

The breakdown of questionnaire responses, interviews and site visits for isoprene are provided below as a proportion of the total numbers conducted across all five substances.

Table 16-8 Breakdown of questionnaire responses, interviews and site visits per substance (all stakeholders; companies, Member State authorities, trade associations, OSH (Occupational Safety and Health) specialists)

Substance	Questionnaire responses[13]	Interviews	Site visits
Isoprene	5.63% (17 out of 302)	6.90% (4 out of 58)	0% (0 out of 9)
Trade Unions	2 responses	n/a	n/a
Other	0% (0 out of 302)	3.45% (2 out of 58)	0% (0 out of 9)

Source: Consultation

The breakdown of questionnaire responses, interviews and site visits for isoprene per Member State are provided below. These results show only a limited number of Member States were contacted via consultation and interviews. In the isoprene report, the potential impact of the low response rate is considered and addressed in section 13.

Table 16-9 Breakdown of questionnaire responses, interviews and site visits per Member State (all stakeholders; companies, Member State authorities, trade associations, OSH (Occupational Safety and Health) specialists)

Country	Questionnaire responses	Interviews	Site visits
Inside the EU			
Austria	0% (0 out of 17)	0% (0 out of 4)	-
Belgium	5.88% (1 out of 17)	0% (0 out of 4)	-
Bulgaria	11.74% (2 out of 17)	0% (0 out of 4)	-
Croatia	0% (0 out of 17)	0% (0 out of 4)	-
Cyprus	0% (0 out of 17)	0% (0 out of 4)	-
Czechia	0% (0 out of 17)	0% (0 out of 4)	-
Denmark	0% (0 out of 17)	0% (0 out of 4)	-
Estonia	0% (0 out of 17)	0% (0 out of 4)	-
Finland	0% (0 out of 17)	0% (0 out of 4)	-
France	0% (0 out of 17)	0% (0 out of 4)	-
Germany	5.88% (1 out of 17)	0% (0 out of 4)	-
Greece	0% (0 out of 17)	0% (0 out of 4)	-
Hungary	0% (0 out of 17)	0% (0 out of 4)	-

[13] The questionnaire responses are higher here as the MSA and OSH questionnaire had substance specific sections. Where these have been completed, they have been added as one response.

Country	Questionnaire responses	Interviews	Site visits
Ireland	0% (0 out of 17)	0% (0 out of 4)	-
Italy	35.29% (6 out of 17)	25% (1 out of 4)	-
Latvia	5.88% (1 out of 17)	0% (0 out of 4)	-
Lithuania	5.88% (1 out of 17)	0% (0 out of 4)	-
Luxembourg	0% (0 out of 17)	0% (0 out of 4)	-
Malta	0% (0 out of 17)	0% (0 out of 4)	-
Netherlands	11.76% (2 out of 17)	50% (2 out of 4)	-
Poland	17.65% (3 out of 17)	0% (0 out of 4)	-
Portugal	0% (0 out of 17)	0% (0 out of 4)	-
Romania	0% (0 out of 17)	0% (0 out of 4)	-
Slovakia	0% (0 out of 17)	0% (0 out of 4)	-
Slovenia	0% (0 out of 17)	0% (0 out of 4)	-
Spain	0% (0 out of 17)	0% (0 out of 4)	-
Sweden	0% (0 out of 17)	0% (0 out of 4)	-
Multiple Member States	0% (0 out of 17)	25% (1 out of 4)	-
Other	0% (0 out of 17)	0% (0 out of 4)	-
Outside the EU			
Iceland	0% (0 out of 17)	0% (0 out of 4)	-
Norway	0% (0 out of 17)	0% (0 out of 4)	-
South Korea	0% (0 out of 17)	0% (0 out of 4)	-
Switzerland	0% (0 out of 17)	0% (0 out of 4)	-
UK	0% (0 out of 17)	0% (0 out of 4)	-
US	0% (0 out of 17)	0% (0 out of 4)	-
Total	**17**	**4**	**0**

Source: Consultation

Notes: In some cases, the input for location was given as several Member States or a list of companies for the same response. In order to not inflate the numbers presented, if this was given as an answer, it is recorded this under 'multiple Member States'.

16.1.5 How the information gathered has been taken into account

A large amount of information has been collected via consultation, particularly through means of the targeted online questionnaires, telephone interviews and email correspondence. Efforts have been made to contact a variety of relevant stakeholders in all of the Member States, for each of the relevant substances, from companies of varying sizes.

The information collected via consultation has enabled the study team to gain a more nuanced understanding of the likely impacts of modifying or introducing OELs, which could not have been obtained otherwise via desk-based research/literature reviews. Through the combination of desk-based research, questionnaire responses, interviews, and site visits, it has been possible to compile a significant amount of detailed information in relation to the potential impacts of introducing the proposed measures.

The table below summarises how the responses in each questionnaire section are used in each report. The majority of the analysis is undertaken and discussed in each of the substance specific reports.

Table 16-10 Questionnaire sections mapped to relevant section in each substance report

Questionnaires and sections	Report section
Companies	
B	Exposure concentrations Exposed workforce Current risk management measures (RMMs)
C	Lowest technically possible and economically feasible option
D	RMMs needed to achieve compliance
E	Voluntary industry initiatives
F	Other benefits
G	Impact of the implementation of other OELs
H	Other comments
Member State Authority	Existing national limits Costs for public administrations Costs Market effects Environmental impacts Indirect benefits Employment
Occupational Health & Safety Experts	Current risk management measures (RMMs) Existing national limits

Questionnaires and sections	Report section
	RMMs needed to achieve compliance
Trade Unions	Voluntary industry initiatives Exposed workforce Benefits
Welding	(Welding only- short interviews) Definition of the problem Benefits

Source: Study team

16.1.6 Information and issues raised by stakeholders

During the stakeholder consultation, the Cobalt Institute submitted three reports prepared specifically for the purpose of providing information for this study.

No similar reports specifically for this study were submitted for the other four substances.

16.2 Annex 2 – Who is affected and how?

Table 16-11 Overview of benefits (total for all provisions) – preferred option 8.5 mg/m³ €millions

Description	Amount €millions
Direct benefits	
Workers & families - Reduced cases of ill health (liver cancer)	0
Workers & families - Reduced cases of ill health (degeneration of olfactory epithelium)	0
Workers & families - Reduced cases of ill health (degeneration of spinal cord white matter)	0
Workers & families - Ill health avoided, incl. intangible costs (M1 to M2)	0
Companies - Avoided costs	0
Public sector - Avoided costs	0
Indirect benefits	
Public sector - Avoided cost of setting an OEL	2.4

Source: Study team

Notes: Benefits are PV discounted over 40 years

Table 16-12 and Table 16-13 give an overview of costs and apply the "one in, one out" approach for the preferred option. The costs are presented as present value costs discounted over 40 years and are not split between one-off and recurrent costs. In the study, adjustment costs are presented as first year and recurrent costs. First year costs include recurrent costs incurred in the first year: this also applies to first year compliance (adjustment plus monitoring and administrative burden) costs.

Table 16-12 Overview of costs – Preferred option 8.5 mg/m³ €millions

	Companies	Public Administrations
Direct adjustment costs	0	1.22

	Companies	Public Administrations
Direct administrative costs	0.11	NA
Direct regulatory fees and charges	NA	NA
Direct enforcement costs	NA	Not estimated
Indirect costs	0	0

Source: Study team

Notes: Costs are PV discounted over 40 years

Enforcement costs are not estimated as they are specific to Member States individual inspection regime.

Table 16-13 Application of the 'one in, one out' approach – Preferred option 8.5 mg/m^3 €millions

	Total
Businesses	
New administrative burdens (INs)	0.19
Removed administrative burdens (OUTs)	0
Net administrative burdens	0.19
Adjustment costs	0
Total administrative burdens	0.19

Source: Study team

Notes: recurrent costs are PV discounted over 40 years.

Table 16-14 Overview of relevant Sustainable Development Goals – Preferred Option 8.5 mg/m³

Relevant SDG	**Expected progress towards the Goal**
SDG 8 Decent work & economic growth	Based on the preferred policy option the introduction of OELs will help to ensure labour rights for the provision of safe and secure workplaces are protected.
SDG 3 Good health and wellbeing	Requirements of the preferred policy option to monitor isoprene in workplaces will help to prove that worker environments will remain safe from hazardous chemical exposure.

Source: Study team

16.3 Annex 3 - Questionnaire

Questionnaire for companies: Isoprene

Fields marked with * are mandatory.

Questionnaire for companies: Isoprene

This survey is part of a study to support a possible amendment of Directive 2004/37/EC on the protection of workers from exposure to carcinogens, mutagens or reprotoxic substances at work (the Carcinogens, Mutagens or Reprotoxic substances Directive, **CMRD**). Specifically, the study assesses the impacts of establishing new limit values for some substances or introducing a substance into Annex I.

The substances being considered are:

- **Polycyclic aromatic hydrocarbons (PAH)**
- **Cobalt and inorganic cobalt compounds**
- **Isoprene**
- **1,4-dioxane**
- **Welding fume**

New OELs are proposed for the first four substances above under the CMRD. In addition, biological limit values (BLV) are proposed for PAH and 1,4-dioxane, and a 15-minute short-term exposure limit value (STEL) is proposed for 1,4-dioxane. ‘Skin sensitisation’ and ‘respiratory sensitisation’ notations are also proposed for cobalt and inorganic cobalt compounds, and ‘skin’ notations are proposed for isoprene, PAHs and 1,4-dioxane.

An amendment to include welding fume in Annex I of the CMRD is also being considered.

This questionnaire is intended for all companies where exposure to **isoprene** takes place.

The study is being undertaken by a consortium comprising RPA Risk & Policy Analysts (United Kingdom), RPA Europe (Italy), RPA Prague (Czech Republic) COWI (Denmark), FoBiG Forschungs- und Beratungsinstitut Gefahrstoffe (Germany), EPRD (Poland) and Force Technology (Denmark) under a contract for the European Commission's Directorate-General for Employment, Social Affairs and Inclusion.

All responses to this questionnaire will be treated in the **strictest confidence** and will only be used for the purposes of this study. In preparing our report for the Commission (which, subsequently, may be published), care will be taken to ensure that specific responses cannot be linked to individual companies.

This questionnaire is intended for a **single facility.** If workers are exposed at multiple facilities, please complete the questionnaire several times or contact the study team.

It will take approximately 15–45 minutes to answer the questionnaire depending on data availability and detail.

The deadline for completion of the questionnaire is the 3 March 2023.

This questionnaire is available in English, French, German, Italian, Polish and Spanish. However, you are welcome to answer the questions in an official language of the European Union of your choice. If you prefer to be interviewed in your language or if you have questions about the survey, please contact: OELs6@rpaltd.co.uk

Abbreviations used in the questionnaire:

CMRD - Carcinogens, Mutagens or Reprotoxic substances Directive 2004/37/EC

LOAEL - Lowest Observed Adverse Effect Level is the lowest tested exposure concentration which is observed to produce an adverse effect in a living organism.

NACE - NACE Revision 2, statistical classification of economic activities in the European Community. See https://ec.europa.eu/eurostat/documents/3859598/5902521/KS-RA-07-015-EN.PDF, page 61 ff.

OEL - The term Occupational Exposure Limit value (OEL) refers to the limit of the time-weighted average (TWA) of the concentration in the air within the breathing zone of a worker, measured or calculated in relation to a reference period of eight hours.

RAC - The Committee for Risk Assessment (RAC) is a scientific committee of ECHA that prepares the opinions related to the risks of substances to human health and the environment. It also assisted DG Employment with the evaluation of MOCA and inorganic arsenic compounds.

RMM - Risk Management Measure

RPE - Respiratory protective equipment

SMEs - Small and Medium-sized Enterprises. Companies with between 50 and 249 employees are usually referred to as medium-sized. Companies with between 10 and 49 employees are usually referred to as small (and with less than 10 employees as micro enterprises). Companies with more than 250 employees are referred to as large companies. For further definitions, please refer to http://ec.europa.eu/growth/smes/business-friendly-environment/sme-definition/index_en.htm

8 hour TWA - 8 hour Time-Weighted Average, measured in parts per million (ppm) or milligrams per cubic metre (mg/m³). The 8 hour TWA is an expression for the average exposure for a typical working day. It is calculated by summing up the concentrations (in ppm or mg/m³) during different periods of a day (usually 8 hours). Each concentration is multiplied by its relevant duration and the total is divided by the entire length of the working day (usually 8 hours) such as in this example:

8h-TWA = (2 hours * 500 ppm + 5 hours * 100 ppm + 1 hours * 700 ppm) / (2 + 5 + 1 hours).

Publication privacy settings

☐ By checking this box, I confirm that I have read the Privacy Statement and agree with the processing of my personal data for the purposes stated therein. I acknowledge that my views could be shared with the European Commission and published with information concerning the type of the organisation for which I submit information, to which I hereby give my consent.

A) About your company

A1) Please provide the following details about your company

* **Name of contact person**

* **Company**

* **Email address of contact person**

Telephone number of contact person

* **Country of facility**

- Austria
- Belgium
- Bulgaria
- Croatia
- Cyprus
- Czechia
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Ireland

Italy
- Latvia
- Lithuania
- Luxembourg
- Malta
- Netherlands
- Poland
- Portugal
- Romania
- Slovak Republic
- Slovenia
- Spain
- Sweden
- Other

If other, please specify

A2) Please define the sector in which your company is active (if possible, using a NACE code)

- C15.20 Manufacture of footwear
- C19.20 Manufacture of refined petroleum products
- C20.14 Manufacture of other organic based chemicals
- C20.17 Manufacture of synthetic rubber in primary forms
- C20.42 Manufacture of perfumes and toilet preparations
- C20.52 Manufacture of glues
- C20.59 Manufacture of other chemical products n.e.c.
- C21.10 Manufacture of pharmaceutical products
- C22.11 Manufacture of rubber tyres and tubes
- C22.19 Manufacture of other rubber products
- C22.22 Manufacture of plastic packing goods
- C28.96 Manufacture of plastics and other rubber machinery
- C28.30 Manufacture of agricultural and forestry machinery
- C29.10 Manufacture of motor vehicles
- C29.32 Manufacture of other parts and accessories for motor vehicles
- C28.22 Manufacture of lifting and handling equipment
- C30.30 Manufacture of air and spacecraft and related machinery
- C32.30 Manufacture of sports goods
- C32.40 Manufacture of games and toys
- C32.50 Manufacture of medical and dental instruments and supplies
- F42.11 Construction of roads and motorways
- F43.91 Roofing activities
- Other

If other, please specify

A3) Please describe your company's overall application of isoprene within the scope of the study

A4) How many workers are employed in your company at the facility for which you are filling out this questionnaire?

A5) Have you any experience of workers having health issues resulting from occupational exposure to Isoprene at the workplace?

A6) Have any workers left the company due to health issues associated with exposure to Isoprene?

A7) What is the annual turnover in EUR at the facility for which you are filling out this questionnaire?

- < €2 million
- €2–10 million
- €10–50 million
- €50–100 million
- > €100 million

Please complete a separate questionnaire for each facility

A8) Please give the name and address (incl. country) of the facility for which you are completing this questionnaire

B) Information about current exposure at your facility

B1) Please specify the most important processes at which exposure to isoprene can occur. You can specify a maximum of four processes.

Process 1

- PROC 1 Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions
- PROC 2 Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
- PROC 3 Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment condition
- PROC 4 Chemical production where opportunity for exposure arises
- PROC 5 Mixing or blending in batch processes
- PROC 6 Calendering operations
- PROC 7 Industrial spraying
- PROC 8a Transfer of substance or mixture (charging and discharging) at non-dedicated facilities
- PROC 8b Transfer of substance or mixture (charging and discharging) at dedicated facilities
- PROC 9 Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
- PROC 10 Roller application or brushing
- PROC 11 Non-industrial spraying
- PROC 12Use of blowing agents in manufacture of foam
- PROC 13 Treatment of articles by dipping and pouring
- PROC 14 Tabletting, compression, extrusion, pelletisation, granulation
- PROC 15 Use as laboratory reagent
- PROC 16 Use of fuels
- PROC 17 Lubrication at high energy conditions in metal working operations
- PROC 18 General greasing/lubrication at high kinetic energy conditions
- PROC 19 Manual activities involving hand contact
- PROC 20 Use of functional fluids in small devices
- PROC 21 Low energy manipulation of substances bound in materials and/or articles
- PROC 22 Manufacturing and processing of minerals and/or metals at substantially elevated temperature
- PROC 23 Open processing and transfer operations with minerals/metals at elevated temperature
- PROC 24 High (mechanical) energy work-up of substances bound in materials and/or articles
- PROC 25 Other hot work operations with metals
- PROC 26 Handling of solid inorganic substances at ambient temperature
- PROC 27a Production of metal powders (hot processes)
- PROC 27b Production of metal powders (wet processes)
- PROC 28 Manual maintenance (cleaning and repair) of machinery
- Other

Please specify the process.

Process 2

- PROC 1 Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions
- PROC 2 Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
- PROC 3 Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment condition
- PROC 4 Chemical production where opportunity for exposure arises
- PROC 5 Mixing or blending in batch processes
- PROC 6 Calendering operations
- PROC 7 Industrial spraying
- PROC 8a Transfer of substance or mixture (charging and discharging) at non-dedicated facilities
- PROC 8b Transfer of substance or mixture (charging and discharging) at dedicated facilities
- PROC 9 Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
- PROC 10 Roller application or brushing
- PROC 11 Non-industrial spraying
- PROC 12Use of blowing agents in manufacture of foam
- PROC 13 Treatment of articles by dipping and pouring
- PROC 14 Tabletting, compression, extrusion, pelletisation, granulation
- PROC 15 Use as laboratory reagent
- PROC 16 Use of fuels
- PROC 17 Lubrication at high energy conditions in metal working operations
- PROC 18 General greasing/lubrication at high kinetic energy conditions
- PROC 19 Manual activities involving hand contact
- PROC 20 Use of functional fluids in small devices
- PROC 21 Low energy manipulation of substances bound in materials and/or articles
- PROC 22 Manufacturing and processing of minerals and/or metals at substantially elevated temperature
- PROC 23 Open processing and transfer operations with minerals/metals at elevated temperature
- PROC 24 High (mechanical) energy work-up of substances bound in materials and/or articles
- PROC 25 Other hot work operations with metals
- PROC 26 Handling of solid inorganic substances at ambient temperature
- PROC 27a Production of metal powders (hot processes)
- PROC 27b Production of metal powders (wet processes)
- PROC 28 Manual maintenance (cleaning and repair) of machinery
- Other

Please specify the process.

Process 3

- PROC 1 Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions
- PROC 2 Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
- PROC 3 Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment condition

- PROC 4 Chemical production where opportunity for exposure arises
- PROC 5 Mixing or blending in batch processes
- PROC 6 Calendering operations
- PROC 7 Industrial spraying
- PROC 8a Transfer of substance or mixture (charging and discharging) at non-dedicated facilities
- PROC 8b Transfer of substance or mixture (charging and discharging) at dedicated facilities
- PROC 9 Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
- PROC 10 Roller application or brushing
- PROC 11 Non-industrial spraying
- PROC 12Use of blowing agents in manufacture of foam
- PROC 13 Treatment of articles by dipping and pouring
- PROC 14 Tabletting, compression, extrusion, pelletisation, granulation
- PROC 15 Use as laboratory reagent
- PROC 16 Use of fuels
- PROC 17 Lubrication at high energy conditions in metal working operations
- PROC 18 General greasing/lubrication at high kinetic energy conditions
- PROC 19 Manual activities involving hand contact
- PROC 20 Use of functional fluids in small devices
- PROC 21 Low energy manipulation of substances bound in materials and/or articles
- PROC 22 Manufacturing and processing of minerals and/or metals at substantially elevated temperature
- PROC 23 Open processing and transfer operations with minerals/metals at elevated temperature
- PROC 24 High (mechanical) energy work-up of substances bound in materials and/or articles
- PROC 25 Other hot work operations with metals
- PROC 26 Handling of solid inorganic substances at ambient temperature
- PROC 27a Production of metal powders (hot processes)
- PROC 27b Production of metal powders (wet processes)
- PROC 28 Manual maintenance (cleaning and repair) of machinery
- Other

Please specify the process.

Process 4

- PROC 1 Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions
- PROC 2 Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
- PROC 3 Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment condition
- PROC 4 Chemical production where opportunity for exposure arises
- PROC 5 Mixing or blending in batch processes
- PROC 6 Calendering operations
- PROC 7 Industrial spraying
- PROC 8a Transfer of substance or mixture (charging and discharging) at non-dedicated facilities
- PROC 8b Transfer of substance or mixture (charging and discharging) at dedicated facilities
- PROC 9 Transfer of substance or mixture into small containers (dedicated filling line, including weighing)

- PROC 10 Roller application or brushing
- PROC 11 Non-industrial spraying
- PROC 12Use of blowing agents in manufacture of foam
- PROC 13 Treatment of articles by dipping and pouring
- PROC 14 Tabletting, compression, extrusion, pelletisation, granulation
- PROC 15 Use as laboratory reagent
- PROC 16 Use of fuels
- PROC 17 Lubrication at high energy conditions in metal working operations
- PROC 18 General greasing/lubrication at high kinetic energy conditions
- PROC 19 Manual activities involving hand contact
- PROC 20 Use of functional fluids in small devices
- PROC 21 Low energy manipulation of substances bound in materials and/or articles
- PROC 22 Manufacturing and processing of minerals and/or metals at substantially elevated temperature
- PROC 23 Open processing and transfer operations with minerals/metals at elevated temperature
- PROC 24 High (mechanical) energy work-up of substances bound in materials and/or articles
- PROC 25 Other hot work operations with metals
- PROC 26 Handling of solid inorganic substances at ambient temperature
- PROC 27a Production of metal powders (hot processes)
- PROC 27b Production of metal powders (wet processes)
- PROC 28 Manual maintenance (cleaning and repair) of machinery
- Other

Please specify the process.

B2) Please provide the number of workers exposed at all exposure levels during a typical working day, for each process.

	Number of workers exposed
Process 1	
Process 2	
Process 3	
Process 4	

B3) Please provide data for inhalation exposure from your most recent measurements of air exposure concentration and include the unit of measurement (8-hour Time Weighted Averages)*

*The 8 hour TWA should ideally be expressed in ppm (parts per million) or milligram per cubic metre (mg /m³).

	Process 1	Process 2	Process 3	Process 4
Lowest exposure level (value, unit)				
Highest exposure level (value)				
Mean exposure level (Arithmetic mean; value, unit)				
Median exposure level (value, unit)				
95th percentile exposure level (value, unit)				
Number of samples (n)				
Year of monitoring				
B4) Please select the sampling method followed	Stationary sampling Personal sampling Personal sampling of inhalation air inside the RPE	Stationary sampling Personal sampling Personal sampling of inhalation air inside the RPE	Stationary sampling Personal sampling Personal sampling of inhalation air inside the RPE	Stationary sampling Personal sampling Personal sampling of inhalation air inside the RPE
B5) Are the workers wearing respiratory protective equipment (RPE) during the activity?	Yes No	Yes No	Yes No	Yes No

B6) Please indicate the standard/analytical method followed	◯ Carbopack-X tubes (active), thermal desorption ◯ Carbotrap B tubes (active), thermal desorption ◯ Tenax TA/Carbograph 1TD tubes (active), thermal desorption ◯ Carbotrap B/Carbopack X /Carboxen 569 tubes (active), Thermal desoption ◯ Radiello diffusive sampler loaded with Carbopack-X, Thermal desoption ◯ Other	◯ Carbopack-X tubes (active), thermal desorption ◯ Carbotrap B tubes (active), thermal desorption ◯ Tenax TA/Carbograph 1TD tubes (active), thermal desorption ◯ Carbotrap B/Carbopack X /Carboxen 569 tubes (active), Thermal desoption ◯ Radiello diffusive sampler loaded with Carbopack-X, Thermal desoption ◯ Other	◯ Carbopack-X tubes (active), thermal desorption ◯ Carbotrap B tubes (active), thermal desorption ◯ Tenax TA/Carbograph 1TD tubes (active), thermal desorption ◯ Carbotrap B/Carbopack X /Carboxen 569 tubes (active), Thermal desoption ◯ Radiello diffusive sampler loaded with Carbopack-X, Thermal desoption ◯ Other	◯ Carbopack-X tubes (active), thermal desorption ◯ Carbotrap B tubes (active), thermal desorption ◯ Tenax TA/Carbograph 1TD tubes (active), thermal desorption ◯ Carbotrap B/Carbopack X /Carboxen 569 tubes (active), Thermal desoption ◯ Radiello diffusive sampler loaded with Carbopack-X, Thermal desoption ◯ Other
B7) If you answered 'other' to B6, please specify				
B8) If you have other exposure data than 8 hour Time Weighted Averages, please specify type of value and air exposure concentration	Type of value (value, unit)	Type of value (value, unit)	Type of value (value, unit)	Type of value (value, unit)

B9) If you have indicated below limit of quantification (LoQ) and/or limit of detection (LoD) in the responses above, what was the LOQ or LOD?

	Value	Unit
Limit of quantification		
Limit of detection		

B10) Could actions related to covid-19 have artificially reduced exposure levels?

- Yes, reduced exposure
- Yes, increased exposure
- No change
- Don't know

B11) Please provide a short explanation for your answer to B10

B12) Do you have any other information on exposure to these substances at your facility?

If you are happy to provide more detailed information about numbers of workers exposed, exposure levels and/or further processes, please email this to OELs6@rpaltd.co.uk

B13) Which Risk Management Measures are in place to control exposure of isoprene in the different processes at this facility? Please tick all that you use. If PPE is essential regardless of the OEL (e.g. for maintenance processes), please indicate this.

	Process 1	Process 2	Process 3	Process 4
Reducing the amount of substance used	☐	☐	☐	☐
Reducing the number of workers exposed	☐	☐	☐	☐
Rotating the workers exposed	☐	☐	☐	☐
Redesign of work processes	☐	☐	☐	☐
Closed systems	☐	☐	☐	☐
Partial hood enclosures	☐	☐	☐	☐
Open hoods over equipment or local extraction ventilation	☐	☐	☐	☐
General ventilation	☐	☐	☐	☐
Pressurised or sealed control cabs	☐	☐	☐	☐

Simple enclosed control cabs	☐	☐	☐	☐
Self-contained breathing apparatus (with bottled air) or airline respirators (air supplied by hose)	☐	☐	☐	☐
Powered air-purifying respirators	☐	☐	☐	☐
Half and full facemasks (negative pressure respirators)	☐	☐	☐	☐
Disposable respirators (FFP masks)	☐	☐	☐	☐
Face screens, face shields, visors	☐	☐	☐	☐
Goggles	☐	☐	☐	☐
Gloves	☐	☐	☐	☐
Continuous measurement to detect unusual exposures	☐	☐	☐	☐
Training and education	☐	☐	☐	☐
Cleaning	☐	☐	☐	☐
Measures for workers’ personal hygiene (e.g. daily cleaning of work clothing, obligatory shower)	☐	☐	☐	☐
Provision of separate storage facilities for work clothes	☐	☐	☐	☐
Formal/external RPE cleaning and filter changing regime	☐	☐	☐	☐
Continuous measurement of air concentrations to detect unusual exposures	☐	☐	☐	☐
Creating a culture of safety	☐	☐	☐	☐
Partial substitution of Isoprene used in this activity in the past	☐	☐	☐	☐
Discontinuation of part of the activity using Isoprene	☐	☐	☐	☐
Other	☐	☐	☐	☐
PPE is essential regardless of the OEL	☐	☐	☐	☐

Other measures

	Process 1	Process 2	Process 3	Process 4
Other (please specify)				

B14) Could there be co-exposure from both isoprene and any of the following substances or processes at this facility? Please tick all that apply.

	Select
Polycyclic aromatic hydrocarbons	☐
Cobalt substances under the CMRD	☐
1,4-dioxane	☐
Perform welding	☐

B15) Is your company making any investments not directly related to exposure to isoprene that are likely to lead to a reduction in exposure to isoprene?

at most 1 answered row(s)

	Select
Investments are being made that will significantly reduce exposure to the isoprene	☐
Investments are being made that may reduce exposure to the isoprene	☐
No investments are planned that will reduce exposure to the isoprene	☐
Don’t know	☐

B16) If any investments are being made in question B15, what are the investments for? Please tick all that apply.

	Select
Compliance with other OELs (please specify which)	☐
Improved risk management measures being implemented alongside other improvements to production facilities	☐
New or improved production facilities that will remove from or reduce exposure to worker	☐
Other, please specify	☐

Compliance with other OELs, please specify

Other, please specify

B17) When will the reduction in worker exposure take effect?

at most 1 answered row(s)

	Select

By the end of 2024	☐
By the end of 2029	☐
By the end of 2034	☐

C) What are the lowest exposure levels that you could achieve

	Value	Unit
C1) What do you think is the lowest technically possible 8 hour TWA air concentration that can be achieved in this facility? (Please specify the units, preferably in mg/m3 or ppm)		☐ mg/m³ ☐ ppm
C2) What do you think is the lowest economically feasible 8 hour TWA air concentration that can be achieved in this facility? (Please specify the units, preferably in mg/m3 or ppm)		☐ mg/m³ ☐ ppm

C3) Any comments on above answers?

C4) Do you have to comply with the European Workplace exposure standard EN 689?

- ○ Yes
- ○ No
- ○ Don't know

D) Compliance with a new OEL under the CMRD

This section considers the Risk Management Measures (RMMs) that would have to be put in place to comply with a new OEL under the CMD.

The following limit values and air concentrations given below are used as policy options for this questionnaire.

Policy Options	Isoprene
Policy Option 1 (corresponds to a calculated excess cancer risk of 4:1000)	129.4 mg/m³
Policy Option 2 (currently the median or mode OEL in EU Member States)	40.0 mg/m³

Policy Option 3 (based on RAC opinion and lowest observed national OEL in the EU)	8.5 mg/m³
Policy Option 4 (corresponds to a calculated excess cancer risk of 4:100000)	1.3 mg/m³

D1) If the OEL was 129.4 mg/m³, which *additional* RMMs would be the most important in helping you to achieve this?

	Process 1	Process 2	Process 3	Process 4
No action required as OEL already achieved	☐	☐	☐	☐
Substitution of substance	☐	☐	☐	☐
Discontinuation of process using the substance	☐	☐	☐	☐
Reducing the amount of substance used	☐	☐	☐	☐
Reducing the number of workers exposed	☐	☐	☐	☐
Rotating the workers exposed	☐	☐	☐	☐
Redesign of work processes	☐	☐	☐	☐
Closed systems	☐	☐	☐	☐
Partial hood enclosures	☐	☐	☐	☐
Open hoods over equipment or local extraction ventilation	☐	☐	☐	☐
General ventilation	☐	☐	☐	☐
Pressurised or sealed control cabs	☐	☐	☐	☐
Simple enclosed control cabs	☐	☐	☐	☐
Self-contained breathing apparatus (with bottled air) or airline respirators (air supplied by hose)	☐	☐	☐	☐
Powered air-purifying respirators	☐	☐	☐	☐
Half and full facemasks (negative pressure respirators)	☐	☐	☐	☐
Disposable respirators (FFP masks)	☐	☐	☐	☐
Face screens, face shields, visors	☐	☐	☐	☐
Goggles	☐	☐	☐	☐
Gloves	☐	☐	☐	☐
Continuous measurement to detect unusual exposures	☐	☐	☐	☐
Training and education	☐	☐	☐	☐

Cleaning	☐	☐	☐	☐
Measures for workers' personal hygiene (e.g. daily cleaning of work clothing, obligatory shower)	☐	☐	☐	☐
Provision of separate storage facilities for work clothes	☐	☐	☐	☐
Formal/external RPE cleaning and filter changing regime	☐	☐	☐	☐
Continuous measurement of air concentrations to detect unusual exposures	☐	☐	☐	☐
Creating a culture of safety	☐	☐	☐	☐
Other (please specify):	☐	☐	☐	☐

Other measures

	Process 1	Process 2	Process 3	Process 4
Other (please specify)				

D2) What is your estimated range of <u>initial investment costs</u> for additional RMMs required at this facility to achieve an OEL of 129.4 mg/m³?

- < €10,000
- €10,000–€100,000
- €100,000–€1 million
- €1–10 million
- > € 10 million
- No additional costs

D3) What is your estimated range of <u>annual recurrent costs</u> for additional RMMs required at this facility to achieve an OEL of 129.4 mg/m³?

- < €1,000
- €1,000–€10,000
- €10,000–€100,000
- > €100,000
- No additional costs

D4) If the OEL was 40.0 mg/m³, which additional RMMs would be the most important in helping you to achieve this?

	Process 1	Process 2	Process 3	Process 4
No action required as OEL already achieved	☐	☐	☐	☐
Substitution of substance	☐	☐	☐	☐
Discontinuation of process using the substance	☐	☐	☐	☐
Reducing the amount of substance used	☐	☐	☐	☐
Reducing the number of workers exposed	☐	☐	☐	☐
Rotating the workers exposed	☐	☐	☐	☐
Redesign of work processes	☐	☐	☐	☐
Closed systems	☐	☐	☐	☐
Partial hood enclosures	☐	☐	☐	☐
Open hoods over equipment or local extraction ventilation	☐	☐	☐	☐
General ventilation	☐	☐	☐	☐
Pressurised or sealed control cabs	☐	☐	☐	☐
Simple enclosed control cabs	☐	☐	☐	☐
Self-contained breathing apparatus (with bottled air) or airline respirators (air supplied by hose)	☐	☐	☐	☐
Powered air-purifying respirators	☐	☐	☐	☐

Half and full facemasks (negative pressure respirators)	☐	☐	☐	☐
Disposable respirators (FFP masks)	☐	☐	☐	☐
Face screens, face shields, visors	☐	☐	☐	☐
Goggles	☐	☐	☐	☐
Gloves	☐	☐	☐	☐
Continuous measurement to detect unusual exposures	☐	☐	☐	☐
Training and education	☐	☐	☐	☐
Cleaning	☐	☐	☐	☐
Measures for workers’ personal hygiene (e.g. daily cleaning of work clothing, obligatory shower)	☐	☐	☐	☐
Provision of separate storage facilities for work clothes	☐	☐	☐	☐
Formal/external RPE cleaning and filter changing regime	☐	☐	☐	☐
Continuous measurement of air concentrations to detect unusual exposures	☐	☐	☐	☐
Creating a culture of safety	☐	☐	☐	☐
Other (please specify):	☐	☐	☐	☐

Other measures

	Process 1	Process 2	Process 3	Process 4
Other (please specify)				

D5) What is your estimated range of initial investment costs for additional RMMs required at this facility to achieve an OEL of 40.0 mg/m³?

- < €10,000
- €10,000–€100,000
- €100,000–€1 million
- €1–10 million
- > € 10 million
- No additional costs

D6) What is your estimated range of annual recurrent costs for additional RMMs required at this facility to achieve an OEL of 40.0 mg/m³?

- < €1,000
- €1,000–€10,000
- €10,000–€100,000
- > €100,000
- No additional costs

D7) If the OEL was 8.5 mg/m³, which additional RMMs would be the most important in helping you to achieve this?

	Process 1	Process 2	Process 3	Process 4
No action required as OEL already achieved	☐	☐	☐	☐
Substitution of substance	☐	☐	☐	☐
Discontinuation of process using the substance	☐	☐	☐	☐
Reducing the amount of substance used	☐	☐	☐	☐
Reducing the number of workers exposed	☐	☐	☐	☐
Rotating the workers exposed	☐	☐	☐	☐
Redesign of work processes	☐	☐	☐	☐
Closed systems	☐	☐	☐	☐
Partial hood enclosures	☐	☐	☐	☐
Open hoods over equipment or local extraction ventilation	☐	☐	☐	☐
General ventilation	☐	☐	☐	☐
Pressurised or sealed control cabs	☐	☐	☐	☐
Simple enclosed control cabs	☐	☐	☐	☐
Self-contained breathing apparatus (with bottled air) or airline respirators (air supplied by hose)	☐	☐	☐	☐
Powered air-purifying respirators	☐	☐	☐	☐

Half and full facemasks (negative pressure respirators)	☐	☐	☐	☐
Disposable respirators (FFP masks)	☐	☐	☐	☐
Face screens, face shields, visors	☐	☐	☐	☐
Goggles	☐	☐	☐	☐
Gloves	☐	☐	☐	☐
Continuous measurement to detect unusual exposures	☐	☐	☐	☐
Training and education	☐	☐	☐	☐
Cleaning	☐	☐	☐	☐
Measures for workers’ personal hygiene (e.g. daily cleaning of work clothing, obligatory shower)	☐	☐	☐	☐
Provision of separate storage facilities for work clothes	☐	☐	☐	☐
Formal/external RPE cleaning and filter changing regime	☐	☐	☐	☐
Continuous measurement of air concentrations to detect unusual exposures	☐	☐	☐	☐
Creating a culture of safety	☐	☐	☐	☐
Other (please specify):	☐	☐	☐	☐

Other measures

	Process 1	Process 2	Process 3	Process 4
Other (please specify)				

D8) What is your estimated range of <u>initial investment costs</u> for additional RMMs required at this facility to achieve an OEL with 8.5 mg/m³?

- < €10,000
- €10,000 - €100,000
- €100,000 - €1 million
- €1 -10 million
- > € 10 million
- No additional costs

D9) What is your estimated range of <u>annual recurrent costs</u> for additional RMMs required at this facility to achieve an OEL with 8.5 mg/m³?

- < €1,000
- €1,000 - €10,000
- €10,000 - €100,000
- > €100,000
- No additional costs

D10) If the OEL was 1.3 mg/m³, which additional RMMs would be the most important in helping you to achieve this?

	Process 1	Process 2	Process 3	Process 4
No action required as OEL already achieved	☐	☐	☐	☐
Substitution of substance	☐	☐	☐	☐
Discontinuation of process using the substance	☐	☐	☐	☐
Reducing the amount of substance used	☐	☐	☐	☐
Reducing the number of workers exposed	☐	☐	☐	☐
Rotating the workers exposed	☐	☐	☐	☐
Redesign of work processes	☐	☐	☐	☐
Closed systems	☐	☐	☐	☐
Partial hood enclosures	☐	☐	☐	☐
Open hoods over equipment or local extraction ventilation	☐	☐	☐	☐
General ventilation	☐	☐	☐	☐
Pressurised or sealed control cabs	☐	☐	☐	☐
Simple enclosed control cabs	☐	☐	☐	☐
Self-contained breathing apparatus (with bottled air) or airline respirators (air supplied by hose)	☐	☐	☐	☐
Powered air-purifying respirators	☐	☐	☐	☐

Half and full facemasks (negative pressure respirators)	☐	☐	☐	☐
Disposable respirators (FFP masks)	☐	☐	☐	☐
Face screens, face shields, visors	☐	☐	☐	☐
Goggles	☐	☐	☐	☐
Gloves	☐	☐	☐	☐
Continuous measurement to detect unusual exposures	☐	☐	☐	☐
Training and education	☐	☐	☐	☐
Cleaning	☐	☐	☐	☐
Measures for workers' personal hygiene (e.g. daily cleaning of work clothing, obligatory shower)	☐	☐	☐	☐
Provision of separate storage facilities for work clothes	☐	☐	☐	☐
Formal/external RPE cleaning and filter changing regime	☐	☐	☐	☐
Continuous measurement of air concentrations to detect unusual exposures	☐	☐	☐	☐
Creating a culture of safety	☐	☐	☐	☐
Other (please specify):	☐	☐	☐	☐

Other measures

	Process 1	Process 2	Process 3	Process 4
Other (please specify)				

D11) What is your estimated range of initial investment costs for additional RMMs required at this facility to achieve an OEL with 1.3 mg/m³?

- < €10,000
- €10,000–€100,000
- €100,000–€1 million
- €1–10 million
- > € 10 million
- No additional costs

D12) What is your estimated range of annual recurrent costs for additional RMMs required at this facility to achieve an OEL with 1.3 mg/m³?

- < €1,000
- €1,000–€10,000
- €10,000–€100,000
- > €100,000
- No additional costs

D13) Would the level of costs incurred to comply with an OEL with 1.3 mg/m³ affect the competitiveness of your company?

Competitors in EU	Significant positive impact Moderate positive impact Limited/no impact Moderate negative impact Significant negative impact
Competitors outside of EU	Significant positive impact Moderate positive impact Limited/no impact Moderate negative impact Significant negative impact

D14) Are you aware of any processes conducted by your downstream users which may result in the release isoprene from your products?

- Yes
- No

If yes, please give a short overview of the process, the concentration of isoprene which may be released.

D15) Any other comments on this section?

E) End of life

E1) At end of life, is there potential for isoprene to be released from your products?

- Yes
- No

If yes, please give a short overview of the process and the concentration of isoprene which may be released.

F) Indirect Benefits

F1) Do you think your company will benefit from any of these indirect benefits if an EU-wide OEL for isoprene is introduced? Please tick all that apply.

	Select
Healthier staff	
Increased productivity of workers	
Improved public image	
Easier to recruit staff	
Easier to retain staff	
Reduced cost of recruitment	
Easier monitoring of exposure	
Savings because company currently has multiple locations in different Member States with different regulations or OELs	
Level playing field with EU competitors	
Other indirect benefits, please specify	
There will be no indirect benefits	

Please specify

G) Is your company working towards voluntary industry targets?

Voluntary industry targets

	Response
G1) Is your company trying to meet voluntary industry targets? If yes, please specify the targets (concentration, units)	
G2) What are the main challenges in meeting the voluntary targets?	
G3) Have you made any assessment of the possible costs of meeting the voluntary targets? If yes, please provide information on costs and cost structure.	

H) Any other comments

H1) Do you have any other comments relevant to this study that you would like to make?

I) Further communication

I1) Please tick if you are happy for the study team to contact you for further clarification or discussion about your responses?

- Yes
- No

I2) Please tick if you would be willing to host a site visit for the study team at this facility. This can be carried out under a non-disclosure agreement.

- Yes
- No

I3) If you prefer this contact to be via a different email or phone number from those you provided at the start of the questionnaire, please provide the details here.

Thank you for your answers!

16.4 Annex 4 – Overview of limit values in Member States

Table 16-15 OELs and STELs in EU Member States and selected non-EU countries for isoprene

Country	OEL [mg/m³]	Specification of OEL	STEL [mg/m³]	Specification of STEL
Austria [3]	-	- Carc	-	
Belgium [4]	-		-	
Bulgaria [5]	40 **		-	
Croatia [6]	-		-	
Cyprus [7]	-		-	
Czechia [8]	-		-	
Denmark [9]	-		-	
Estonia [10]	-		-	
Finland [11]	-		-	
France [12]	-		-	
Germany [1,2,13]	8.4 *	- Carc	67.2 *	- 15 min average value, Carc
Greece [14]	-		-	
Hungary [15]	-		-	
Ireland [16]	-		-	
Italy [17]	-		-	
Latvia [1,2,18]	40 **		-	
Lithuania [19]	40 **	- Carc	-	
Luxembourg [20]	-		-	
Malta [21]	-		-	
Netherlands [22]	-		-	
Poland [1,2,23]	100 **		300 **	- 15 min average value
Portugal [24]	-		-	

Country	OEL [mg/m³]	Specification of OEL	STEL [mg/m³]	Specification of STEL
Romania [25]	-		-	
Slovakia [26]	-		-	
Slovenia [27]	-		-	
Spain [28]	-		-	
Sweden [29]	-		-	
European Union	-		-	
RAC [2]	8.5		-	
Non-EU countries				
Australia [30]	-		-	
Brazil [31]	-		-	
Canada, Ontario [32]	-		-	
Canada, Québec [33]	-		-	
China	-		-	
India [34]	-		-	
Japan, MHLW [35]	-		-	
Japan, JOSH [1,36]	8.4 ^^^	- Carc	-	
Norway [37]	-		-	
Russia [38]	40 (V) [%]		-	
South Korea	-		-	
Switzerland [1,2,39]	8.5 *	- Carc	68 *	- Carc
Turkey [40]	-		-	
United Kingdom [41]	-		-	
USA, ACGIH [42]	-		-	

Country	OEL [mg/m³]	Specification of OEL	STEL [mg/m³]	Specification of STEL
USA, NIOSH [43]	-		-	
USA, OSHA [44]	-		-	

Notes:
RAC = Committee for Risk Assessment
MHLW = Ministry of Health, Labour and Welfare
JSOH = Japan Society for Occupational Health
ACGIH = American Conference of Governmental Industrial Hygienists
NIOSH = National Institute for Occupational Safety and Health
OSHA = Occupational Safety and Health Administration
(V) = vapour
** Binding value according to country-specific source*
*** Binding value according to reply of Member State authority on questionnaire*
**** Binding value according to report on OEL-deriving systems from 2018. Status was not checked since 2018.*
^ Indicative value according to country-specific source
^^ Indicative value according to reply of Member State authority on questionnaire
^^^ Indicative value according to the Final report for OEL/STEL deriving systems from 2018. Status was not checked since 2018.

% According to (country-specific source) unclear if value is binding or indicative
Carc = notation for carcinogenicity
- no value available

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Country	OEL [mg/m³]	Specification of OEL	STEL [mg/m³]	Specification of STEL

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16.5 Annex 5 – Relevant sectors

Table 16-16 Analysed sectors with risk of exposure to Isoprene

NACE code	NACE full name	Short name for sector
19.20	Manufacture of refined petroleum products	Refined petroleum products
20.17	Manufacture of synthetic rubber in primary forms	Synthetic rubber production

Source: Study team.

16.6 Annex 6 – Consistency and synergies of establishing OELs under CMRD

Additionally to the CMRD, isoprene is currently on a list of prohibited substances as part of the Cosmetics Products Regulation (EC) 1223/2009. Isoprene does not currently have any REACH requirements outside of registration and does not have any foreseen REACH Authorisations or Restrictions in the future. As such, the introduction of OELs under the CMRD for isoprene does not need to be consistent with any EU regulations outside of the prohibition of isoprene for use in cosmetic products. Therefore, the introduction of OELs for isoprene will not present any issues with existing or future EU regulation and will compliment the cosmetics regulation by ensuring wider spread protection of workers as well as consumers.

16.7 Annex 7 - Isoprene – Degeneration of olfactory epithelium

16.7.1 Software used

Results are obtained using the EFSA web-tool for BMD analysis, which uses the R-package PROAST, version 70.0, for the underlying calculations.

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16.7.2 Data Description

The endpoint to be analyzed is: effect.

Data used for analysis:

conc	effect	n
0	1	30
198	2	30
623	5	29
1981	11	30

Information pertaining to this endpoint.

16.7.3 Selection of the BMR

The BMR (benchmark response) used is an extra risk of 10% compared to the controls.

The BMD (benchmark dose) is the dose corresponding with the BMR of interest.

A 90% confidence interval around the BMD will be estimated, the lower bound is reported by BMDL and the upper bound by BMDU.

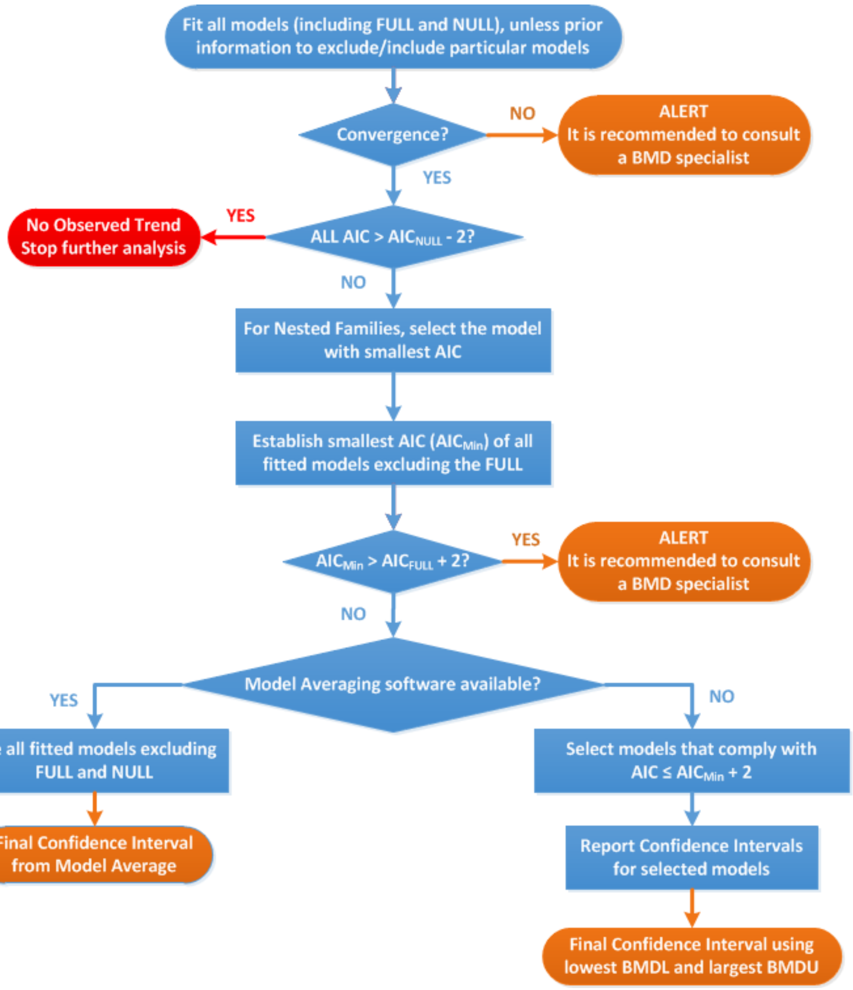
16.7.4 Specification of Deviations from Default Assumptions

Default set of fitted models:

Model	Number of parameters	Formula
Null	1	$y = a$
Full	no. of groups	$y = \text{group mean}$
Logistic	2	$y = \frac{1}{1 + \exp(-a - bx)}$
Probit	2	$y = pnorm((x - a) \cdot b)$
Log-logistic	3	$y = a + \frac{1 - a}{1 + \exp\left(c \cdot \log\left(\frac{b}{x}\right)\right)}$
Log-probit	3	$y = a + (1 - a) \cdot pnorm\left(c \cdot \log\left(\frac{x}{b}\right)\right)$
Weibull	3	$y = a + (1 - a)\left(1 - \exp\left(-\left(\frac{x}{b}\right)^c\right)\right)$
Gamma	3	$y = pgamma(bx; c)$
Two-stage	3	$y = a + (1 - a)\left(1 - \exp\left(-\frac{x}{b} - c\left(\frac{x}{b}\right)^2\right)\right)$
Exp model 3	3	$y = a \cdot \exp(bx^d)$
Exp model 5	4	$y = a \cdot (c - (c - 1)\exp(-bx^d))$
Hill model 3	3	$y = a \cdot \left(1 - \frac{x^d}{b^d + x^d}\right)$
Hill model 5	4	$y = a \cdot \left(1 + (c - 1)\frac{x^d}{b^d + x^d}\right)$

For the Exp and Hill family, the study team fit models with 3 and 4 parameters as listed in the table. The 3-parameter model is selected if the difference in AIC is smaller than 5, otherwise the 4-parameter model is selected.

16.7.4.1 Procedure for selection of BMDL



16.7.5 Results

Response variable: effect

16.7.6 Fitted Models

model	No.par	loglik	AIC	accepted	BMDL	BMDU	BMD	conv
null	1	-52.25	106.50		NA	NA	NA	NA
full	4	-44.78	97.56		NA	NA	NA	NA
two.stage	3	-44.82	95.64	yes	308.0	890	479	yes
log.logist	3	-44.80	95.60	yes	108.0	1200	456	yes
Weibull	3	-44.82	95.64	yes	101.0	1230	459	yes
log.prob	3	-44.78	95.56	yes	119.0	1120	448	yes
gamma	3	-44.82	95.64	yes	95.9	1200	462	yes
LVM: Expon. m^3-	3	-44.86	95.72	yes	86.3	1330	466	yes
LVM: Hill m^3-	3	-44.86	95.72	yes	86.3	1330	466	yes

16.7.7 Estimated Model Parameters

two.stage
estimate for a- : 0.03264
estimate for BMD- : 478.7
estimate for c : 1e-06

log.logist
estimate for a- : 0.03185
estimate for BMD- : 456.2
estimate for c : 1.076

Weibull
estimate for a- : 0.03162
estimate for BMD- : 459.4
estimate for c : 0.9659

log.prob
estimate for a- : 0.03264
estimate for BMD- : 447.8
estimate for c : 0.5988

gamma
estimate for a- : 0.03175
estimate for BMD- : 462.3
estimate for c : 0.9641

EXP
estimate for a- : 1.595
estimate for BMD- : 465.6
estimate for d- : 0.5168
estimate for th(fixed) : 0
estimate for sigma(fixed) : 0.25

HILL
estimate for a- : 1.595
estimate for BMD- : 465.5
estimate for d- : 0.5185
estimate for th(fixed) : 0
estimate for sigma(fixed) : 0.25

16.7.8 Weights for Model Averaging

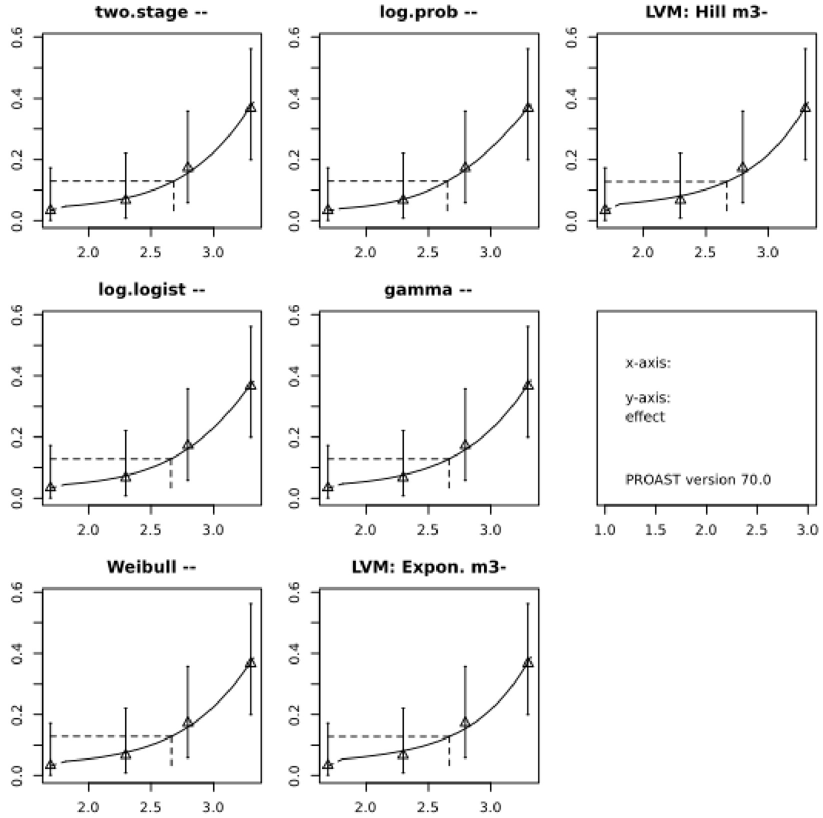
two.stage	log.logist	Weibull	log.prob	gamma	EXP	HILL
0.14	0.15	0.14	0.15	0.14	0.14	0.14

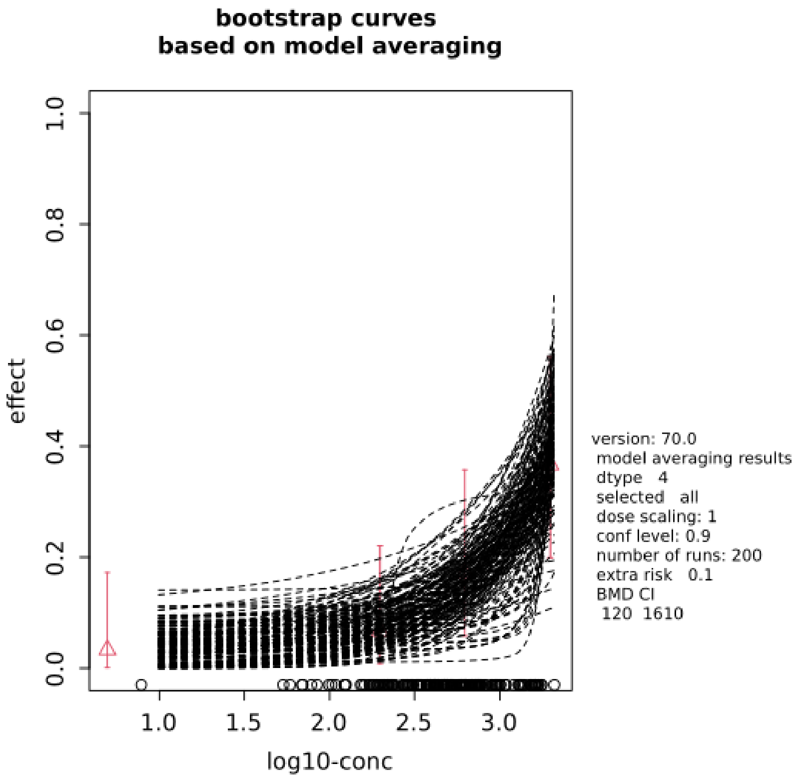
16.7.9 Final BMD Values

subgroup	BMDL	BMDU
all	122	1610

Confidence intervals for the BMD are based on 200 bootstrap data sets.

16.7.10 Visualization





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