SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Naphthalene

EC No 202-049-5

CAS No 91-20-3

Evaluating Member State(s): United Kingdom

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2016

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Naphthalene was placed on the CoRAP because the worker inhalation DNEL of 25 mg/m^3 (8-hour Time Weighted Average (8-hr TWA)) used in the registration dossiers is substantially higher than the national occupational exposure limits (OELs) of 0.5 mg/m^3, 8-hr TWA and short term limit established in Germany in 2011[2]. Exposure data obtained at the time of the Existing Subtances Regulation (ESR) review suggests workers may be exposed to levels significantly above the new German OEL. It is important to determine how the use profile and exposure situation has changed since the previous review. Also, there is evidence that substitutes may now be available for some uses.

The DNEL value in question relates to inflammatory reactions in the olfactory epithelium, where tumours have been observed in rats. Therefore irritation to the respiratory tract, repeated dose inhalation toxicity and carcinogenicity were all included within the scope of the human health hazard evaluation. In addition, an assessment of haemolytic anaemia was made since this effect is a lead health concern for naphthalene.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

The following EU wide legislation includes specific provisions for naphthalene:

Biocidal Products Directive (98/8/EC): Napthalene is listed in Annex I "Active substances identified as existing" and Annex II "Active substances to be examined under the review programme" as product type 19 ("Repellant and attractants"). No satisfactory application was submitted within the permitted timeframe therefore a non-inclusion decision was taken and from 29 July 2008 naphthalene has not been permitted to be used in mothballs supplied to the EU market.

Cosmetics Regulation (Regulation (EC) No. 1223/2009): Napthalene is listed as entry no. 1167 in Annex II "List of substances prohibited in cosmetic products" meaning it must not be used as an ingredient in cosmetic products.

Water Framework Directive (2008/105/EC): Naphthalene is listed as a priority substance. Environmental quality standards have been established for naphthalene. There are an annual average EQS for inland and other surface waters of 2 µg/l and maximum allowable concentration for inland and other surface waters of 130 µg/l.

Pollutant Release and Transfer Register (Regulation (EC) No. 166/2006): Naphthalene is listed as entry no 68 in Annex II of this regulation and is therefore one the pollutants for which information on releases must be submitted to a central European register providing certain conditions are met. The capacity thresholds triggering reporting are:

- Threshold for release to air: 100 kg/year
- Threshold for release to water: 10 kg/year
- Threshold for release to land: 10 kg/year

[2] A list of OELs worldwide for naphthalene can be found at: http://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx (accessed June 2018). In 2018, the German OEL was revised again to 2 mg/m^3 (8-hr TWA) accompanied by a skin notation (see: https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/TRGS-900.pdf?__blob=publicationFile) (accessed October 2018) .

- Threshold for off-site transfer of pollutants: 100 kg/year
- Manufacture, process or use threshold: 10,000 kg/year

Inland Transport of Dangerous Goods Directive (2008/68/EC): Napthalene is listed with UN no.1334 and is subject to the rules for transporting dangerous goods established by this directive.

First IOELV directive (2000/39/EC): This directive brought the limit value for naphthalene of 50 mg/m^3 (8-hr TWA) that was established under the 1st ILV directive into scope of the Chemical Agents Directive.

Previous assessments covering the human health effects and use patterns of naphthalene include:

- Existing Substances Regulation (Regulation (EEC) No. 793/93): Naphthalene was included in the first priority list of substances. The risk assessment report was published in 2003 with an addendum covering a risk assessment for the environment published in 2007[3].
- US Department of Health and Human Services, Agency for Toxic Substance and Disease Registry (2005)[4]. Toxicological Profile for naphthalene, 1-mehtylnaphthalene and 2-methylnaphthalene.
- UK Health Protection Agency (2007)[5]. Naphthalene health effect, incident management and toxicology. Information on naphthalene (also called naphthene or naphthalin), for responding to chemical incidents.
- IARC (2002)[6]. Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene.
- SCOEL (2010). Recommendation from the Scientific Committee on Occupational Exposure Limits for naphthalene. SCOEL/SUM/90 (European Commission, 2010)
- IPCS (2000)[7]. International Programme on Chemical Safety, Poisons Information Monograph 363.
- DECOS (2012)[8]. Naphthalene. Evaluation of the genotoxicity and carcinogenicity. Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety (DECOS), a Committee of the Health Council of the Netherlands
- Danish EPA (2015)[9]. Survey of naphthalene (CAS 91-20-3). Environmental project No. 1721, 2015. ISBN no. 978-87-93352-34-6.
- WHO (2010)[10]. WHO Guidelines for Indoor Air Quality: Selected Pollutants. ISBN-13: 978-92-890-0213-4
- AGS, Ausschuss für Gefahrstoffe (2018). AGW - Begründung zu Naphthalin in TRGS 900[11]

[3] https://echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation/-/substance-rev/2491/term (accessed November 2016)

[4] http://www.atsdr.cdc.gov/ToxProfiles/tp67.pdf (accessed November 2016)

[5] https://www.gov.uk/government/publications/naphthalene-properties-incident-management-and-toxicology (accessed November 2016)

[6] http://monographs.iarc.fr/ENG/Monographs/vol82/ (accessed November 2016)

[7] http://www.inchem.org/documents/pims/chemical/pim363.htm (accessed November 2016)

[8] https://www.gezondheidsraad.nl/sites/default/files/Naftaleen201230.pdf (accessed November 2016)

[9] http://mst.dk/service/publikationer/publikationsarkiv/2015/jul/survey-of-naphthalene/ (downloaded November 2016)

[10] https://www.ncbi.nlm.nih.gov/books/NBK138704/ (accessed November 2016)

[11] http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/Arbeitsplatzgrenzwerte.html__nnn=true (accessed October 2018)

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in Table 1 below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	✓
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures (update EU-wide OEL)	✓
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

Not applicable.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Naphthalene does not meet the criteria outlined in Article 57 for identification as a substance of very high concern.

4.1.3. Restriction

Although the eMSCA considers that the registrants' DNEL is too high, there is no evidence that any registered use of naphthalene is creating unacceptable risks to workers. No restrictions are currently foreseen. Instead, the eMSCA proposes that the EU-wide OEL value of 50 mg/m^3 should be revised (see section 4.1.4).

4.1.4. Other EU-wide regulatory risk management measures

The eMSCA concludes that for naphthalene, setting an OEL under workplace legislation provides the best framework to determine an appropriate level for worker exposure and the corresponding risk management measures.

The lead health concerns for naphthalene are haemolytic anaemia and carcinogenicity. Now and in the future, (potential) exposures in the workplace are the principal exposure scenarios of concern.

Evidence from humans drives the concern for haemolytic anaemia since the main experimental species (rats, mice and rabbits) do not appear to be a suitable model for this effect. In humans, the occurrence of haemolytic anaemia has been reported in at least 30 individuals, typically following single or repeated oral intake of naphthalene mothballs but also following inhalation and dermal exposure to naphthalene from clothing. Individuals who are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD) may be more susceptible to the haemolytic effects of naphthalene than others in the general population. Owing to the circumstances surrounding the poisoning incidents, it is not possible to determine the doses involved and the nature of the dose-response relationship cannot be identified. It is therefore not possible to calculate a derived no effect level (DNEL) for this effect and perform a quantitative risk characterisation. At the time of the ESR review, an investigation was performed into the feasibility of conducting a workplace survey to look for signs of haemolytic anaemia. However, it was determined that the only suitable population for such a study (the workforce of a mothball manufacturing plant was identified because they were exposed to high levels of naphthalene without confounding exposures) was too small to draw meaningful conclusions. No further information was therefore requested and it was concluded in the ESR Risk Assessment Report (RAR) that body burdens in the mg/kg range may be of concern for haemolytic anaemia.

Very little new information has emerged since the ESR review to shed further light on a no-effect level for haemolytic anaemia in humans. In the light of this continuing uncertainty, the conclusion remains that body burdens in the mg/kg range may be of concern. It is also the case that there is no evidence to clarify whether or not naphthalene exposed workers currently experience haemolytic anaemia; if they do, then one can infer from the absence of reports that the degree of effect is not sufficient to prevent them from attending work.

The concern for carcinogenicity is driven by experimental evidence, particularly from studies in rats. In long-term repeated exposure studies, nasal tumours have been observed at levels that also caused non-neoplastic inflammatory changes and it appears likely that inflammation is a necessary precursor for the tumours. The ESR review concluded that the tumours observed in animal studies are likely to have arisen via a non-genotoxic mechanism and this conclusion has been upheld by the mode of action (MoA) analysis performed during this evaluation.

The postulated mode of action (MoA) for the nasal tumours in rats proposes that naphthalene is metabolised to cytotoxic metabolites by a CYP enzyme (CYP2F) in tumour-forming tissues. Those metabolites are responsible for the inflammation and regenerative hyperplasia which precede carcinogenesis. The presence of a CYP2F enzyme in humans indicates that there is a potential for similar naphthalene metabolism in humans. The anatomical, physiological and metabolic differences between rats and humans, including breathing route, anatomy of the nasal cavity and (based on findings from *in vitro* studies) the likely lower rate of naphthalene metabolism in humans are noted. On the basis of these differences, it is possible that the consequences of naphthalene inhalation in humans will vary from those observed in the rat.

There is no evidence of nasal tumours resulting from naphthalene exposure in humans. However, the absence of case reports or other forms of epidemiological study of this issue cannot be considered to represent convincing evidence that the tumours observed in rats are not relevant to humans.

In mice receiving inhalation exposure to naphthalene, tumours were not observed in nasal tissue. However, it is not known whether the mouse or rat is a better model for the effects of naphthalene inhalation exposure.

Therefore the total information available is not sufficient to conclude that the finding of nasal tumours in rats exposed to naphthalene by inhalation is not relevant for humans (albeit that humans might well be at least quantitiatively less sensitive to such an effect). The current Carc Cat. 2 classification is based on this perspective.

In setting their long-term inhalation DNEL of 25 mg/m^3 (8-hr TWA), the registrants chose to rely on information obtained from an unpublished survey of workers at 12 European abrasives producers, conducted in 2010. Few details from this survey were provided in the registration. Company doctors are reported to have never observed blood anomalies or haemolytic anaemia or other occupational health effects in workers, some of whom had been employed for up to 40 years. However, the registrants have not provided sufficient information about the endpoints that were assessed in medical examinations of these workers, nor the frequency of examinations, to understand how comprehensive these assessments were. It is claimed that workers were regularly exposed to levels approaching 25 mg/m^3 (8-hr TWA). However, no information has been provided to confirm the levels of exposure these workers were subjected to in their daily work and a more recent study in this sector (Sucker *et al*, 2016) reported a maximum personal 8-hr TWA value of 11.58 mg/m^3 (see table 31). The registrants have therefore not provided sufficient evidence to demonstrate that their DNEL will be protective of worker's health and the eMSCA considered alternative routes by which an appropriate and robust DNEL can be derived.

If the conventional DNEL setting approach is followed, in the absence of reliable dose response data from humans, a suitable starting point should be selected from studies in animals. The no-observed adverse effect concentration (NOAEC) from the 90-day inhalation study by Dodd *et al* (2012) of 0.52 mg/m^3 provides such a starting point. At the next dose administered to rats in this study, 5.24 mg/m^3, only minimal hyperplasia was observed in the respiratory/transitional epithelium suggesting the true no-effect concentration might lie somewhere between 0.52 and 5.24 mg/m^3. Since no further information is available to identify a more accurate no-effect concentration, it would be necessary to use the value of 0.52 mg/m^3 as the starting point which, if the conventional assessment factors are applied, leads to a worker, long-term inhalation DNEL of 0.053 mg/m^3.

However, a recent workplace study (Sucker *et al*, 2016) found no consistent evidence for nasal inflammation in workers occupationally exposed to levels up to 10 mg/m^3 (8-hour time weighted average (TWA)) naphthalene. In this study, a battery of tests were performed to look for signs of nasal inflammation and adverse effects on olfactory function. Endoscopic examinations of nasal tissues revealed that slight to moderate inflammation was present in participants from the high exposed, moderately exposed and reference groups (which had daily naphthalene exposures of 6.97±3.10 mg/m^3 (8 hr TWA) (arithmetic mean±standard deviation), 0.66±0.27 mg/m^3 (8-hr TWA) and 0.15±0.10 mg/m^3 (8-hr TWA) respectively). A comparison of readings taken on Monday and Thursday revealed an increase in endoscopy examination scores (suggesting more severe inflammation) in some individuals from each group and a decrease in scores (suggesting less severe inflammation) from other individuals, with a greater tendency (statistically significant) for scores to increase (Monday – Thursday) in moderately and high exposed workers compared with the reference group. However, there were no differences between the moderate and high exposed groups, despite the 10-fold higher naphthalene exposure in the high exposed group. No consistent changes were observed in biomarkers for inflammation in nasal lavage or sputum samples from the exposed and reference groups. Also, where statistical differences were observed between the exposed and reference groups, there was often a high degree of overlap in the range of results (for example, for total endoscope scores, the Thursday readings ranged from 0-13 in the high exposed group, from 3-13 in the moderately exposed group and from 0-9 in the reference group). Complicating the analysis is the fact that both exposure groups were also exposed to inhalable and respirable dusts including ceramic grain and silica which could have

contributed to the observed nasal inflammation. It is therefore difficult to determine what role naphthalene might have played in any nasal effects observed in these workers. Overall, there was no indication of a substantial effect of naphthalene inhalation on nasal irritation, with exposures up to about 7 mg/m^3 (8-hr TWA). On this basis, a DNEL of 0.053 mg/m^3 (8-hr TWA) will be a very precautionary value given the lack of consistent evidence for inflammatory changes associated with naphthalene in workers with daily exposure to levels of naphthalene over 100 times higher than this DNEL.

It is also worth noting that the DNEL is at the low end of the range of exposures recorded for office workers that are spatially separated from areas where naphthalene is in use (exposures for these office workers ranged from 0.05 – 1.05 mg/m^3 (8-hr TWA) (see table 31)). This suggests that if exposures are to be maintained below this DNEL, it is likely that there would need to be a major redesign of the sites where the data for Sucker *et al* were collected and potentially other sites using naphthalene. Requiring the downstream use chain for naphthalene registrants to adopt this DNEL would also set higher standards of control for these sites compared with sites where exposure to naphthalene arises because it is a component in a substance of unknown or variable composition (UVCB) or generated as a process by-product. For example, Price and Jaycock (2008) suggested exposure to naphthalene can be expected to be in the range 0.01 – 0.3 mg/m^3 (8-hr TWA) for refining and petroleum industries, asphalt (paving and roofing) and industries using pitch to manufacture refractory materials or graphite electrodes. For these reasons the eMSCA does not think that a DNEL of 0.053 mg/m^3 provides a workable reference point from which to derive a control strategy for naphthalene.

Due to the lack of understanding of the most appropriate experimental models for the effects of naphthalene in humans, the eMSCA does not consider that requiring further experimental studies is an appropriate course of action. Instead, the eMSCA proposes that an EU-wide OEL will be the most appropriate way to manage risks. Setting an EU-wide limit value would not only target the sectors of use that have been covered by this evaluation, but would also target other sectors where exposure to naphthalene arises because it is a component in a substance of unknown or variable composition (UVCB) or because it is generated as a process by-product. It would ensure that consistent standards of control are adopted wherever there is occupational exposure to naphthalene and that these standards apply across all EU-territories.

The current EU-wide Indicative Occupational Exposure Limit Value (IOELV) of 50 mg/m^3 (8-hr TWA) was introduced via the first Indicative Limit Value Directive (91/322/EEC) and was directly transposed into the current system via the second IOELV Directive (2006/15/EC). Although the IOELV has been reviewed by the Scientific Committee on Occupational Exposure Limits (SCOEL, 2010), the review took place at a time when potentially relevant experimental studies were ongoing. SCOEL therefore declined to recommend a limit value pending publication of this data.

The studies SCOEL were waiting for have now been published along with a new workplace study (Sucker *et al*, 2016) and all of the new evidence has been considered in this evaluation. Since the IOELV is twice as high as the registrants' DNEL of 25 mg/m^3 (8-hr TWA) and five times higher than the levels in air measured by Sucker *et al*, (2016) for directly exposed workers (up to around 10 mg/m^3) the eMSCA concludes that the IOELV is not providing any incentive for employers to improve workplace control. The current IOELV should therefore be revised.

In considering what number should be adopted for the OEL, it will be useful to understand the levels in air that are achievable with the currently applied controls and working practices. REACH registrations only describe the registrants' recommended risk management measures but do not provide clarity about the measures currently implemented by downstream users and the associated levels of exposure.

A key piece of information to take into account in setting the OEL is the biological monitoring data obtained by Sucker *et al,* summarised in table 12. This showed that the majority of non-smoking workers carrying out tasks involving direct exposure to

naphthalene at levels of up to 10 mg/m^3 (8-hr TWA) do not appear to clear the body burden of naphthalene accrued during the working week over the weekend. The 95th percentile levels of unriary 1- and 2-napthol in directly exposed workers in pre-shift samples on Monday was 958 µg/L compared with 85 µg/L in workers with indirect exposure and 18 µg/L in workers with no or rare exposure. Although Sucker *et al* did not measure body burdens, the potential body burden corresponding to the exposures estimated for the grinding wheel scenario can be calculated. If it is assumed that an average worker weighs 70 kg and inhales 10 m^3 air per shift, and that there is 100% absorption by the inhalation route, the body burden accrued by the end of the week may be around 2.8 mg/kg (this value is based on an estimated elimination constant (k_{el}) of 0.5/d derived by the registrants from the biomonitoring data presented by Sucker et al and does not take a possible additional contribution from dermal exposure into account). . This value should be considered commensurate with the "low mg/kg" range identified in the ESR RAR as potentially of concern for the possibility of producing haemolytic anaemia. There was no evidence in this study that maintaining an elevated body burden of naphthalene was evidently detrimental to the health of the workers studied. However, significant uncertainties apply: the study focussed on examinations of the nasal passages, markers for haemolytic anaemia and G6PD deficiency were not investigated; there is uncertainty surrounding the dose-response relationship for haemolytic anaemia, particularly taking into account that around 4% of the European population may have the G6PD deficiency making them more susceptible to naphthalene induced haemolytic anaemia, and; there is uncertainty surrounding the dose-response relationship for nasal inflammation, with the possibility that such inflammation could have the potential to progress to nasal tumour development in humans. The eMSCA argues that, with all these uncertainties, it seems sensible to aim to limit exposure to levels that do not cause workers to retain a residual body burden of naphthalene from one week to the next.

The high urinary 1- and 2-napthol levels measured by Sucker *et al* (2016) could potentially have arisen as a result of either inhalation or dermal exposure or a combination of the two. The eMSCA has been informed that it is standard practice for these workers to wear gloves if there is the potential for direct skin contact with naphthalene. Assuming that appropriate gloves are being worn and suitable management systems are in place to ensure the gloves are used correctly, this directs attention towards inhalation as being the main route of exposure.

The conclusion is therefore reached that airborne exposures to naphthalene should be kept below 10 mg/m^3 (8-hr TWA).

To ensure body burdens are kept within acceptable levels, it is not clear how far below 10 mg/m^3 it is necessary to reduce airborne exposure. Ideally this decision should be informed by additional information linking measured airborne exposures with biological levels across a range of sectors where there is the potential for exposure to naphthalene. Such an extensive survey will require the voluntary participation of a wide range of companies and workers and it seems unrealistic to place this as a requirement on the REACH registrants of naphthalene. This is therefore identified as a recommendation from this evaluation.

It also seems appropriate to reflect on the potential exposures associated with the current operating conditions and risk management measures identified in the naphthalene REACH exposure scenarios.

For the manufacture of naphthalene and the use of naphthalene as a feedstock/ intermediate, worst case modelled estimates for PROCs 4, 8a, 8b and 9 suggest airborne exposure may exceed 10 mg/m^3 if a worker performs these tasks exclusively for the entire shift. It is possible that worker exposure has been overestimated, for example a higher level of containment may be implemented than has been assumed in the exposure calculations and the time workers spend working directly with naphthalene may be much less than has been assumed. Unless more details are provided in registrations about the way processes are currently operated it will not be possible to refine these worst case estimates.

The information provided in registrations and from Sucker *et al* about exposure to naphthalene during the manufacture of abrasives suggests that additional control measures should be implemented to further limit the release of naphthalene to air during activities involving direct handling of naphthalene i.e. weighing, mixing, sieving, pressing and moulding (see section 7.12.1.1.4 for details).

Very little information is available about the formulation, military use and service life of naphthalene containing smoke bombs/grenades. This is another sector where naphthalene exposures may be sufficiently high that workers retain a residual body burden from one week to the next. Further information should be obtained to clarify working practices in this sector. Decisions can then be taken about the need (or not) to implement additional control measures e.g. containment or LEV to limit the release of naphthalene particulate and vapour to air.

In summary, in addition to the conclusion that the existing EU-wide OEL for naphthalene should be revised, the following recommendations are made:

- To ensure that it is transparent in the exposure scenario how all relevant work activities are covered, either a specific contributing scenario for routine cleaning and maintenance activities should be provided or registrants should indicate which of the already chosen contributing scenarios apply to these activities. Registrants should update registrations with this information without undue delay.

- To allow authorities to better understand the current operating conditions and any risk management measures that are used, and to put the exposure estimates into context, all registrants should provide additional descriptions of the the tasks/activities that are performed and the risk management measures that are applied for all uses covered in their CSRs. Registrants are recommended to update registrations with this information without undue delay.

- All sectors of industry where there is a potential for exposure to levels of naphthalene that could approach or exceed 10 mg/m^3 (8-hr TWA) should consider gathering information on levels in air and corresponding biological levels under current working conditions. Where there is evidence that body burdens in workers regularly exceed background levels at the start of the working week, operating conditions and risk management measures should be re-examined. The Biologischer Arbeitsstoffreferenzwert (BAR) of 35 µg total urinary 1- and 2-naphthol/L urine established by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) may be a useful benchmark to use for this assessment. If it appears necessary to reduce worker exposure, additional controls should be implemented in accordance with the hierarchy of control described in the Chemical Agents Directive (98/24/EC). In addition to the sectors covered in this evaluation, it may also be useful to investigate exposure to naphthalene in other sectors such as those where UVCB mixtures are used which contain naphthalene as an impurity and sectors where naphthalene is emitted as a process by-product.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Not applicable.

5.2. Other actions

Not applicable

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

New data has become available since SCOEL published its recommendation in March 2010. SCOEL and DG Employment are therefore recommended to prioritise this substance for setting of a new OEL-value.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Naphthalene was included in the first Priority List of substances to be assessed under the Existing Substances Regulation (EEC/793/93). Sections of the Risk Assessment Report (RAR) covering risks to human health were finalised in 2003, and the environmental risk assessment was finalised in 2007. The RAR identified a need for reducing the risks to human health for a number of uses of naphthalene, namely:

- All occupational exposure scenarios, except the professional use of coal tar soaps and shampoos;
- Consumer use of mothballs and
- Consumer exposure following the laying of damp proofing.

A Risk Reduction Strategy (RRS) document was therefore prepared to examine options to address these risks. This was finalised in 2007 and covered the following uses:

- Manufacture of naphthalene;
- Use in phthalic anhydride manufacture and other chemical synthesis;
- Blending and use of creosote;
- Manufacture of mothballs;
- Manufacture and use of coal tar paints and waterproof membranes;
- Professional use of consumer products e.g. creosote products and coal tar pitch based damp proof laying;
- Manufacture of grinding wheels;
- Consumer use of mothballs and creosote;
- Consumer exposure following damp proofing.

This evaluation aimed to confirm that the measures identified in the ESR RRS have been taken into account by the Registrants in their CSRs.

After the ESR RRS was completed, the IOELV for naphthalene that is listed in the 1st IOELV directive (50 mg/m^3, 8-hr TWA) was reviewed by DG Employment's Scientific Committee on Occupational Exposure Limits (SCOEL). In 2010, SCOEL concluded that it was "not feasible to derive a health-based limit" but that their conclusion should be reassessed when further data about the carcinogenic potential of naphthalene became available. The German authorities have also reviewed the MAK value for naphthalene and a new limit of 0.5 mg/m^3 (8-hr TWA) was established in 2011[12]. Given the uncertainties about the sustainability of an IOELV of 50 mg/m^3, the evaluation examined the available toxicological data for naphthalene to see if the Registrant's DNELs were appropriate.

[12] http://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx (accessed November 2016). This limit was revised to 2 mg/m^3 in 2018 (see: https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/900/900-naphthalin.pdf?__blob=publicationFile&v=3 , accessed October 2018)

There was also evidence that substitutes for naphthalene may be available for some uses. The evaluation therefore looked at the use pattern for naphthalene to see how this has changed since the ESR work was completed.

Table 2 shows a list of evaluated endpoints with corresponding outcomes. More details can be found in the relevant sections below.

Table 2: Summary of endpoints evaluated

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Acute Toxicity (Haemolytic anaemia)	Haemolytic anaemia confirmed. Insufficient information was available for DNEL derivation.
Irritation to the respiratory tract	Effects on olfactory and respiratory epithelia of the nasal cavity have been observed in rats after acute exposure to naphthalene. NOAELs could not be identified from these studies. However, the DNEL derived for repeated dose toxicity is considered to be protective for this endpoint.
Repeated dose toxicity	A DNEL was derived for non-neoplastic lesions caused by exposure to naphthalene by inhalation.
Carcinogenicity	The nasal tumours in rats cannot be dismissed as being irrelevant to humans. The DNEL derived for repeated dose toxicity is also considered to be protective for carcinogenicity.
Exposure (human health)	There is evidence that the use pattern has changed since the ESR review owing mainly to changes in use as a biocide and in personal care products. It is not possible to tell how widely the recommendations made in the ESR RRS have been implemented based on the information provided in REACH registrations and it is recommended that additional descriptive information is provided on the current operating conditions and risk management measures that are applied at sites manufacturing and using naphthalene since this will help to put quantitative exposure estimates into context. It is also recommended that registrants update their dossiers with scenarios to cover routine cleaning and maintenance. There is a concern that the current risk management approach that is adopted in some sectors may result in directly exposed workers maintaining a residual body burden of naphthalene from one week to the next . Further attention needs to be paid in particular to limiting airborne exposure since this seems to be the dominant route.

7.2. Procedure

The evaluation was targeted to the human health hazard and exposure concerns outlined above. No evaluation of the environmental fate, hazard or risk assessment was undertaken.

On the basis of an opinion of the ECHA Member State Committee and because of initial grounds for concern relating to the numerical value of the DNEL adopted by the registrants and about the potential exposure levels associated with certain uses, naphthalene CAS No 91-20-3 (EC No 202-049-5) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2016. The updated CoRAP was published on the ECHA website on 17 March 2016. The Competent Authority of the United Kingdom (hereafter called the evaluating MSCA / eMSCA) was appointed to carry out the evaluation.

The initial assessment started on 27 May 2016.

Analytical information provided in the dossiers was assessed to confirm substance identity and composition.

The information assessed in the evaluation included that in the registration dossiers, publically available information (see references in section 7.14) and information provided to the eMSCA by the registrants and representatives of industry sectors using naphthalene.

The eMSCA held a teleconference with the registrants on 26 July 2016 to discuss the evaluation process. A first draft of the use and exposure assessment was sent to the registrants on 12 December 2016 to confirm that the information being presented in the evaluation report was factually correct and that no confidential exposure and use information had been included in the non-confidential sections of the report. This prompted interactions between the eMSCA and representatives of the abrasive manufacturing sector who agreed to provide further information to the eMSCA about the way naphthalene is used in the manufacture of abrasives.

The new information was provided on 13 February 2017 and was taken into account by the eMSCA along with information provided at a teleconference with the registrants and representatives of the abrasive manufacturers on 7 March 2017.

Since the information available to the eMSCA in March 2017 was not sufficient to reach a conclusion about risk and the adequacy of the recommended RMMs for each of the exposure scenarions covered in REACH registrations, a draft decision document was prepared. This asked for information to justify the approach taken to derive the long-term inhalation DNEL. Requests were also made for more information about the methods used to control naphthalene in air and the working practices that are used to limit worker contact with naphthalene during specific activities.

During the commenting period, the registrants provided further information about the approach taken to set their long-term inhalation DNEL. At this point the eMSCA took the decision to terminate the decicion making process and conclude the evaluation with a recommendation for the EU-wide OEL to be revised. Although the requested information about controls and working practices had not been received and may be useful for the limits setting process, the REACH decision making process does not seem to be the most efficient way to obtain this requested information and it is desireable to avoid delay.

7.3. Identity of the substance

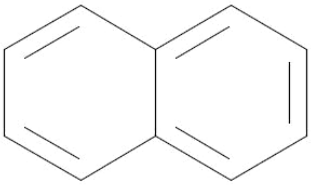
Table 3 displays the identity of the substance according to the ECHA dissemination website.

Table 3

SUBSTANCE IDENTITY	
Public name:	naphthalene
EC number:	202-049-5
CAS number:	91-20-3
Index number in Annex VI of the CLP Regulation:	601-052-00-2
Molecular formula:	$C_{10}H_8$
Molecular weight range:	128.17 g/mol
Synonyms:	Albocarbon Dezodorator Moth flakes Naphthaline Tar camphor White tar NSC 37565 Naphthene

Type of substance ☒Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



Very limited information was provided by most of the registrants to confirm the identity of the registered substance. It is recommended that registrants consider the requirements of Annex VI 2.3.5 to ensure that they are compliant and have data specific to their registration.

Most registrants provided some analytical information to support the composition reported in section 1.2 of their dossiers, but registrants are reminded that they should include sufficient information for the analysis to be reproduced. Table 4 gives the typical non-confidential composition.

Table 4

Constituent			
Constituents	**Typical concentration**	**Concentration range**	**Remarks**
naphthalene	>80%		Exact concentration confidential

7.4. Physico-chemical properties

Table 5 lists the physicochemical properties for naphthalene from the ECHA dissemination website. All of the information is taken from published articles or handbooks.

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Solid white flakes/granules with aromatic odour
Melting/freezing point	79°C
Boiling point	218°C
Vapour pressure	10.5 Pa at 25 °C
Water solubility	31.7 mg/L at 25°C
Partition coefficient n-octanol/water (Log Kow)	3.7 at 25°C
Flammability	Flammable
Flash Point	78.5°C
Explosive properties	The explosive limits by volume of fuel at 25 °C and 760 mm Hg for naphthalene have been quoted at 0.9 to 5.9 in Lange's Handbook (1992) and Kirk-Othmer (1991) where the original reference is to data obtained by the US Bureau of Mines (Jones and Scott, 1946)
Granulometry	Supplied in molten mass, granules or flakes
Dissociation constant	Waived
Relative density	1.085 at 20°C (naphthalene pure)

7.5. Manufacture and uses

7.5.1. Quantities

Table 6 gives the tonnage information from the ECHA dissemination website.

Table 6

AGGREGATED TONNAGE (PER YEAR)			
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t
☐ 10,000 – 100,000 t	☒ **100,000 – 1,000,000 t**	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

7.5.2.1 Manufacture

Naphthalene may be produced from coal tar or petroleum with coal tar being the most common source. A document published by the Danish EPA in 2015 suggests that over 92% of world production in 2012 was produced from coal tar (Danish EPA, 2015). At the time of this evaluation, 13 active registrants were listed on ECHA's dissemination site located in the UK (1), Czech Republic (2), Spain (3), Belgium (2), Germany (3), Denmark (1), Italy (1)[13]. One inactive Registrant located in the Netherlands was also listed. This is a slight change to the situation that was reported in the ESR review (ECB, 2003). When information was gathered for the ESR review, companies producing naphthalene were located in the UK, Belgium, France, Italy, Netherlands, Denmark, Germany, Austria and Spain. The Austrian tar distillation plant closed around 1999 and the plant in France closed in 2005.

At the time of the ESR review, one company used both coal tar and petroleum as sources for naphthalene, the remaining companies used coal tar as their only source. Production figures from individual producers ranged from 4,000 to 70,000 tonnes per annum. The total EU production was estimated at 200,000 tonnes per annum of which 60,000 tonnes was exported and 152,000 tonnes used in EU. The total amount currently used in the EU, including imports, is slightly higher than the total EU production estimated for the ESR review.

Modern sites producing naphthalene generally do so under controlled conditions and in contained systems with several sites operating under strictly controlled conditions (SCC). Since naphthalene is processed at temperatures of around 90°C, pipelines are sealed and insulated to maintain the necessary temperatures and workers operate the plant remotely from control rooms. Naphthalene is supplied either in the molten state or as solid granules/flakes. Where naphthalene is supplied in the molten state, it is possible to maintain SCC throughout the production process. This is not possible where naphthalene is supplied as granules/flakes.

The following manufacturing process information is based on descriptions provided in the ESR report.

7.5.2.1.1 Production from coal tar

Naphthalene is produced from coal tar fractions by crystallisation and distillation. Distillation of coal tar produces several fractions including the middle fraction (naphthalene oil) which is the most abundant source of naphthalene and contains about 50% of the naphthalene available from coal tar. The middle fraction is allowed to cool in shallow pans and the naphthalene crystallises. The crude naphthalene produced may then be distilled further. The yield of crude naphthalene is 4.8 kg/100 litres of coal tar. The naphthalene oil fraction is then further processed to produce naphthalene. This processing can involve the distillation of the naphthalene oil to produce a crude grade with a crystallisation point of 74°C to 78°C. This crude grade is suitable for applications such as the manufacture of phthalic anhydride. A purer grade can be produced by treating the naphthalene oil fraction with sulphuric acid followed by neutralisation and redistillation to give a product with a crystallising point of over 79°C. However, this method does not completely remove thionaphthalene which is the main impurity in the crude naphthalene. Alternatively, the more commonly adopted method is to carry out a crystallisation of the naphthalene oil to produce a pure grade that does not contain thionaphthalene and other impurities. The pure grades produced by these methods can be used for applications such as insecticides. Drained oils remaining from this purification of the naphthalene oil may be blended for use in creosote oils or if not suitable they can be used in the manufacture of carbon black.

As well as the naphthalene oil, various other fractions are also produced which can contain naphthalene. These oil fractions are further processed to separate commercially viable chemicals such as anthracene from anthracene oil. Alternatively they are used in blends,

[13] https://echa.europa.eu/registration-dossier/-/registered-dossier/15924 (accessed 17 January 2017)

for example in base oil for road tar production. At the time of the ESR review, it was noted that drained oils remaining from this further processing could be blended to produce creosote, which may contain up to 25% naphthalene. Information provided informally to the eMSCA during the evaluation suggests that modern creosote formulations do not contain such high levels of naphthalene. A personal communication from Koppers Denmark to the authors of the Danish EPA report stated the usual naphthalene content in creosote is now around 5% (Danish EPA, 2015). Any remaining oils (these may contain about 4% naphthalene) may be sold for the manufacture of carbon black. At the time of the ESR review it was understood that some producers may supply heating oils containing up to 10% naphthalene. The eMSCA does not know if this is still the case.

7.5.2.1.2 Production from petroleum

Naphthalene may also be produced from petroleum fractions high in methylnaphthalenes. Dealkylation is carried out at high temperature and pressure in the presence of hydrogen to produce naphthalene that is 99% pure and low in sulphur. The ESR review indicated that this method was only used by one European producer. Precise details of the process were not reported. The literature details several methods that involve two principal steps. The first is the production of an aromatic oil in the naphthalene - alkylnaphthalene boiling range by hydroaromatization or cyclisation. The second step is the dealkylation of such oils either thermally or catalytically. The naphthalene that is produced, usually by crystallisation, is recovered as a high quality product, usually by fractional distillation.

Naphthalene is also recovered from the stream of methyl naphthalenes formed in cracking of heavy liquids (naphthas and gas oils) for ethylene production.

7.5.2.2 Use

Since the ESR review, the range of uses for naphthalene in the EU has narrowed and several uses resulting in exposure to professionals and consumers have ceased. Table 7 provides a comparison of uses covered by current registrations with the uses identified in the ESR report.

Table 7: Identified uses for naphthalene

USES	Registered use(s)	Uses identified in the ESR review*
Uses as intermediate	Use as a feedstock in the manufacture of other substances under SCC Use as an intermediate	Use as a feedstock in the manufacture of other substances Use as an intermediate
Formulation	Formulation of smoke bombs/grenades (military use)	Formulation into pyrotechnics Formulation of mothballs Formulation of coal tar paints and waterproofing membranes Formulation of creosote
Uses at industrial sites	Distribution Use of naphthalene in the abrasive industry	Distribution Use of naphthalene in the abrasive industry
Uses by professional workers	Military use of smoke bombs/grenades (including reloading)	Use of pyrotechnics Use of creosote Use of coal tar paints and waterproofing membranes Use of coal tar shampoos/soaps Use of mothballs

Uses by consumers		Use of creosote Use of coal tar paints and waterproofing membranes Use of coal tar shampoos/soaps Use of mothballs
Article service life	Service life of smoke bombs/grenades	Service life of pyrotechnics Service life of mothballs Service life of coal tar paints and waterproofing membranes

* Uses in grey are not reported in REACH registrations for naphthalene

7.5.2.2.1 Use as an intermediate

The majority of naphthalene produced and imported into the EU is used as an intermediate in the manufacture of phthalic anhydride, azo dyes, naphthalene sulphonic acids, alkylated naphthalene solvents, 2-naphthol, pharmaceuticals and insecticides. Table 8 lists the tonnages directed to different manufacturing processes reported in the ESR review. This level of detail is not provided in registration dossiers so it is not possible to update the tonnages directed to specific chemical manufacturing processes. However, aggregated information indicates that currently over 200,000 tpa naphthalene is used as an intermediate including use under SCC.

Table 8: Best estimates from the ESR review for naphthalene tonnages used in production streams using naphthalene as feedstock (ECB, 2003)

Use	**Tonnage (from ESR report)**
Manufacture of phthalic anhydride	40,000 tpa
Manufacture of azo dyes	46,000 tpa
Manufacture of naphthalene sulphonic acids	24,000 tpa
Manufacture of alkylated naphthalene solvents	15,000 tpa
Manufacture of 2-naphthol	12,000 tpa
Manufacture of pharmaceuticals	4,000 tpa
Total	**141,000 tpa**

One major use for naphthalene is as an intermediate in the manufacture of phthalic anhydride. The ESR review reported that this process was carried out at 3 sites (ECB, 2003). ECHA's dissemination site now lists 29 active registrants and 3 inactive registrants across many EU countries (site accessed on 11 October 2016). The aggregated tonnage of these registrations is 100,000 to 1,000,000 tpa. Ortho-xylene is an alternative feedstock and the amount of naphthalene that is used depends on the relative prices of these two substances (Griego *et al*, 2008, Danish EPA, 2015).

Naphthalene is used in the production of azo dyes via the intermediates 2-naphthol and naphthalene sulphonic acids. Historically this was a major use accounting for 46,000 tpa in 1986 (BUA, 1989). The eMSCA does not have information on whether and how this has changed in the in the intervening 30 years.

Naphthalene is used to produce naphthalene sulphonic acids by reaction with formaldehyde and sulphuric acid and subsequent neutralisation with sodium hydroxide and ammonia. The principal use for naphthalene sulphonic acids is for the manufacture of plasticisers for

concrete. Naphthalene sulphonic acids are also used in the manufacture of an ingredient for plasterboard (wallboard or drywall), as dispersants in synthetic and natural rubbers, in tanning agents (syntans) for the leather industry, as dispersants in pesticide formulations and in lead-acid battery plates. Naphthalene sulfonic acids are also used in the synthesis of 1-naphthol and 2-naphthol, precursors for various dyestuffs, pigments, rubber processing chemicals and other chemicals and pharmaceuticals. There is understood to be only negligible residual naphthalene remaining in the naphthalene sulphonic acids after reaction. The tonnage information reported in the ESR review dates from 1986. More recent information obtained for the Danish EPA report suggests that around 50% of global naphthalene demand and 70% of China's demand is now used to manufacture naphthalene sulphonic acids (Danish EPA, 2015). The eMSCA does not know if the EU has a similarly high demand.

At the time of the ESR review, one company used naphthalene to manufacture alkyl naphthalene sulfonates. These surfactants are used in many industrial applications as nondetergent wetting agents that effectively disperse colloidal systems in aqueous media. The major commercial applications are in the agricultural chemical industry, which uses alkyl naphthalene sulfonates for wettable powder and wettable granular (dry-flowable) formulations, and the textile and fabric industry, which utilizes the wetting and defoaming properties for bleaching and dyeing operations.

The ESR review identified one company using naphthalene to manufacture 2-naphthol. The assumption in the ESR review that about 12,000 tonnes of naphthalene per annum is used in this process may be inaccurate since this intermediate is used in the manufacture of azo dyes and there may have been some double counting in assigning tonnages to these uses.

The 1989 BUA report estimated that 4,000 tonnes of naphthalene were used as a feedstock in various "miscellaneous" applications in 1986. No details are provided, but one of these may have been the manufacture of the insecticide 1-naphthyl-N-methylcarbamate (trade names Carbaryl, or Sevin, although this substance is not believed to be produced in significant quantities within the EU). The eMSCA does not have any more recent information.

7.5.2.2.2 Smoke bombs

Naphthalene is used in pyrotechnics to simulate explosions or create black smokes. The REACH registrations limit this use to smoke bombs and grenades for military use. Previously it was also used to create special effects in the film industry. Although this use is not covered in registrations, it cannot be excluded that some special effects companies may import small quantities of naphthalene containing pyrotechnics. The ESR review states that around 15 tpa of naphthalene were being used to manufacture pyrotechnics across eight sites; four in the UK, two in Germany, and one each in France and Italy. It is not known if all of the sites identified at the time of the ESR review are still operating.

7.5.2.2.3 Abrasives

Naphthalene is used as an artificial pore former in the manufacture of grinding wheels to give a high porosity product. At the time of the ESR review, there were at least 3 companies in the EU using a total of 350 tpa naphthalene to produce grinding wheels. Further information was gathered for the risk reduction strategy from companies involved in the manufacture of grinding wheels in the UK, in other EU Member States, through trade associations representing abrasives manufacturers in Member States and also with manufacturers themselves. Several consultees reported using increased quantities of naphthalene and thought that this trend would continue over the next few years. Only two companies reported decreasing consumption figures. As a result of this new information, it became apparent that at least 12 sites were making grinding wheels in the EU (one consultee suggested that there may be 12 producers in Germany alone). It was estimated that around 900 – 1,000 tpa naphthalene was being used for this purpose.

Currently it is estimated that around 20-25 companies across Europe use naphthalene to manufacture abrasives (Sucker *et al*, 2016). Information from REACH registrations suggests the total tonnage currently used for this purpose lies between the tonnages reported in the ESR review and the risk reduction strategy.

Options to substitute naphthalene with other substances were considered in the ESR RRS. These include 1,4-dichlorobenzene (CAS No. 106-46-7), bubbled alumina and glass spheres, butyl carbamate, plastics and plant-derived pore formers such as crushed nuts and nut shells, wood chippings, rice and olive stones. Although some companies submitting information for the RRS indicated substitution was an option for them, others identified barriers relating to product quality and safety problems for certain products. Recently work has been carried out to investigate the suitability of oxalic acid as a pore forming agent[14]. In principle, the material may be suitable. However, it was found necessary to coat oxalic acid granules with a water repellent coating to prevent its rehydration during processing. The coating agent that was used in this study (30% stearic acid) produced cracks in the grinding wheels and it was not possible to develop a suitable granulation process within the time frame of the project. It is not clear what other efforts companies have made to find substitutes for naphthalene since the risk reduction strategy document was finalised. However, the eMSCA has been told informally that the abrasives sector is actively looking for alternatives and some companies have already achieved complete substitution. No further details about these substitutions were available.

7.5.2.2.4 Uses identified in the ESR report but not covered in registrations

Mothballs

At the time of the ESR review, about 1000 tpa naphthalene was being used to manufacture moth repellants with most production being located at one site in Belgium. It was noted that around 90% of the production at this site was exported out of the EU. Although naphthalene was listed in Annex I of the Biocidal Products Directive (98/8/EC) as an existing active ingredient, no application was submitted within the required timeframe so a non-inclusion decision was taken. Since 29 July 2008, it has not been permitted to supply mothballs containing naphthalene to the EU market although there may be some remaing use in museums to protect articles preserved in storage drawers/cupboards from attack by pests (Danish EPA, 2015).

Creosote

The ESR review reported that around 10,000 tpa naphthalene was being used to produce creosote (ECB, 2003). Creosote and coal tar creosote are complex mixtures of coal tar derivatives which may include naphthalene. They are commonly used as wood preservatives for use against wood-destroying insects and wood-rotting fungi. When the ESR review was conducted, creosote was approved for both amateur and professional use and could contain up to 25% naphthalene according to specifications described in EN 13991:2003. Of the three grades described in this European Standard, only Grades B and C are now produced. Grade B may contain up to 2% naphthalene. This is recommended for pressure impregnation of poles for overhead power and telecommunication lines and for structural timbers. Grade C is a higher boiling point grade and does not contain naphthalene.

In 2003, creosote was typically used for outdoor *in situ* painting of wooden articles where long service was required such as fences, telegraph poles and railway sleepers. Creosote was not allowed for use inside residential property. In 2003, prohibitions on amateur use introduced via Directive 2001/90/EC came into force, halting consumer use for outdoor treatment of e.g. fences. Approvals for professional and industrial creosote/coal tar creosote products were allowed to continue, subject to restrictions on the specification of

[14] https://www.dbu.de/OPAC/ab/DBU-Abschlussbericht-AZ-29452.pdf (site accessed 22 November 2016, document in German)

the products and restrictions on situations where wood that has been treated with creosote/coal tar creosote could be used. These restrictions are now detailed in Annex XVII, entry 31, of the REACH Regulation. The purpose of the restriction was to limit exposure to benzo[a]pyrene and water extractable phenols and not specifically naphthalene.

Subsequent to this, the use of creosote as a wood preservative has been reviewed under the Biocidal Products Directive. As a result of the review, creosote has been included in Annex 1 of Directive 98/8/EC subject to the conditions described in Directive 2011/71/EU[15]. From 01 May 2013 wood preservatives containing creosote need to be authorised for use in the EU and approvals have now been granted.

Coal tar paints and waterproofing membranes

At the time of the ESR review, tar containing naphthalene was used in some specialist paints and waterproof membranes. This use accounted for around 26 tpa naphthalene. The ESR RAR reported that waterproofing membranes contained about 1% naphthalene. Coal tar paints contained about 1-2%, coal tar epoxy paints contained less than 0.1% and coal tar polyurethane sealers less than 1%. These paints and membranes were generally used by the building trade. Waterproof membranes were supplied in 2.5 litre containers up to 200 litre drums. These were generally used to retrospectively waterproof floors and walls, and could be applied to wet surfaces. These systems were estimated to account for about 10% of the waterproofing market. One producer reported that about 600,000 litres of waterproof membrane were used each year in the UK. The ESR RAR stated that tar paints were not used in Germany and that the Scandinavian countries were moving away from them. Information provided from trade associations for the ESR RRS document suggested that naphthalene containing products were no-longer used and the eMSCA has not found evidence to contradict this information. However, if such products are manufactured outside the EU, it would be possible for companies and consumers to import small quantities of naphthalene containing products via internet sales.

Coal tar shampoos and soaps

Shampoos and soaps are regulated under the Cosmetics Regulation (Regulation (EC) No. 1223/2009). Napthalene is listed as entry no. 1167 in Annex II " list of substances prohibited in cosmetic products" meaning it must not be used as an ingredient in cosmetic products. If coal tar shampoos and soaps containing naphthalene are still produced outside the EU, consumers could obtain these shampoos and soaps via internet sales or purchases made while visiting non-EU countries.

7.5.2.2.5 Other substances that may contain naphthalene as a constituent

C_{10}-C_{12} aromatic hydrocarbon solvents

For the purposes of REACH registration, hydrocarbon solvents have been grouped into 9 categories based on the principle constituents[16] and this convention was also used for submissions to the OECD high production volume (HPV) programme (McKee *et al*, 2015). Naphthalene is an identified constituent of solvents falling into category 2, C_{10}-C_{12} aromatics (CAS No. 64742-94-5). This category was redesignated as C_{10}-C_{13} aromatic hydrocarbon solvents for the OECD HPV programme (OECD 2012).

[15] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:195:0046:0051:EN:PDF.

[16] Further information about the naming convention adopted for REACH registrations of hydrocarbon solvents is available at: http://www.reachcentrum.eu/Consortia%20Documents/P-I163/Other/P-I163_HSPA_Naming_convention_2011.03.pdf (accessed on 17 January 2017).

Solvents covered by this category are UVCBs. McKee *et al* (2015) identifies 4 compositions covered by this category. These are referred to as C_{10} aromatics which cover the carbon number range C_9-C_{11} (composition >99% aromatics with either < or > 1% naphthalene) and C_{10}-C_{13} aromatics which cover the carbon number range C_{10}-C_{13} (composition >99% aromatics with either < or > 1% naphthalene). The upper limit for naphthalene in any composition is 10% (OECD, 2012). These solvent mixtures are registered for a wide range of uses, including use in coatings, cleaning agents, lubricants, oil and gas production, metal working fluids/rolling oils, binders and release agents, agrochemicals, road and construction applications, use in laboratories, use in water treatment chemicals, use as a fuel and use in functional fluids. Several of these uses may be performed by consumers including use in coatings, use in cleaning agents, use in lubricants, use in agrochemicals, use as a fuel and use in functional fluids.

Jet fuels

Napthalene may be present in certain aviation fuels. JP-5, JP-8, and Jet A fuels are kerosene-based jet fuels. Kerosene-based hydrocarbon fuels are complex mixtures of up to 260+ aliphatic and aromatic hydrocarbon compounds in the C_6 - C_{17+} range, possibly encompassing 2000+ isomeric forms. This includes varying concentrations of substances such as benzene, n-hexane, toluene, xylenes, trimethylpentane, methoxyethanol, naphthalenes (including polycyclic aromatic hydrocarbons [PAHs]), and certain other C_9 - C_{12} fractions (i.e., n-propylbenzene, trimethylbenzene isomers) (Ritchie, 2003). Naphthalene has been used as a marker in studies examining the exposure of military personnel to JP 8 fuel (Chao *et al*, 2005, Chao *et al*, 2006).

Other petroleum/coal tar distillates

The Danish EPA report indicated that naphthalene may be present in tars used to make asphalt. It may also be present in the PAH mixtures that are found in extender oils and associated with carbon black and in fuels including heating oil (Danish EPA, 2015). The Danish EPA report presents a list of products where naphthalene has been measured in levels ranging from 0.2 to 2800 mg/kg. The highest levels were reported for tattoo inks, wood tar and printed matter. Some toothbrushes were also reported to contain high levels.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)

Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
601-052-00-2	Naphthalene	202-049-5	91-20-3	Acute Tox. 4* Carc. 2 Aquatic Acute 1 Aquatic Chronic 1	H302 H351 H400 H410		

7.6.2. Self-classification

- In the registration(s)*:*

Registrants apply the harmonised classification and additionally one Registrant self-classifies as; Flam. Solid 2; H228

- Additionally the following hazard classes are notified among the aggregated self-classifications in the C&L Inventory*:*

Flam. Sol. 2 H228 – Flammable solid
Flam. Sol. 1 H228 – Flammable solid

Asp. Tox. 1 H304 – May be fatal if swallowed and enters airways
STOT RE 1 H373 (eyes, blood) – May cause damage to organs (eyes, blood) through prolonged or repeated exposure

Aquatic Chronic 3 H412 – Harmful to aquatic life with long leasting effects
Aquatic Chronic 2 H411 – Toxic to aquatic life with long lasting effects

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

The human health hazards of naphthalene have been assessed under the Existing Substances Regulation (ESR) (EC 2003). Currently, naphthalene is classified for the following endpoints in Annex VI of the CLP Regulation - Acute Tox. 4* (oral), Carc. 2, Aquatic Acute 1 and Aquatic Chronic 1. Classification for carcinogenicity was based on observations of rare nasal tumours (respiratory epithelial adenomas and olfactory epithelial neuroblastomas) in rats following exposure to naphthalene by inhalation.

Haemolytic anaemia and inflammatory reactions in the olfactory epithelium are the areas of concern. These effects have been considered in detail in order to calculate Derived No Effect Levels (DNELs) and to address the issue of human relevance.

Information in the registration dossier that was published after the ESR Review was considered. A literature search for information published post 1 January 2008 was performed by the eMSCA and revealed a number of case reports of haemolytic anaemia together with several pieces of literature relevant to the discussion about the effects on the olfactory epithelium following exposure to naphthalene. Since the publication of the ESR Review, a number of short term studies, in which rats were exposed to naphthalene by inhalation, have been conducted. In addition, there have been reports considering the relevance of the findings in rats to humans. The new information has been presented in section 7.9. The findings support and expand upon the data presented in the ESR Review.

Concentrations have been converted from ppm to mg/m^3 using a conversion factor of 5.24 as calculated by the International Agency for Research on Cancer (IARC Monographs Volume 82).

For completeness, relevant information from the EU ESR Review has also been included. The remaining sections under human health have been left blank.

7.9.1. Toxicokinetics

The information in italics below has been taken from the ESR Review (2003).

The limited information available in humans indicates that naphthalene is readily absorbed by all routes of exposure and animal data shows that almost complete and rapid absorption occurs following ingestion.

Information on dermal absorption of naphthalene is scarce. Available data show that after radioactively labelled naphthalene was applied to the skin of 5-8 male Sprague Dawley rats (over a surface area of 13cm^2), half of the naphthalene was absorbed within 2.1 hours (Turkall et al. 1994).

Metabolism in rodents is chiefly by P450 oxidation, with subsequent glutathione conjugation, as well as epoxide hydroxylation to naphthalene 1,2-dihydrodiol. There is some evidence that significant enterohepatic recirculation of naphthalene metabolites occurs in rodents.

In humans, naphthalene is metabolised to 1-naphthol, 2-naphthol and 1,2- and 1,4-naphthoquinone. In vitro studies in human liver microsomes and human lung preparations indicate that epoxide hydrolase is involved in the metabolic pathway by which naphthalene is metabolised to naphthalene 1,2-dihydrodiol.

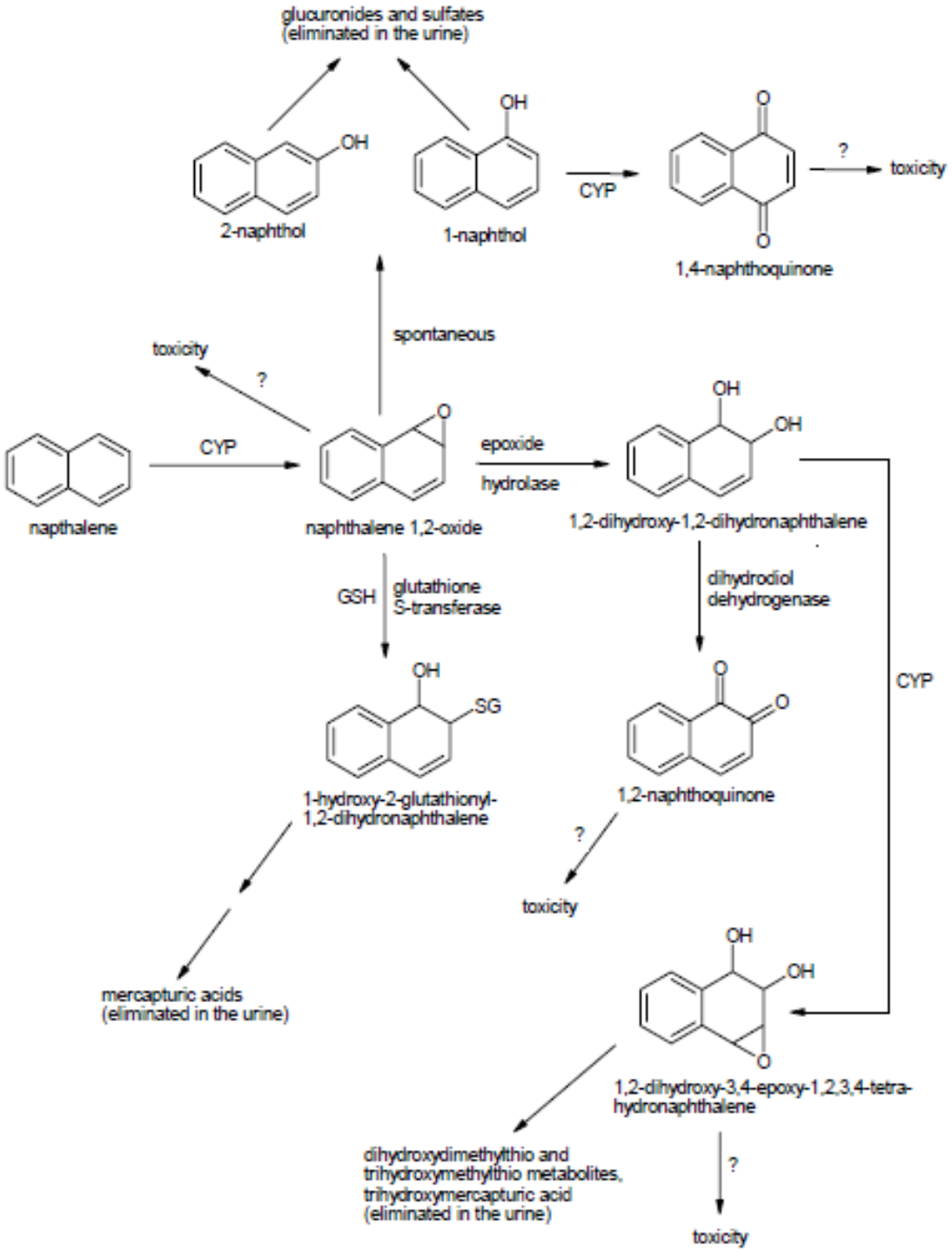
After a single dose of labelled naphthalene (20mg/kg in in olive oil) was administered to 54 male Wistar rats by intraperitoneal injection, plasma levels of the radioactive label declined in a biphasic fashion, with half-lives of 0.8 and 99 hours in phases I and II, respectively (Kilanowicz et al. 1999).

The proposed metabolic pathway is illustrated in figure 7.9.1.

Individuals who are deficient in G-6-PD (glucose-6-phosphate dehydrogenase) are particularly sensitive to haemolytic anaemia produced by naphthalene (Gosselin et al., 1984). This deficiency is genetically determined and occurs more often in males. The defect results in an inability by the red blood cell to maintain a balance between reduced and oxidised glutathione which in turn results in an increased susceptibility to oxidative attack by exogenous chemicals. It seems probable that the oxidative attack, following exposure to naphthalene, can occur following redox cycling of the naphthalene metabolites 1-naphthol and the quinone.

Nkhoma et al. (2009) conducted a scientific review and meta-analysis to ascertain the global prevalence of G-6-PD deficiency and estimated the prevalence of this deficiency to be 3.9% in Europe.

The urine is the main route of rapid excretion in humans and animals.



CYP = cytochrome P450 enzyme(s); GSH = reduced glutathione; SG = glutathione

Figure 7.9.1 Naphthalene metabolism (Agency for Toxic Substances and Disease Registry; ATSDR (2005))

7.9.2. Acute toxicity and Corrosion/Irritation

An assessment of the acute oral, dermal and inhalation toxicity of naphthalene is provided in this section. This includes a consideration of both systemic and site of contact effects (i.e. irritation to the respiratory tract).

7.9.2.1. Acute toxicity

Oral

The existing acute toxicity classification of naphthalene has not been reconsidered as part of this evaluation. However, an assessment of the haemolytic anaemia observed in animals and in humans after acute exposure has been made. The information in italics below has been taken from the ESR Review (EC 2003).

ESR Review of naphthalene (2003)

Acute toxicity studies in rats and mice are available. However, since these studies gave no information about haemolytic anaemia, they have not been included here. Studies in dogs are described below.

In an early poorly conducted study a single oral dose of 400 mg/kg or 1,500 mg/kg naphthalene was administered in the diet to two dogs (Zuelzer and Apt, 1949). On the eighth day there was a reduction of the haemoglobin to 6.6 gm/100 ml and 10.2 gm/100 ml (from 9.3 and 14.4 gm/100 ml) for the low and high dose, respectively. Both animals showed an increase in the number of Heinz bodies in erythrocytes, and reticulocytosis began on the 7th day reaching a maximum on the 10th day. Lethargy, vomiting and diarrhoea were also noted in the dog treated with the higher dose. Complete recovery was achieved 1-2 weeks after administration.

Information from the ESR Review about the acute toxicity of naphthalene in humans is as described in the following paragraphs.

There are a great many case reports in the literature of acute haemolytic anaemia produced by naphthalene. The signs and symptoms of haemolytic anaemia associated with naphthalene exposure are well described (e.g. Gosselin et al., 1984, Mack, 1989).

The first signs and symptoms of toxicity are usually dark urine, pallor, abdominal pain, fever, nausea, vomiting and diarrhoea. On clinical examination the liver and spleen were enlarged. Haematological effects are fragmentation of red blood cells with anisocytosis and poikilocytosis, jaundice, anaemia with a reduction in haemoglobin levels and haematocrit values and resulting reticulocytosis and leucocytosis. More severe reactions also include Heinz body formation, haemoglobinuria and mild methaemoglobinaemia. In young children deaths have occurred due to kernicterus (a severe neural condition associated with high levels of bilirubin in the blood). In older children and adults renal failure may occur. Liver damage has also been described, but as a rare occurrence.

Naphthalene was used in the past as an antihelminithic (antiparasitic) *agent. It has not been possible to obtain any details of this use, although some sources (e.g. ACGIH, 1991) indicate that the dose levels used were in the range 0.1-0.5 g three times daily, approximately equivalent to 4-20 mg/kg/day. However no other details are given, particularly with respect to whether or not there were any side effects at these dose levels.*

Twelve cases of oral ingestion by young children of naphthalene-containing mothballs have been reported (Melzer-Lange and Walsh-Kelly, 1989; Todisco, 1991; Zuelzer and Apt, 1949; Shannon and Buchannon, 1982; Zinkham and Childs, 1958; Mackell et al., 1951). The majority of the children were aged between 1-3 years. Seven were male and 2 female (the sex of the remaining three cases was not specified). The first signs of toxicity were usually seen within hours to up to 2 days after exposure. Haemolytic anaemia was diagnosed in all cases and signs and symptoms were similar to those described above, with haemoglobin levels falling to 2-6 g/100 ml in 10 cases (average haemoglobin concentration in children aged one year is 12.5 g/100 ml; Wright, 1971). No deaths occurred. In one case haemolysis was reported to have begun 24 to 72 hours after exposure (Shannon and Buchannon, 1982). G-6-PD deficiency was reported in all of the cases (8) in which it was investigated. The amount of naphthalene ingested was not known for any of these cases although consumption apparently ranged from between having sucked one mothball to approximately half its size to swallowing whole two to three mothballs. According to one review naphthalene mothballs usually weigh between 500 and 3,600 mg and contain 100% naphthalene (Mack, 1989). It should, however, be noted that further consumption, and

perhaps repeated exposure may have occurred without the knowledge of the parents. Thus no firm conclusions regarding any dose-response relationship can be drawn.

Quantitative details of intake levels of naphthalene producing effects in children are available in the secondary literature. However such data on doses received are old and are difficult to substantiate and therefore should be used with caution. For example, Sollmann (1957) mentions a very early report which apparently stated that 2 g naphthalene taken over a 2-day period killed a 2 year old child (Prochownik, 1911), but it has been impossible to obtain a copy of the original report.

A few cases of haemolytic anaemia following ingestion of naphthalene have also been reported in teenagers or adults. An early report described a case study of a 16 year old female who had deliberately consumed approximately 6 g of naphthalene, although it is not stated how this estimation was made (Gidron and Leurer, 1956). Within 12-hours she was suffering from abdominal pain and vertigo. On day 2 after the ingestion her erythrocyte count had approximately halved, her urine had darkened in colour and she complained of pain in the kidneys. Despite a blood transfusion on day 2 she had become jaundiced on day 3. Treatment, including another blood transfusion continued. By day 7 the jaundice had subsided. On day 8 her erythrocyte count began to rise and the urine returned to a normal colour. Pain in the kidneys was reported to have continued for "some days". G-6-PD status was not assessed. Based on the requirement for two blood transfusions it seems possible that the estimated 6 g of naphthalene ingested represents a lethal dose to humans.

Haemolytic anaemia (with no red blood cells being seen on blood microscopy) was reported in a female who had drunk approximately 50 ml of an oil which was reported to contain a "high concentration" of naphthalene (Ostlere et al., 1988). The female was apparently not G-6-PD deficient. Her sister also drank the oil and did not show any signs of toxicity.

A secondary literature source cited an incident occurring in 1902 in which severe pain in the bladder and a severe impairment in vision were reported within nine hours of a man taking 5 g unpurified naphthalene over a 13-hour period (Grant, 1974). Vision apparently remained severely impaired 1 year after the incident. Due to the age of the report, the unpurified nature of the naphthalene and the lack of other similar reports, despite its past use as a medicine, no conclusions should be drawn from this report.

Information found subsequent to the ESR Review

A literature search (covering the period from January 2008 - present) carried out by the eMSCA in August 2016 revealed no additional animal studies with naphthalene for this endpoint but seven case reports of individuals reporting a single exposure to naphthalene mothballs were found (Kapoor et al. 2014, Annamalai et al. 2012, Kundra et al. 2015, Lim et al. 2009, Roumieu et al. 2015, Chauhan et al. 2014, Deo et al. 2016).

In one of the reports, a 15 year old boy had accidentally consumed a single mothball (Deo et al. 2016). His symptoms were more severe than those in the other case studies, with a methaemoglobin level of 25.3%. However it is not clear when this measurement was taken in relation to mothball consumption. Medical staff found that he was glucose-6-phosphate dehydrogenase (G-6-PD)-deficient. This case study shows that consumption of a single mothball can result in severe acquired methaemoglobinaemia in a G-6-PD-deficient individual. The actual dose consumed by the individual is unknown.

The second report described a 33 year old female who had been complaining of fatigue (Roumieu et al. 2015). A marabout gave the female a potion containing seeds, pigeon and a mothball in an attempt to cure her fatigue, but the woman was taken to hospital three days later with a number of symptoms including fatigue, confusion and jaundice. She was diagnosed with regenerative normochromic, normocytic anaemia and haemolysis. G-6-PD and methaemoglobin levels were normal in this patient. Her symptoms improved following a transfusion of packed red blood cells and intravenous hydration.

The remaining 5 cases confirmed that naphthalene exposure can result in haemolytic anaemia in humans. The patients described in the case studies were between 2 and 29 years of age and had consumed mothballs (some accidentally; some deliberately). In the cases where the number of mothballs consumed was ascertained, the patients consumed between 3 and 12 mothballs. The symptoms presented were similar to those described above. No deaths were reported in these case studies. In one case, G-6-PD levels could not be measured due to patient refusal. In the four remaining cases, G-6-PD levels were normal.

NOAEL identification for acute oral toxicity

In contrast to the consistent reports describing cases of haemolytic anaemia in humans following oral exposure to naphthalene, haemolytic anaemia was not observed in experimental animals (rats and mice). Although evidence of haematotoxicity was found in dogs, the study was conducted poorly. Therefore there does not appear to be a suitable animal model. In March 2010, the Scientific Committee on Occupational Exposure Limits (SCOEL) produced a report on naphthalene. Regarding haemolytic anaemia, the SCOEL also concluded that, 'there are no useful experimental data from which to extrapolate to humans for this endpoint.'

Due to the lack of a suitable animal model, the uncertainty about the doses consumed by humans in cases of poisonings and the lack of exposure-response information, establishing a NOAEL or a LOAEL for systemic effects following acute exposure to naphthalene is not possible. On this basis and using the estimation of 6g of naphthalene as a lethal dose to humans, the eMSCA concurs with the conclusion in the ESR Review that values in the mg/kg range are considered to give rise to concern for acute haemolytic anaemia. Assuming a body weight of 60kg for a typical adult female, 6g of naphthalene (*Gidron and Leurer, 1956*) would equate to a lethal dose of 100 mg/kg bw.

Dermal

ESR Review of naphthalene (2003)

No information was available to inform specifically about the acute toxicity of naphthalene following dermal exposure.

Information found subsequent to the ESR Review

No new information is available.

Therefore the possibility of a systemic effect following exposure to naphthalene via the dermal route cannot be excluded.

Inhalation

ESR Review of naphthalene (2003)

No information was available to inform specifically about the acute toxicity of naphthalene following inhalation exposure.

Information found subsequent to the ESR Review

No new information is available.

Therefore the possibility of a systemic effect following exposure to naphthalene via the inhalation route cannot be excluded.

7.9.2.2. Corrosion/Irritation

The potential for naphthalene to cause skin and/or eye irritation has not been evaluated. The local effects of this substance on the respiratory tract following single or short term exposure have been considered below.

Irritation to the respiratory tract

ESR Review of naphthalene (2003)

No information on the respiratory tract irritation potential of naphthalene was presented in the ESR Review.

Information found subsequent to the ESR Review

Two studies have been conducted to provide information relevant to a consideration of the carcinogenic mechanism of action in rats.

Study in rats – 1 and 5 day(s) exposure, 6 hour duration

Dodd et al. (2010) administered naphthalene vapour to F344 and Sprague Dawley (SD) rats for either 1 day (6 hours) or 5 days (6 hours/day). Animals were sacrificed by intraperitoneal injection of phenobarbital and subsequent exsanguation on the day after the last exposure to naphthalene. Animals in recovery groups were sacrificed fourteen days after the last exposure to the test substance. In both the 1 day and 5 day studies, the nasal tissues underwent histopathological examination.

No clinical observations attributable to naphthalene exposure were reported during or following treatment for the 1-day and 5-day studies. Similarly, there were no significant exposure-related effects on bodyweight and no gross pathological lesions attributable to naphthalene exposure were observed.

(i) Five rats/sex/strain were exposed to naphthalene (99.9% pure) at 0, 0.1, 0.3, 1, 10 and 30ppm (equivalent to 0, 0.52, 1.57, 5.24, 52.4 and 157mg/m^3) for 6 hours (whole body exposure). Necrotic lesions were reported in both the olfactory and the respiratory epithelia.

Nasal olfactory epithelium necrosis was observed in a concentration-dependent manner from 0.52 mg/m^3 in SD rats and from 5.24 mg/m^3 in F344 rats, with severity grades ranging from minimal to moderately severe. The extent and severity of the lesions increased with dose according to the study author. However, quantitative data to substantiate this description are not available. The incidences of this effect are provided in the table below. The necrosis reported at 0.52 and 1.57 mg/m^3 was described as minimal and was also observed in one SD female control. At ≤ 1.57 mg/m^3, the lesions were not observed in every transverse section that was examined.

Table 9: Incidence of nasal olfactory epithelium lesions in rats following naphthalene exposure (Dodd et al. 2010)

Exposure concentration, mg/m^3	F344 Males	F344 Females	SD Males	SD Females
0	0/5	0/5	0/5	1/5
0.52	0/5	0/5	2/5	1/5
1.57	0/5	0/5	3/5	2/5
5.24	5/5	4/5	4/5	4/5
52.4	5/5	5/5	5/5	5/5
157	5/5	5/5	5/5	5/5

Nasal respiratory epithelium necrosis was first observed at 5.24 mg/m^3 in 1 male SD rat only and was described as minimal. At 52.4 mg/m^3, this effect was observed in all treated animals (both strains), as tabulated below. No quantitative information on the severity of these lesions is available.

Table 10: Incidence of nasal respiratory epithelium necrosis in rats following naphthalene exposure (Dodd et al. 2010)

Exposure concentration, mg/m^3	F344 Males	F344 Females	SD Males	SD Females
0	0/5	0/5	0/5	0/5
0.52	0/5	0/5	0/5	0/5
1.57	0/5	0/5	0/5	0/5
5.24	0/5	0/5	1/5	0/5
52.4	5/5	5/5	5/5	5/5
157	5/5	5/5	5/5	5/5

In conclusion, this study showed that the olfactory epithelium was a more sensitive target for naphthalene toxicity than the respiratory epithelium, and that the SD was a more sensitive strain than F344. Necrotic lesions in the olfactory epithelium were noted at all exposure levels in male and female SD rats following a single exposure to naphthalene. Additionally, olfactory epithelium necrosis was observed in one control female SD rat. Information on the severity of these lesions at different exposure levels was limited; no quantitative data were provided. It is possible that the effects observed at the lowest test concentration of naphthalene and in the control rat were all of minimal severity. However, from the data provided in this study, it is not possible to identify reliably a NOAEC. The lowest test concentration of 0.52 mg/m^3 is therefore considered conservatively to be a LOAEC under the conditions of this study.

(ii) Ten rats/sex/strain were similarly exposed to 0.1, 1 and 10ppm (equivalent to 0.52, 5.24 and 52.4 mg/m^3) naphthalene (99.9% pure) for 5 days (6 hours/day, whole body exposure). Five rats sex/strain were in the control group. Additionally, there were 5 rats/sex/strain and 10 rats/sex/strain in the 0 mg/m^3 and 52.4 mg/m^3 recovery groups, respectively.

Among these animals, effects on the nasal respiratory epithelium were not reported. However, nasal olfactory epithelium degeneration was characterised together with its relative position in the nasal cavity:

- Level III - ethmoid recess near anterior end of pharyngeal duct;
- Level IV - centre of ethmoid recess;
- Level V - posterior end of ethmoid recess and pharyngeal duct.

Lesions observed on the olfactory epithelium in this study were described as degenerative. Additionally, evidence of prior and ongoing necrosis was reported.

In SD rats at the lowest concentration (0.52 mg/m^3), nasal olfactory epithelium degeneration was observed in 2/10 test females and 0/10 males. No lesions were seen in controls. Necrotic lesions were seen in 10/10 females and 9/10 males at 5.24 mg/m^3 and in all animals at the top concentration (52.4 mg/m^3). The region of the nasal cavity characterised as level III was more sensitive than levels IV and V. Level III was closer to the front of the nasal cavity. The degenerative lesions were graded from minimal to moderately severe. Full details are provided in the table below.

At the lowest concentration (0.52 mg/m^3), nasal olfactory epithelium degeneration was not observed in F344 rats. However, this effect was observed at Level III of the nasal cavity in 8/10 male and 10/10 female F344 rats at 5.24 mg/m^3. At the top concentration (52.4 mg/m^3), nasal olfactory epithelium degeneration was more severe and more widespread than at the mid concentration, covering Levels III, IV and V as shown in the table below.

Table 11: Incidence and Severity of nasal Olfactory Epithelium Degeneration (Dodd et al. 2010)

	F344 Males	F344 Females	SD Males	SD Females
Location	0 mg/m^3			
Level III	0/5	0/5	0/5	0/5
Level IV	0/5	0/5	0/5	0/5
Level V	0/5	1/5 (0.2)**	0/5	0/5
	0.52 mg/m^3			
Level III	0/10	0/10	0/10	2/10 (0.2)
Level IV	0/10	0/10	0/10	0/10
Level V	0/10	0/10	0/10	0/10
	5.24 mg/m^3			
Level III	8/10 (0.8)	10/10 (1.0)	9/10 (0.9)	10/10 (1.0)
Level IV	0/10	0/10	0/10	0/10
Level V	0/10	0/10	0/10	0/10
	52.4 mg/m^3			
Level III	10/10 (2.7)	10/10 (2.9)	10/10 (2.8)	10/10 (2.7)
Level IV	10/10 (3.0)	10/10 (3.0)	10/10 (2.9)	10/10 (2.8)
Level V	4/10 (0.5)	7/10 (1.5)	9/10 (2.5)	7/10 (1.8)

** Values in parentheses denote the mean group severity score, where 0 = not remarkable, 1 = minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe and 5 = severe/high

Following a recovery period of 14 days, the incidence of nasal olfactory epithelium degeneration did not change in SD rats exposed to 52.4 mg/m^3 naphthalene for 5 days, or in Levels III and IV in F344 rats. A reduced incidence of this effect was observed in Level 5 of F344 rats only. However, the severity of the observed lesions did reduce in both strains of rat and was only minimal by the end of the recovery period as shown in table below.

Table 12: Nasal Olfactory Epithelium Degeneration in recovery groups (Dodd et al. 2010)

	F344 Males	F344 Females	SD Males	SD Females
Location	0 mg/m^3 + Recovery			
Level III	0/5	0/5	0/5	0/5
Level IV	0/5	0/5	0/5	0/5
Level V	2/5 (0.4)**	0/5	0/5	0/5
	52.4 mg/m^3 + Recovery			
Level III	10/10 (1.0)	10/10 (1.1)	10/10 (1.0)	10/10 (1.1)
Level IV	10/10 (1.1)	10/10 (1.1)	10/10 (1.0)	10/10 (1.2)
Level V	1/10 (0.1)	3/10 (0.3)	9/10 (0.9)	8/10 (0.8)

** Values in parentheses denote the mean group severity score, where 0 = not remarkable, 1 = minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe and 5 = severe/high

In SD rats, nasopharyngeal goblet cell hyperplasia/hypertrophy was observed in both sexes at the top dose only.

In F344 rats, goblet cell hyperplasia/hypertrophy was observed in 1/10 males and 1/10 females at the lowest concentration (minimal severity), in 2/10 males and 1/10 females at the next concentration (minimal severity) and in all animals at the highest concentration (minimal to mild severity), as tabulated below.

Table 13: Incidence and severity of nasopharyngeal goblet cell hyperplasia/hypertrophy (Dodd et al. 2010)

	F344 Males	F344 Females	SD Males	SD Females
Location	0 mg/m^3			
Level IV	0/5	0/5	0/5	0/5
Level V	0/5	0/5	0/5	0/5
	0.52 mg/m^3			
Level IV	0/10	0/10	0/10	0/10
Level V	1/10 (0.1)**	1/10 (0.1)	0/10	0/10

	5.24 mg/m^3			
Level IV	2/10 (0.2)	1/10 (0.1)	0/10	0/10
Level V	1/10 (0.1)	1/10 (0.1)	0/10	0/10
	52.4 mg/m^3			
Level IV	10/10 (1.6)	7/10 (1.2)	1/10 (0.1)	3/10 (0.3)
Level V	10/10 (2.0)	10/10 (2.0)	5/10 (0.6)	8/10 (0.8)

** Values in parentheses denote the mean group severity score, where 0 = not remarkable, 1 = minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe and 5 = severe/high

Nasopharyngeal goblet cell hyperplasia/hypertrophy was observed in 2 F344 rats (1 male and 1 female) at 0.52 mg/m^3. However the mean group severity score of this lesion was only 0.1 in both sexes. Furthermore, although this lesion was not observed in control animals in the main phase of the study, it was observed at the end of the recovery period in 1/5 male F344 control rat and therefore the effect observed at 0.52 mg/m^3 is not considered to be treatment-related.

Following a 14 day recovery period, complete recovery from nasopharyngeal goblet cell hyperplasia/hypertrophy was observed in SD rats (both sexes) exposed to 52.4 mg/m^3 naphthalene. In F344 rats, recovery from these effects was not complete after 14 days but there were reductions in incidence and severity of this lesion as shown in the table below.

Table 14: Incidence and severity of nasopharyngeal goblet cell hyperplasia/hypertrophy in recovery groups (Dodd et al. 2010)

	F344 Males	F344 Females	SD Males	SD Females
Location	0 mg/m^3 + Recovery			
Level IV	1/5 (0.2)**	0/5	0/5	0/5
Level V	1/5 (0.2)	0/5	0/5	0/5
	52.4 mg/m^3 + Recovery			
Level IV	7/10 (0.8)	6/10 (0.8)	0/10	0/10
Level V	5/10 (0.7)	10/10 (1.5)	0/10	0/10

** Values in parentheses denote the mean group severity score, where 0 = not remarkable, 1 = minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe and 5 = severe/high

In conclusion, nasal olfactory epithelium degeneration was observed in 2/10 SD females at the lowest concentration (0.52 mg/m^3) and therefore a NOAEC cannot be identified from this study. The effects observed at 0.52 mg/m^3 occurred at a low incidence and severity and therefore 0.52 mg/m^3 is considered to be a conservative LOAEC.

4 hour exposure

In order to assess whether the route of exposure affected the pattern of non-neoplastic nasal lesions in rats, Lee et al. (2005) exposed male SD rats to naphthalene by inhalation (described here) and by intraperitoneal injection (described in section 7.9.2.2.2). In order to characterise the lesions and allow a comparison between the routes of exposure, higher concentrations of naphthalene were administered in this study compared to in the previous studies.

Male rats (6 /group) were exposed to filtered air (controls) and naphthalene (dissolved in acetonitrile) at concentrations of 3.4±0.5 ppm or 23.8±1.7 ppm (equivalent to 17.8±2.6 mg/m^3 and 125±8.9 mg/m^3) for 4 hours. All rats were sacrificed using sodium phenobarbital and exsanguination 24 hours after exposure to naphthalene. The anterior and posterior parts of the nasal cavity were examined histopathologically and the observations are provided in the table below.

Effects on the olfactory epithelium were not observed in rats exposed to filtered air.

24 hours after exposure to 17.8 mg/m^3 naphthalene, observations of severe cellular lesions were confined to the olfactory mucosa only. A correlation between injuries and the pattern

of airflow in the nasal cavity was established, with more severe injuries being observed in the anterior part of the nasal passage in comparison to the posterior part.

Table 15: Lesions of the olfactory epithelium in rats following a 4 hour exposure to naphthalene via inhalation, Lee et al. (2005)

	Anterior part of nasal passage	Posterior part of nasal passage
Controls	none	none
17.8 mg/m^3	• Continuity of the olfactory mucosa was broken by areas of necrotic olfactory receptor cells • Reduced volume of cytoplasm from sustentacular cells above the nuclei • Vacuoles in the olfactory epithelium • Patches of exfoliated cells • Injury was confined around the dorsal medial meatus	• Continuity of the olfactory mucosa was broken by areas of necrotic olfactory receptor cells • Reduced volume of cytoplasm from sustentacular cells above the nuclei • Vacuoles in the olfactory epithelium • Injury was confined around the dorsal medial meatus
125 mg/m^3	• Numerous exfoliated cells and cell debris trapped in the nasal passage	• Numerous exfoliated cells and cell debris trapped in the nasal passage • Numerous intraepithelial vacuoles • Reduced volume of cytoplasm from sustentacular cells of the dorsal medial meatus Injury at this dose was not evenly distributed across the posterior part of the nasal passage. Lesions extended ventrally along the medial meatus.

Since lesions were observed at both concentrations, the results of this study do not allow a NOAEC to be identified. However, the study demonstrates that following inhalation exposure to naphthalene, the extent of lesions on the olfactory epithelium of rats correlates with the pattern of airflow.

NOAEC identification for irritation to the respiratory tract following inhalation exposure

The available information does not allow a NOAEC to be identified because lesions were observed at all concentrations in the short term inhalation studies. However, since lesions at the lowest concentration level occurred at a low incidence and appear to have been of low severity (Dodd et al. 2010), 0.52 mg/m^3 has been identified as a conservative LOAEC.

Additional information: intraperitoneal route

To analyse the effects of systemic exposure, naphthalene (in corn oil) was administered to rats (3/group) at doses of 0, 25, 50, 100 or 200 mg/kg bw by intraperitoneal injection (Lee et al. 2005). All rats were sacrificed using sodium phenobarbital and exsanguination 24 hours after exposure to naphthalene. The anterior and posterior parts of the nasal cavity were examined histopathologically.

Adverse effects on the olfactory epithelium were observed at 100 and 200 mg/kg bw only. The injuries at this dose level were more widespread than those occurring after inhalation. A greater degree of injury was observed in the posterior region compared to the anterior region as shown in the table below.

Table 16: Lesions of the olfactory epithelium in rats following exposure to naphthalene via intraperitoneal injection, Lee et al. (2005)

	Anterior part of nasal passage	Posterior part of nasal passage
0, 25, 50 mg/kg bw	none	none
100 mg/kg bw	Although widespread injury was reported in this region, no further details were provided.	<u>Dorsal medial meatus</u> • Occasional degeneration of sustentacular cell cytoplasm • Intraepithelial vacuoles <u>Rest of olfactory epithelium</u> • Extensive exfoliation • Large vacuoles and loss of cilia in ciliated columnar cells
200 mg/kg bw	Although widespread injury was reported in this region, no further details were provided.	• Severe cellular exfoliation across this region (including basal cells) • Large vacuoles and loss of cilia in ciliated columnar cells

Since similar effects were observed in rats following exposure to naphthalene by inhalation and intraperitoneal exposure, the results suggest that the lesions may be attributable to local metabolism and are not necessarily site-of-contact effects.

In this study, values of 50 mg/kg bw and 100 mg/kg bw can be identified for the NOAEL and LOAEL, respectively.

7.9.3. Sensitisation

Not evaluated.

7.9.4. Repeated dose toxicity

Studies evaluated as part of the ESR Review have not been re-evaluated. The descriptions of the findings reported in the ESR Review have been copied and included in italics below for information.

7.9.4.1. Summary and discussion of repeated-dose toxicity

Oral

ESR Review of naphthalene (2003)

Studies in rats, mice and rabbits are available. However, these do not provide any information on haemolytic anaemia or non-neoplastic nasal lesions and have therefore not been included in this evaluation. Rodents do not appear to be a suitable model for naphthalene-induced haemolytic anaemia in humans.

Studies in dogs

7 day study

In a poorly conducted study with no controls, an average daily dose of 220 mg/kg/day was administered in the diet to a single dog over 7 days (Zuelzer and Apt, 1949). During an

observation period of 36 days, lethargy, ataxia and diarrhoea were observed beginning on the fifth day of treatment. Also on the fifth day of treatment the white blood cell count rose from 14,400 to 25,500 and Heinz bodies appeared in the majority of erythrocytes. On the ninth day there was a reduction of the haemoglobin to 2.4 gm/100 ml, red blood cell count to 1.3.106 and haematocrit to 7.5 volumes % (from 13.1 gm/100 ml, 6.78.106 and 41.5, respectively). The clinical signs and reductions in haematological parameters resolved over 36 days. An optical examination was not conducted.

Haemolytic anaemia was observed in a 15 year old male who was reported to have developed a liking for sucking naphthalene mothballs and a 19 year old female who "intermittently sucked and chewed" naphthalene mothballs during her pregnancy (Zinkham and Childs, 1958). Signs and symptoms were the same as those described for acute ingestion of naphthalene. Both individuals were G-6-PD deficient. There was no indication of level or duration of exposure in either case.

Information found subsequent to the ESR Review

No new information is available.

Dermal

ESR Review of naphthalene (2003)

No information specifically on dermal exposure is available, although dermal exposure to naphthalene solid and vapour may have occurred in the studies summarised in the inhalation section.

Information found subsequent to the ESR Review

No new information is available.

Inhalation

ESR Review of naphthalene (2003)

Studies in rats

13 week study

In a well conducted unpublished study, groups of 10 male and 10 female rats were exposed nose only for 6 hours/day, 5 days a week for 13 weeks to 0, 2, 10 or 58 ppm (approximately 0, 10, 50 or 300 mg/m^3) vapourised naphthalene (Huntingdon Research Centre, 1993a). A gross pathological examination was carried out on a wide range of tissues and a microscopic examination was carried out on a range of tissues including the lungs, liver, kidneys, adrenals, testes, eyes and optic nerve. Prior to terminal sacrifice, samples of blood were taken from all rats for haematological and clinical chemistry evaluation. In high dose animals body weight gain was reduced by 43% and 34% in males and females, respectively and was associated with reduced food consumption. There were no toxicologically significant haematological or clinical chemistry findings observed. Similarly, no significant changes were noted in organ weight or gross pathology.

Microscopic analysis of the nasal epithelium revealed treatment-related effects at all dose levels. The severity of the effects was dose-related. At the highest exposure level (300 mg/m^3) changes included erosion of the olfactory epithelium, hyperplasia of basal cells in the olfactory epithelium and loss of Bowmans' glands. At the lowest exposure level (10 mg/m^3) changes in olfactory epithelium were less marked but included slight disorganisation, mild erosion (in one rat), minimal atrophy, rosette formation (an attempt

at proliferative repair by the olfactory neuroepithelium), occasional degenerate cells, loss of Bowmans' glands and minimal hyperplasia. There were no treatment related effects observed in the lungs or nasal respiratory epithelium at this dose. There were no observed changes in the nasal passages of control animals. In one low dose rat there was evidence of squamous metaplasia of the respiratory epithelium, however as this lesion was not seen in the other rats at higher doses this lesion was not considered toxicologically significant. The effects at 10 mg/m^3 were generally minimal in severity and seen in only small numbers of animals, and therefore appear to represent the low end of the dose-response curve for nasal effects. Overall, signs of damage to the olfactory epithelium were seen at all doses down to 10 mg/m^3 (2 ppm), and a NOAEL cannot be identified for local effects.

4 week study

In a well conducted unpublished study, groups of 5 male and 5 female rats were exposed nose only for 6 hours/day, 5 days a week for 4 weeks to 0, 1, 3, 10, 29 or 71 ppm (approximately 0, 5, 15, 50, 150 or 370 mg/m^3) vapourised naphthalene (Huntingdon Research Centre, 1993b).

Investigations were similar to the 13-week study performed in the same laboratory. Results were similar to those observed in the 13-week study. High dose animals showed approximately a 50% reduction in body weight gain associated with reduced food consumption. There was no evidence of systemic toxicity. Local effects were observed with signs of proliferative repair in the nasal olfactory epithelium changes observed at all doses down to 5 mg/m^3 (1 ppm), and therefore a NOAEL for local effects cannot be identified.

For both the 4 and 13-week studies the mechanism by which the observed effects in the olfactory nasal epithelium arise is unclear, although the effects may be mediated by locally produced metabolite(s) of naphthalene. The relevance of these effects to human health is uncertain, as there may be significant species differences in local metabolism. However, there is no evidence to indicate that these effects are not relevant to human health.

105 week toxicity/ carcinogenicity study (US NTP study)

Groups of 49 male and 49 female F344/N rats were exposed to 0, 10, 30 or 60 ppm naphthalene vapour (>99% pure) (approximately equivalent to 0, 50, 150 or 300 mg/m^3) in inhalation chambers for 6 hours/day, 5 days/week for 105 weeks (NTP, draft report 2000[17]). Additional groups of 9 male and 9 female rats were exposed to 10, 30 or 60 ppm naphthalene for 18 months for evaluation of toxicokinetic parameters.

In this study, the vapour generator was comprised of a heated mantle surrounding a glass reaction flask. Heated nitrogen was metered into the flask to carry the vapourised naphthalene out of the generator. The temperature of the bulk chemical was maintained below the melting point and the temperature of the vapour above the bulk naphthalene was maintained between 66° and 71°C. The vapour was carried into the exposure room via a heated Teflon line.

All animals were observed twice daily with clinical findings and body weights recorded every 4 weeks beginning at week 4 and every 2 weeks beginning at week 92. Complete necropsy and microscopic examinations were performed on all core study animals.

Survival rates of all exposed groups were similar to those of chamber controls. Survival rates at the end of the study in control, low, medium and high dose males were 24/49, 22/49, 23/49 and 21/49, respectively. The corresponding rates in the females were 28/49, 21/49, 28/49 and 24/49, respectively. At termination, mean body weights of all exposed

[17] Only the draft report was available at the time of the ESR Review the eMSCA has checked the final version of the report and made a couple of minor changes to the ESR Review text included in this document.

groups of male rats were 4-11% lower than those of controls. No significant differences were noted in mean body weights of the treated females compared to control animals. There were no treatment-related clinical signs of toxicity in any of the treatment groups.

The incidences of a variety of non-neoplastic lesions of the nasal tract in both sexes were statistically significantly greater in naphthalene exposed animals than controls. These lesions included, in the olfactory epithelium: atypical (basal cell) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration; in the respiratory epithelium: hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia; and glandular hyperplasia and squamous metaplasia. In general, the severity of the olfactory and glandular lesions increased with increasing exposure concentrations.

Since lesions were observed at all concentration levels in this study, it is not possible to identify a NOAEC.

Further to the summary above, the eMSCA considers the following data from the NTP study relevant for the evaluation of naphthalene-induced carcinogenicity. The incidences and severity of the observed non-neoplastic effects are provided in the three following tables.

Table 17: Incidence and severity of non-neoplastic effects in the olfactory epithelium (NTP, 2000)

Sex	Males				Females			
Dose/ mg/m^3	**0**	**52.4****	**157**	**314**	**0**	**52.4**	**157**	**314**
Atypical hyperplasia	0/49	48/49 (2.1)*	45/48 (2.5)	46/48 (3.0)	0/49	48/49 (2.0)	48/49 (2.4)	43/49 (2.9)
Atrophy	3/49 (1.3)	49/49 (2.1)	48/48 (2.8)	47/48 (3.5)	0/49	49/49 (1.9)	49/49 (2.7)	47/49 (3.2)
Chronic inflammation	0/49	49/49 (2.0)	48/48 (2.2)	48/48 (3.0)	0/49	47/49 (1.9)	47/49 (2.6)	45/49 (3.4)
Hyaline degeneration	3/49 (1.3)	46/49 (1.7)	40/48 (1.7)	38/48 (1.5)	13/49 (1.1)	46/49 (1.8)	49/49 (2.1)	45/49 (2.1)
Neuroblastoma	0/49	0/49	4/48	3/48	0/49	2/49	3/49	12/49

* The values in parentheses denote the average severity of the effect in affected animals where 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
( ) The average severity of the lesions was calculated by dividing the total severity score for a particular exposure by the total number of animals examined.
** The exposure concentrations in this table differ very slightly from the values provided in the text from the ESR Review. The values in the table above were converted from ppm to mg/m^3 using a conversion factor of 5.24 (IARC Monographs Volume 82) whereas a conversion factor of 5 was used in the ESR Review.

Table 18: Incidence and severity of non-neoplastic effects in the respiratory epithelium (NTP, 2000)

Sex	Males				Females			
Dose/ mg/m^3	**0**	**52.4****	**157**	**314**	**0**	**52.4**	**157**	**314**
Hyperplasia	3/49 (1.0)*	21/49 (2.2)	29/48 (2.0)	29/48 (2.2)	0/49	18/49 (1.6)	22/49 (1.9)	23/49 (1.7)
Squamous metaplasia	0/49	15/49 (2.1)	23/48 (2.0)	18/48 (1.8)	0/49	21/49 (1.6)	17/49 (1.5)	15/49 (1.8)
Hyaline	0/49	20/49	19/48	19/48	8/49	33/49	34/49	28/49

degeneration		(1.2)	(1.4)	(1.2)	(1.0)	(1.2)	(1.4)	(1.2)
Goblet cell hyperplasia	0/49	25/49 (1.3)	29/48 (1.2)	26/48 (1.2)	0/49	16/49 (1.0)	29/49 (1.2)	20/49 (1.0)
Adenoma	0/49	6/49	8/48	15/48	0/49	0/49	4/49	2/49

* The values in parentheses denote the average severity of the effect in affected animals where 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Table 19: Incidence and severity of non-neoplastic effects in the nasal cavity (NTP, 2000)

Sex	Males				Females			
Dose/ mg/m^3	**0**	**52.4**	**157**	**314**	**0**	**52.4**	**157**	**314**
Glandular hyperplasia	1/49 (1.0)*	49/49 (2.2)	48/48 (2.9)	48/48 (3.5)	0/49	48/49 (1.9)	48/49 (3.1)	42/49 (3.3)
Glandular squamous metaplasia	0/49	3/49 (3.0)	14/48 (2.1)	26/48 (2.5)	0/49	2/49 (2.0)	20/49 (2.5)	20/49 (2.8)

* The values in parentheses denote the average severity of the effect in affected animals where 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Neoplastic effects are reported in Section 7.9.6.

Studies in mice

14 day study

Groups of between 4 and 10 male and female B6C3F1 mice were exposed to 0, 10 or 30 ppm naphthalene by inhalation for 6 hours daily, 5 days a week for 14 days (NTP, 1992). It was stated that no biologically significant changes in haemolytic parameters were observed at any dose level. Other signs of toxicity were not assessed and a general NOAEL cannot be identified from this limited study.

104 week carcinogenicity study (US NTP study)

*In a carcinogenicity study by the same group of workers, groups of 140/*dose *B6C3F1 mice were exposed to 0 or 10 ppm/day (0, 50 mg/m^3/day) and groups of 270/*dose *to 30 ppm/day (150 mg/m^3/day) naphthalene vapour for 6-hours/day, 5 days/week for up to 104 weeks (NTP, 1992). All animals were observed daily and body weights recorded at least monthly. Necropsy was performed on all animals. Complete histopathological examinations were performed on control and high exposure concentration animals and on all animals found dead or killed moribund prior to the end of the study. Histopathology of the lungs and nasal cavities was also performed on low exposure concentration mice. Serial slit-lamp biomicroscopy and indirect ophthalmoscopic examinations were performed on 5 animals of each sex from all groups at 6-month intervals.*

Survival rates were generally good, particularly in the exposed groups. Survival of control males was significantly lower than exposed males. Survival rates at the end of the study in control, low and high dose males were 26/70, 52/69 and 118/133, respectively. The corresponding rates in the females were 59/69, 57/65 and 102/135, respectively. (The low survival in the control males was reported to be due to "wound trauma" and secondary infection resulting from increased fighting in the group). No significant differences were noted in mean body weights of the treated animals compared to control animals. There were no treatment-related clinical signs of toxicity in any of the treatment groups and there

were no treatment-related ocular changes in any of the selected animals throughout the study.

Non-neoplastic changes were only seen in the lungs and nose. A dose-related increase in alveolar and bronchial inflammation (3/139 (2%); 34/134 (25%); 108/270 (40%)[18] in 0, 10 and 30 ppm groups) with macrophage accumulation, lymphocyte infiltration and alveolar epithelial hyperplasia was noted in all groups. The severity of the lung effects was described as minimal to mild but was reported to be more pronounced in exposed animals than controls. Virtually all of the exposed animals, and none of the controls, showed nasal epithelium inflammation with olfactory epithelium metaplasia and respiratory epithelium hyperplasia in the nose. These effects mainly occurred in the posterior nasal cavity and were described as minimal to mild.

Since lesions were observed in all exposure groups, a NOAEC cannot be identified from this study.

Further to the summary above, the eMSCA considers that the following data are relevant, summarising the incidences of non-neoplastic lesions in the nasal cavity of mice (NTP, 1992).

Table 20: Incidence and severity of non-neoplastic findings in the nasal cavity in mice exposed to naphthalene for 2 years (NTP, 1992)

Sex	Males			Females		
Dose (mg/m^3)	**0**	**52.4****	**157**	**0**	**52.4**	**157**
Chronic inflammation	0/70	67/69 (2.2)*	133/135 (2.6)	1/69 (2.0)	65/65 (2.3)	135/135 (2.4)
Metaplasia of the olfactory epithelium	0/70	66/69 (2.5)	134/135 (2.6)	0/69	65/65 (2.5)	135/135 (2.4)
Hyperplasia of the respiratory epithelium	0/70	66/69 (2.6)	134/135 (2.8)	0/69	65/65 (2.5)	135/135 (2.7)

* Denotes average severity grade, where 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
** The exposure concentrations in this table differ very slightly from the values provided in the text from the ESR Review. The values in the table above were converted from ppm to mg/m^3 using a conversion factor of 5.24 (IARC Monographs Volume 82) whereas a conversion factor of 5 was used in the ESR Review.

Neoplastic findings are described in Section 7.9.6.

Human information

Several cases of adverse health effects have been reported following repeated exposure to naphthalene. The principal route of exposure appears to be inhalation although dermal exposure to the vapour may also have occurred and the possibility of additional oral exposure cannot be discounted.

Eighteen cases of haemolytic anaemia, following exposure to naphthalene vapours, have been reported (Shannon and Buchannon, 1982; Valaes et al., 1963; Dawson et al., 1958; Cock, 1957; Grigor et al., 1966). The majority of the cases were neonates. Fourteen were male and 4 female. Exposure to naphthalene vapour was via clothing and blanketing which had been stored with naphthalene mothballs. The signs and symptoms of anaemia were

[18] Value changed from that reported in ESR Report (108/170, 63%) as that appears to have been an error.

as described above in Section 7.9.2.1*. Two cases of neonatal kernicterus were reported and death occurred in one of the neonates. G-6-PD deficiency was reported in 11/17 cases where it was investigated. One study, which included 6 neonates who were G-6-PD deficient and another 7 who were not, stated that the haemolysis was more severe in those who were deficient (Valaes et al., 1963). The level and duration of exposure was not known in any of these cases, although hospital admissions were commonly made within two weeks of birth. Dermal exposure to solid naphthalene may have occurred in one case for which it was stated that the clothing was "impregnated" with naphthalene mothballs (Dawson et al., 1958).*

No conclusions can be drawn, with respect to the role of naphthalene exposure, from a single case report of aplastic anaemia in a 68-year old woman, who had been employed in a clothing resale shop for 39 years, where she was exposed to paradichlorobenzene and naphthalene (Harden and Baetjer, 1978).

A poorly reported paper described eye effects in a group of 21 workers who were involved in manual processes where they came into contact with solid, molten and presumably vaporised naphthalene (Ghetti and Mariani, 1956). The exposure duration is unclear from the report but appears to vary from 1-5 years. Optical lens opacities were noted in 8 workers. However "almost all" of the lesions were pin-point peripheral opacities of the nucleus of the lens, which "largely unaffected" the vision of the individuals. These opacities were described as "slight" (could only be detected by slit lamp). Also, the individuals themselves were reported to be unaware of any damage. However details of two of the cases were presented, and in these two cases cataracts and more marked diffuse opacities were reported. Overall it is not clear from the information provided, whether the effects reported were in excess of that expected in the general population.

A secondary literature source (Grant, 1974) reported three cases of decreased visual acuity, chorioretinitis or lens cataract formation in men occupationally exposed to naphthalene during the early 1900s (Van der Hoeve, 1906; Gottstein et al., 1926). Other signs of naphthalene toxicity did not occur and naphthalene exposure levels (to the solid and/or vapour) were not known. Similarly Gosselin (1984) cited another early reference which apparently claimed that corneal ulceration and cataracts were noted in a worker who had been exposed to naphthalene vapour and dust (Adams and Henderson, 1930). No conclusions as to the potential of naphthalene to cause eye damage can be drawn from these early case reports in view of the lack of information on exposure to other chemical or physical agents which may act as confounders.

Information found subsequent to the ESR Review

Studies in rats

90 day inhalation study

Since the publication of the ESR Review, one key repeated dose inhalation toxicity study has been conducted in rats.

F344 rats (10/sex/group) were exposed to naphthalene vapour (99.9% pure) at concentrations of 0, 0.1, 1, 10 and 30 ppm (equivalent to 0, 0.52, 5.24, 52.4 and 157 mg/m^3) for 90 days (6h/day, 5 days/week, whole body exposure). Animals were sacrificed on the day after the last exposure to naphthalene (Dodd et al. 2012).

Additional groups of animals were retained for a recovery period of 4 weeks. There are some inconsistencies in the report relating to the recovery groups, but there appears to have been a recovery group for all exposure levels (10 rats/ sex/ exposure group).

According to the study authors, the results were similar in both sexes. However, data were presented for males only, therefore statements on 'both sexes' relate to the study authors' conclusions.

Nasal tip and Level I of the nasal cavity (transitional/respiratory epithelium)

Low grade inflammation was observed at the nasal tip and Level I of the nasal cavity (transitional/respiratory epithelium) in controls and all exposure groups. The study authors considered that these findings were not treatment-related. The eMSCA concurs with this view and thus on this basis it is considered that there were no treatment-related nasal lesions observed in rats exposed to 0.52 mg/m^3 in this study.

Olfactory epithelium

No effects on the olfactory epithelium were observed in either sex exposed to 5.24 mg/m^3 naphthalene, as shown the table below. At 52.4 and 157 mg/m^3, lesions of the olfactory epithelium including necrosis and degeneration were observed in both sexes. A 'prominent' basal cell hyperplasia was described as occurring in association with the degeneration of the olfactory epithelium. Effects reported in this study occurred in a concentration-related manner.

Table 21: Incidence and severity of lesions of the olfactory epithelium in male rats following exposure to naphthalene by inhalation for 90 days

Exposure (mg/m^3)	0	0.52	5.24	52.4	157
Level II					
Basal cell hyperplasia	-	-	-	7/10 (1.0)	10/10 (1.7)
Degeneration/necrosis	-	-	-	8/10 (1.5)	10/10 (1.7)
Level III					
Basal cell hyperplasia	-	-	-	8/10 (0.8)	10/10 (1.9)
Degeneration/necrosis	-	-	-	10/10 (1.4)	10/10 (2.3)
Level IV					
Basal cell hyperplasia	-	-	-	9/10 (1.0)	10/10 (2.1)
Degeneration/necrosis	-	-	-	10/10 (2.0)	10/10 (2.7)
Level V					
Basal cell hyperplasia	-	-	-	6/10 (0.6)	10/10 (2.0)
Degeneration/necrosis	-	-	-	9/10 (1.1)	10/10 (1.8)

Residual olfactory epithelial degeneration and basal cell hyperplasia were observed in the recovery groups although there were small reductions in the severity and incidence of these lesions at the end of the recovery period, as tabulated below.

Table 22: Incidence and severity of lesions of the olfactory epithelium in the recovery groups of male rats following exposure to naphthalene by inhalation for 90 days and 4 subsequent weeks of recovery

Exposure (mg/m^3)	0	0.52	5.24	52.4	157
Level II					
Basal cell hyperplasia	-	-	-	8/9 (0.89)	8/10 (1.9)
Degeneration/necrosis	-	-	-	6/9 (0.89)	8/10 (1.3)
Level III					
Basal cell hyperplasia	-	-	-	7/9 (0.78)	10/10 (1.9)
Degeneration/necrosis	-	-	-	9/9 (1.0)	10/10 (1.7)
Level IV					
Basal cell hyperplasia	-	-	-	6/9 (0.67)	10/10 (1.8)
Degeneration/necrosis	-	-	-	8/9 (0.89)	10/10 (1.4)
Level V					
Basal cell hyperplasia	-	-	-	2/9 (0.22)	9/10 (1.4)
Degeneration/necrosis	-	-	-	-	6/10 (0.6)

Transitional/respiratory epithelium

In animals exposed to 5.24 mg/m^3 naphthalene vapour, there was minimal hyperplasia in the transitional/ respiratory epithelium, as shown in the table below. At 52.4 and 157 mg/m^3, mild hyperplasia and minimal squamous metaplasia were observed in the respiratory epithelium.

Table 23: Incidence and severity of lesions of the transitional/respiratory epithelium in rats following exposure to naphthalene by inhalation for 90 days

Exposure (mg/m^3)	0	0.52	5.24	52.4	157
Level I					
Inflammation	6/10 (0.8)	6/10 (0.9)	5/10 (0.8)	5/10 (0.6)	4/10 (0.4)
Level II					
Squamous metaplasia	-	-	-	8/10 (0.9)	8/10 (0.8)
Hyperplasia	-	-	10/10 (1.0)	10/10 (1.4)	10/10 (1.4)

At the end of the 4 week recovery period, there was complete recovery from squamous metaplasia and hyperplasia in the transitional/ respiratory epithelium with the exception of a single observation of hyperplasia in a male who had been exposed to 52.4 mg/m^3 naphthalene, as shown in the table below.

Table 24: Incidence and severity of lesions of the transitional/ respiratory epithelium in the recovery groups of rats following exposure to naphthalene by inhalation for 90 days and 4 subsequent weeks of recovery

Exposure (mg/m^3)	0	0.52	5.24	52.4	157
Level I					
Inflammation	5/10 (0.6)	6/10 (0.7)	6/10 (0.7)	8/9 (1.0)	8/10 (0.9)
Level II					
Squamous metaplasia	-	-	-	-	-
Hyperplasia	-	-	-	1/9 (0.11)	-

In addition to the observations tabulated above, goblet cell hyperplasia was observed in the nasopharyngeal ducts of a small number of rats exposed to 5.24, 52.4 and 157 mg/m^3 naphthalene. After 4 weeks of recovery, this lesion was observed in a single male at 52.4 mg/m^3 only.

Conclusion

Since no treatment-related effects were reported at the lowest level of exposure, a NOAEC of 0.52 mg/m^3 has been identified from this study.

13 week Inhalation study

In addition, the same group of scientists exposed F344 rats (5/sex/group) to 0, 0.1, 1, 10 and 30 ppm naphthalene (equivalent to 0, 0.52, 5.24, 52.4 and 157 mg/m^3) for 6 hours per day 5 days per week for 13 weeks (Meng et al. 2011). Limited information about the observed effects on the respiratory and olfactory epithelia is available because the primary aim of this study was to investigate whether naphthalene increased mutations in the p53 tumour suppressor gene in the nasal tissues of rats. However, the observed effects appear to be consistent with those observed in the new key study described above (Dodd et al. 2012). At 5.24 mg/m^3, minimal hyperplasia was observed in the transitional/ respiratory epithelium. From 52.4 mg/m^3, adverse effects were observed in both the olfactory and respiratory epithelia.

This study supports a NOAEC of 0.52 mg/m^3 in rats for non-neoplastic lesions in the nasal cavity following exposure to naphthalene.

Information found subsequent to the ESR Review

Human information

Bio-monitoring study

Recently, a biomonitoring study of workers exposed to naphthalene in the abrasives industry has been conducted (Sucker et al. 2016). This cross-sectional study (dated 28/10/16) was conducted by the IPA (Institut für Prävention und Arbeitsmedizin der Deutschen Gesetzlichen Unfallversicherung). Three production plants in Germany and two in Austria were included in the study. As detailed in Section 7.12.1.1.5 of this Evaluation Report, a variety of short-term (15-min TWA) and full-shift (8-hour TWA) inhalation exposures were measured in different work areas in these factories. Exposures for the highest exposure group were in the ranges 3.47-69.6 mg/m^3 (15-min TWA) and 3.62-11.58 (mg/m^3 (8-hour TWA). Some exposures therefore exceeded national workplace limits. The study aimed to identify any clinical signs of toxicity related to naphthalene exposure over a 3-month period in 2014. In particular, there was a focus on signs of irritation and/or inflammation of the nasal mucosa. The study was not designed to provide information on whether any observed nasal lesions might have potential to progress to nasal tumours.

The potential effect of naphthalene exposure on the blood system was not investigated in this study.

The study was conducted from 20th July to 23rd October 2014. This period included the least favourable exposure conditions (i.e. seasonally high naphthalene exposure levels due to high exterior temperatures) and avoided the possibility of seasonal effects such as those that might arise from environmental allergens (especially pollen in the spring) or seasonal respiratory tract infections (mainly in winter).

Effects potentially related to naphthalene exposure were identified via a combination of questionnaires (filled in by study participants) and medical examinations. Medical examinations took place before workers started their shift on Mondays and after the workers finished their shift on Thursdays. The examinations were conducted by a healthcare professional and comprised of the following:

- otorhinolaryngological examinations to identify clinical signs of irritation/inflammation and damage to the nasal mucosa, including endoscopy of the nasopharyngeal cavity and acoustic rhinometry, and investigation of the sensitivity of the nasal mucosa;
- investigation of the olfactory response to identify clinical signs of an impaired sense of smell;
- investigation of biomarkers in the nasal lavage, sputum and blood to assess possible subclinical signs of irritation/inflammation and damage to the upper respiratory tract due to reactive metabolic products and oxidative stress;
- investigation of naphthalene odour perception to identify habituation effects;
- recording the subjective perception of naphthalene exposure in terms of the intensity of olfactory (odour intensity, nuisance level, nausea) and trigeminal sensations (e.g. stinging, burning, sharp) in the region of the eyes and nose, and in terms of specific stimulating symptoms (e.g. nasal irritation) and non-specific symptoms (e.g. headaches, nausea) by means of a questionnaire.
- In addition, a blood sample was used to verify the allergy status and a urine sample to verify the smoking status through cotinine.

Urinary levels of the naphthalene metabolites 1-naphthol and 2-naphthol were measured before and after shift as biological markers of exposure. The obtained values were used,

together with work history and the results of air monitoring, to divide the subjects into 3 groups: highly exposed; moderately exposed and the reference group. Exposure levels for those workers who volunteered for further assessment were as follows:

Table 25: Naphthalene exposure levels in the biomonitoring study (Sucker et al. 2016)

Exposure Group	Air monitoring (mg/m³) 8-hour TWA			Biomonitoring (µg/g creatinine)		
	Median	**Mean**	**Range**	**Median**	**Mean**	**Range**
Reference (n=22) (no or rare naphthalene exposure)	0.13	0.15±0.10	0.05 - 0.36	19	18±11	6 - 40
Moderate (n=17) (indirect naphthalene exposure)	0.59	0.66±0.27	0.20 - 1.22	108	108±49	43 - 210
High (n=22) (direct naphthalene exposure)	6.30	6.97±3.10	2.46 - 11.58	1256	1489±999	293 - 4352

The numbers of workers in each exposure group differ slightly from the numbers provided in Table 11 section 7.12.1.1.5. This is because a number of employees were subsequently re-allocated to a different exposure group based on the activities they carried out.

It was noted that the workers included in the study may also have been exposed to ceramic grain, silica or other inhalable dusts.

Thirty two male workers volunteered to be included in the study alongside 31 reference subjects who had not worked with naphthalene for 10 years or more. Employees who had smoked in the last 12 months were not eligible to take part in the study. Raised levels of cotinine, indicative of smoking, were observed in two employees, who were subsequently excluded from the study.

Workers were excluded from the study if they had a previous or current medical condition of the upper respiratory tract or a significant medical condition associated with the impairment of the sense of smell.

There were 22, 17 and 22 participants in the reference, moderately exposed and highly exposed groups, respectively. The average age of workers in the highly exposed group was 10 years younger than those in other groups.

The questionnaires revealed that complaints of eye-related effects were significantly more likely to be reported by the highly-exposed workers than the reference group. Significantly more nasal complaints were reported by employees in both exposed groups compared to reference subjects. These effects were generally stronger on Thursdays than those reported on Mondays. Employees reported that these effects were clearly noticeable only when handling naphthalene directly. After the end of the shift, virtually no complaints were present any longer.

Following endoscopic examination, ENT (ear, nose and throat) specialists reported slight to moderate nasal inflammation. Although a significant difference between the moderate and high exposure groups was not identified at the end of shift on Thursdays, there were significant differences between the reference and exposed groups.

Acoustic rhinometry did not provide evidence of nasal swelling related to naphthalene exposure. Trigeminal sensitivity of the nasal mucosa tended to increase with increased exposure. However, differences between exposure groups were not statistically significant.

Nasal septum perforations, which occur with a prevalence rate of approximately 1% in the general population, were observed in 2/22 workers in the high exposure group. However,

one of these employees had previously had surgery of the nasal septum and was therefore considered to be inherently at increased risk of the observed effect. The second employee had undergone surgery for nasal polyps in the past. It is unclear whether the surgery could have led to the nasal septum perforations. It is uncertain whether these observations are related to naphthalene exposure.

Samples of nasal lavage fluid and induced sputum were obtained from participants pre- and post-shift in order to measure levels of biomarkers indicative of inflammation in the upper and lower respiratory tract, respectively.

Nasal lavage: Quantification of neutrophil granulocytes did not provide any evidence of acute inflammation. Measured levels of 8-isoprostane (indicator of oxidative stress) and leukotriene B_4 (indicator of inflammation) decreased over the course of the working week in reference subjects but increased over this period in the exposed groups. However, variation of these values over time or between groups was not significant and therefore these markers do not provide strong evidence of oxidative stress or inflammation in this study.

High levels of another potential indicator of chronic inflammation (C-reactive protein) were observed in both the reference and moderately exposed groups only. Likewise, no difference was noted in levels of Substance P (another potential indicator of inflammation) over time or between groups. Attempts to quantify levels of interleukin 6 (IL-6) were unsuccessful because the concentration was below the level of the detection in 91% of the samples. No effect of group or time was identified for levels of IL-8 in the nasal lavage.

Matrix metalloproteinase-9 (MMP-9) is a mediator known to play a role in inflammatory processes. An increase in MMP-9 levels from Monday to Friday was observed in the exposed groups only. Tissue inhibitor of metalloproteinase-1 (TIMP-1) is an inhibitor of MMP-9 and levels of this marker were lower in exposed subjects than in reference subjects on both Mondays and Thursdays. As noted by the study authors, an increased concentration of MMP-9 could suggest that there was inflammation in the nasal region. The MMP-9/TIMP-1 ratio was higher at the end of the shift in the high exposure groups than in the reference or moderate exposure groups. However, the differences between groups for both these markers were not statistically significant.

There was a significant correlation between the exposure index and the levels of two biomarkers measured before the shift on Mondays: total protein and IL-8.

Overall, a clear, consistent pattern of changes to the key biomarkers in nasal lavage was not apparent; the data provide only limited evidence of inflammation in the upper respiratory tract of exposed subjects.

Induced sputum: There was a significant correlation between naphthalene exposure (internal and external indices) and the levels of neutrophil granulocytes and substance P measured after the shift on Thursdays. These markers are both considered to indicate a possible inflammatory response in the lower respiratory tract. In contrast, the MMP-9/TIMP-1 ratio did not differ between groups. However, the patterns observed for other markers were very similar to those seen in the nasal lavage and do not provide a clear picture. Therefore the results provide only limited evidence of inflammation in the lower respiratory tract.

Blood: Two markers of inflammation were also assayed in blood samples.

Levels of IL-6 were below the detection limit in approximately two thirds of the samples and therefore this marker was excluded from the investigation.

Club cell protein 16 (CC16) is protective against inflammatory processes in the lung. Levels of CC16 in the blood were quantified because a low concentration of this protein may indicate tissue damage. The levels of CC16 were lower in exposed subjects than in

reference subjects, both on Monday (before shift) and Thursday (after shift). A significant decrease in CC16 levels from Monday to Thursday was noted in all groups, although the decrease in the high exposure groups was slightly greater than in other groups. There was a statistically significant association between the levels of CC16 protein measured at the end of the week and internal exposure, and also between blood serum CC16 levels and external exposure. However, as noted by the study author, there was a large degree of overlap of the confidence intervals for each group.

Overall, in this study, clinical and subclinical signs of slight acute inflammation in the nasal mucosa of both exposed groups were reported. Clear exposure-response relationships were not observed, but measurements of some parameters differed between reference subjects and exposed subjects. However, as concluded by the study authors themselves, there was a large degree of overlap in the observations derived for each study group. Furthermore, it cannot be dismissed that co-exposure of workers to other chemicals may have confounded this study. For these reasons, the data do not allow any firm conclusions to be made about the toxicity of naphthalene. The data are considered at most to provide only limited evidence that exposure to naphthalene in this work place may be causing nasal irritation and inflammation in humans. The study did not provide any information on naphthalene's potential to induce haemolytic anaemia in humans.

The authors summarised the results of the study as follows:

> *"In summary, no consistent pattern of (inflammatory) effects was seen, either in the moderately or in the highly exposed group. For some parameters (e.g. nasal endoscopic score) minor but statistically significant differences between the exposed group and the reference group have been observed which are compatible with mild acute inflammatory effects. On the other hand, in a great part of parameters, particular regarding biomarkers, there was no consistent difference between the moderately and highly exposed groups and also no adversity developed over time within the working week covered in this study. In parameters that showed (statistically significant) differences between the reference group and the exposed groups there was often a considerable overlapping of values between the groups. In view of the broad range of the naphthalene exposure by more than one order of magnitude it seems questionable that the described differences are only due to naphthalene itself. The overall exposure situation including inhalable and respirable dust, especially from ceramic grain or silica, has to be taken into consideration."*

7.9.5. Germ cell Mutagenicity

This endpoint was not evaluated.

7.9.6. Carcinogenicity

Naphthalene is classified as a Category 2 Carcinogen in Annex VI of the CLP Regulation (EC 2008/1272). Treatment-related increases in the incidence of neuroblastoma in the olfactory epithelium and adenoma in the respiratory epithelium were observed in rats following inhalation exposure to naphthalene (NTP 2000). Additionally, lung tumours were observed in mice following chronic exposure to naphthalene by inhalation (NTP, 1992). However the findings is mice were not considered to be of relevance to humans. Therefore the harmonised classification of naphthalene for carcinogenicity was based on the nasal tumours observed in rats.

7.9.6.1. Summary and discussion of carcinogenicity

Inhalation

ESR Review of naphthalene (2003)

Study in rats

Groups of 49 male and 49 female F344/N rats were exposed to 0, 10, 30 or 60 ppm naphthalene vapour (>99% pure) (approximately equivalent to 0, 50, 150 or 300 mg/m^3) in inhalation chambers for 6 hours/day, 5 days/week for 105 weeks.

Neuroblastoma of the nasal olfactory epithelium was observed in males from the 30 and 60 ppm groups (4/48 and 3/48, respectively) and in all exposed groups of female rats (2/49, 3/49 and 12/49 at 10, 30 and 60 ppm, respectively). This neoplasm did not occur in chamber control rats or male rats exposed to 10 ppm. In addition, this tumour has not been observed in the historical chamber control rats in NTP 2-year inhalation studies. Increases were also observed in adenomas of the respiratory epithelium in males from all exposure groups (control: 0/49, 10 ppm: 6/49, 30 ppm: 8/48 and 60 ppm: 15/48) and females from the 30 and 60 ppm exposure groups (control: 0/49, 30 ppm: 4/49 and 60 ppm: 2/49). Compared to concurrent chamber controls the increases in respiratory epithelium adenomas were statistically significant in males but not females. The draft report states that nasal adenomas have not been observed in NTP historical chamber control rats. No lung tumours were observed.

In addition to the nasal neoplasms, the incidences of a variety of non-neoplastic lesions of the nasal tract in both sexes were statistically significantly greater in naphthalene exposed animals than controls. These lesions included, in the olfactory epithelium: atypical (basal cell) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration; in the respiratory epithelium: hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia; and glandular hyperplasia and squamous metaplasia. In general, the severity of the olfactory and glandular lesions increased with increasing exposure concentrations.

Overall this study demonstrated an increase in the incidence of respiratory epithelial adenomas in naphthalene exposed males from 10 ppm and females from 30 ppm and olfactory epithelial neuroblastomas (a very rare tumour type) in males from 30 ppm and females from 10 ppm. These tumours occurred at sites where non-neoplastic inflammatory changes also occurred and are considered to be treatment-related.

Studies in mice

104 week study (NTP, 1992)

Groups of 70 male and 70 female B6C3F1 mice were exposed to 0 or 10 ppm naphthalene vapour and groups of 135 males and 135 females to 30 ppm naphthalene vapour (>99% pure) (equivalent to 0, 50 and 150 mg/m^3/day) in inhalation chambers for 6 hours/day, 5 days/week for 104 weeks (NTP, 1992).

A statistically significant increase occurred in the incidence of alveolar/bronchiolar adenomas in high-exposure females (controls: 5/69, 7%; 10 ppm: 2/65, 3%; 30 ppm: 28/135, 21%; historical incidence and range in NTP inhalation studies in female mice: 5.8%, 0-10%). One alveolar/bronchiolar carcinoma was also noted in a high-dose female (1%) but as the historical control incidence is 2.8% (range 0-6%) no significance can be placed on this finding. Exposed males also showed an increased incidence in alveolar/bronchiolar adenomas and carcinomas. However these increases were not statistically significant and/or were within historical control values (adenomas: 7/70 (10%); 15/69 (22%); 27/135 (20%); 69/478 (14.4%), carcinomas: 0/70; 3/69 (4%); 7/135 (5%); 30/478 (6.3%), in control, low and high exposure and NTP historical controls, respectively).

Overall this study demonstrated an increase in the incidence of benign adenomas in female mice at a site where non-neoplastic inflammatory changes also occurred. There was no increase in malignant tumours. Other than the non-neoplastic changes in the lungs and nose no other signs of general toxicity were noted and it is possible that the study could

have included a higher concentration of naphthalene. That is, the study could have been more rigorous but is none the less, adequate.

6 month study

In a limited and briefly reported inhalation study groups of 30 male and female Strain A/J mice were exposed to 0, 10 or 30 ppm naphthalene (equivalent to 0, 50 and 150 mg/m^3/day) for 6 hours/day, 5 days/week for 6 months (Adkins et al., 1986). Survival was unaffected by treatment. Body weight and signs of toxicity were not reported. Macro- and microscopic examinations were only conducted on the lungs. There was an increase in the incidence of lung adenomas, although it is not clear if this increase was statistically significant (Controls: 21%, 10 ppm: 29%, 30 ppm: 30%). No other details were given. Overall due to the high incidence of lung adenomas in controls, the small numbers of animals used and the limited study length, no meaningful conclusions can be drawn from these findings.

Dermal

There is no information available.

Human information

Two brief reports are available of four cases of laryngeal cancer which occurred in workers engaged in the purification of naphthalene (Wolf, 1976; 1978). It is difficult to define from the reports whether the author identified these four cases independently or whether they were brought to his attention by an external source. However, it is clear from the reports that all the cases were smokers and were exposed to other substances including coal tar volatiles. Overall, no conclusion can be drawn from these reports regarding the role, if any, of naphthalene in the production of these cancers.

Information found subsequent to the ESR Review

No further carcinogenicity studies have been conducted since the ESR Review

7.9.6.2. Conclusion on carcinogenicity - Mode of Action (MoA)

The text in italics, below, has been taken from the ESR Review (EC 2003) and included for information.

In view of the negative results obtained in the in vivo genotoxicity studies, naphthalene is considered to be non-genotoxic. Given this, the tumours in the animal studies are considered to arise via a non-genotoxic mechanism and consideration must therefore be given to other potential mechanisms underlying the carcinogenic response.

An *in vivo* Unscheduled DNA Synthesis (UDS) study (stae tissues sampled) and an *in vivo* bone marrow micronucleus assay gave negative results, as described in the ESR Review. The eMSCA considers that there is no information available to change the weight-of-evidence-based approach presented in the ESR Review which concluded that naphthalene-induced tumours are likely to have resulted from a non-genotoxic mechanism.

Cytotoxicity

In relation to the rat nasal tumours, the tumours develop only at the sites where non-neoplastic inflammatory changes also occur (changes such as atrophy, hyperplasia and metaplasia). Thus, it is considered that the development of the nasal tumours in the rat is a consequence of chronic tissue injury, for which an identifiable threshold of effect will exist, although currently not identified. However, the available data do not allow the identification of a threshold for chronic tissue damage, nor is there any clear information

on whether or not local tissue metabolism is involved in the toxicity of naphthalene to the nasal epithelium.

There are anatomical differences in the nasal passages between rats and humans, and differences in breathing pattern (rats are obligate nasal breathers) which may affect airflow and deposition patterns of naphthalene. Thus, there is some uncertainty concerning the relevance of the rat nasal effects to human health. However, overall, it is not possible to dismiss the rat nasal olfactory data as being of no relevance for humans.

The development of naphthalene-induced mouse lung adenomas is unlikely to be of relevance to human health due to species differences in pulmonary metabolism. In vitro studies with lung microsomal preparations clearly showed that mouse lung preparations metabolised naphthalene at substantially greater rates (up to 100-fold) than those from hamster, rat or monkey. Furthermore, intra-peritoneal dosing of 50 mg/kg naphthalene led to specific toxicity to Clara cells in the lungs of mice, but no such toxicity was observed in rats even at 1,600 mg/kg. In addition, no lung tumours were seen in rats. Hence, the pattern of toxicological evidence indicates that the mouse is more susceptible to the pulmonary toxicity of naphthalene than other species, and therefore the observed pulmonary adenomas seen in mice at 30 ppm (150 mg/m^3) are not considered to be of relevance to human health.

Based on the information presented in the ESR Review, the eMSCA concurs with the conclusion that lung adenomas observed in mice are not relevant to human health and that the nasal tumours (neuroblastoma and adenoma) may be relevant for human health. On this basis, the eMSCA's analysis of naphthalene-induced carcinogenesis has focussed on the nasal tumours observed in rats.

7.9.6.3. Additional evaluation (2016/2017)

At the Naphthalene State of the Science Symposium (NS3) held in 2006, the panel noted that the maximum tolerated dose (MTD) had been exceeded in both rats and mice and that the available data were strongly supportive of cytotoxicity having a role in the formation of the observed tumours. The panel considered that naphthalene is not a classical genotoxic carcinogen (North et al. 2008). Although it was concluded that focal cellular proliferation enhanced (and possibly enabled) the occurrence of nasal tumours, the panel could not rule out the possibility of genotoxicity being involved on the basis of evidence of irritation, but not tumours, occurring in the mouse nose (Bogen et al. 2008).

Additionally, the panel postulated that if one were to use the results of the rodent bioassays to estimate tumour rates in humans, the resultant predicted incidence would considerably exceed the observed rate in humans (North et al. 2008) and therefore meaningful predictions of tumour incidences in humans cannot be obtained via a simple linear extrapolation from data on rats exposed to cytotoxic concentrations of naphthalene (Bogen et al. 2008).

Magee et al. (2010) carried out a retrospective population risk assessment by extrapolating the data from rats (NTP, 2000) to estimate the incidence of respiratory epithelial adenomas and olfactory epithelial neuroblastomas one would expect to observe in the US population. The estimation was based on naphthalene Unit Risk Factors proposed by the US Environmental Protection Agency (EPA) based on the tumours observed in rats. The study authors found that cancer potency estimates based on the rat NTP bioassay significantly overestimated the total number of nasal tumours actually observed in the US population and therefore considered that the rat may be an inappropriate model for estimating the risk of naphthalene-induced nasal tumours in humans.

The panel at the Naphthalene State of the Science Symposium also noted that the toxicity is caused by metabolites of naphthalene rather than naphthalene itself (Bogen et al. (2008).

Since the Symposium, a number of authors have further considered the potential of naphthalene to induce nasal tumours. The following information is considered to be of relevance to the assessment of the carcinogenic mode of action of naphthalene.

Metabolism

Naphthalene is understood to be metabolised by CYP2F (and/or other CYPs) to the reactive epoxide, which in turn is conjugated with glutathione. Cytotoxicity is associated with GSH depletion in cells, chronic inflammation, and regenerative hyperplasia have been reported to follow naphthalene metabolism (Rhomberg et al. 2010).

Although collocation of CYP2F activity and cytotoxicity could indicate causality, it is possible that collocation could just be coincidental (Rhomberg et al. 2010) and the possibility that other CYP enzymes are involved cannot be excluded. However, the low concentration of CYP2F in the rat lung together with the absence of tumours in this location supports the postulation that CYP2F does have some involvement in the primary metabolism of naphthalene.

Morris and Buckpitt (2009) measured the uptake of naphthalene in the upper respiratory tract of F344 rats (6-12 males/ group and 7-8 females/group) with a focus on the olfactory epithelium. Naphthalene (1, 4, 10 or 30 ppm; equivalent to 5.24, 21, 52.4 and 157 mg/m^3) was administered to rats (nose-only) at inspiratory flow rates of 150 or 300 ml/min. An inhibitor of cytochrome P450 (CYP450), namely 5-phenyl-1-pentyne (PP), was administered to additional groups of rats (7-8/sex/group) prior to naphthalene exposure.

In rats <u>not</u> pre-treated with PP, the efficiency of naphthalene uptake decreased with increasing concentration of naphthalene. In addition, it was noted that flow rate significantly affected uptake: naphthalene uptake was lower at a flow rate of 300 ml/min than at 150 ml/min. The findings were similar in both sexes although the uptake efficiency was higher in males than in females.

In rats pre-treated with PP (both sexes), the efficiency of naphthalene uptake did not vary significantly with concentration and was lower than animals not exposed to PP. The activity of metabolites in the olfactory mucosa was approximately 80% lower in pre-treated rats. Since PP inhibits CYP450, the lower naphthalene uptake efficiency in the presence of PP supports the assertion that naphthalene is metabolised by CYP enzymes in the nasal olfactory mucosa.

These findings do not rule out a role for CYP2E1 in naphthalene metabolism because this CYP isozyme is also inhibited by PP. Data comparing the activity of CYP2F to CYP2E1 is lacking but some reported evidence suggests that CYP2F is more efficient and could therefore be the primary CYP enzyme in naphthalene metabolism (Rhomberg et al. 2010). This assertion is supported by meaurements of the efficiency of naphthalene oxide generation using recombinant CYP2F4 from rats (Baldwin et al. 2005 as cited by Rhomberg et al. 2010) and recombinant CYP2F2 from mice (Schultz et al. 1999 as cited by Rhomberg et al. 2010). The efficiency of epoxide generation by recombinant CYP2F4 and CYP2F2 from rodents was similar (V_{max} of 107 min^{-1} and 104 min^{-1}, respectively). Metabolism of naphthalene to 1-naphtol via recombinant CYP2E1 from humans was less efficient (V_{max} of 8.4 min^{-1}) (Cho et al. 2006 as cited by Rhomberg et al. 2010).

In summary, the evidence is considered to support a role for CYP enzymes (CYP2F and/ or other isozymes) in the initial metabolism of naphthalene.

7.9.6.3.1. MoA Analysis

The eMSCA has additionally assessed the MoA of the nasal tumours using the IPCS (International Programme on Chemical Safety) conceptual framework (Sonich-Millin et al., 2001).

7.9.6.3.1.1. Postulated Mode of Action

The postulated mode of action (MoA) proposes that naphthalene is metabolised to cytotoxic metabolites by a CYP enzyme (CYP2F) in tumour-forming tissues. Those metabolites are responsible for the inflammation and regenerative hyperplasia which precede carcinogenesis.

7.9.6.3.1.2. Key events

The key events in the proposed mode of action are the initial metabolism of naphthalene by a CYP enzyme to reactive intermediates (eg expoxides) which lead to GSH depletion, cytotoxicity , inflammation, hyperplasia and eventually tumours in the target tissues. Evidence of cytotoxicity (atypical hyperplasia, atrophy, chronic inflammation and hyaline degeneration in the olfactory epithelium and hyperplasia, squamous metaplasia, hyaline degeneration and goblet cell hyperplasia in the respiratory epithelium) was measured in the NTP study in which the nasal tumours were observed, and also in the NTP study in mice, in which tumours were observed in the lung only. The studies did not examine GSH depletion or the initial metabolism of naphthalene to the epoxide.

In addition, the nasal tissue was examined histopathologically in recently conducted inhalation studies in rats (Dodd et al. 2010, 2012).

7.9.6.3.1.3. Exposure-response relationship (data provided in section 7.9.4.)

2 year NTP inhalation study in rats

Olfactory epithelium

In controls, no incidences of neuroblastoma were reported and the key events in the olfactory epithelium (atypical hyperplasia, atrophy, chronic inflammation, hyaline degeneration) were of minimal severity or non-existent in this group. The key events were observed in almost all of treated animals in all dose groups, whilst tumours were observed at all doses in females and at the mid and high doses in males.

The severity of atypical hyperplasia, atrophy and chronic inflammation increased with dose in both sexes. However, the severity of hyaline degeneration did not increase in an exposure-dependent manner in either sex. In females, the increased severity of the non-neoplastic findings in the nasal tissue was consistent with the exposure-related increased incidence of neuroblastoma.

Generally, the results indicate that neuroblastoma occurred at doses at which the key events were observed. However, there were no reports of neuroblastoma in low dose males despite the incidences and severities of non-neoplastic lesions being similar in both sexes. The reason for the sex difference in the incidence of tumours in the olfactory epithelium is unclear.

Respiratory epithelium

Similarly, no incidences of adenoma were reported in controls and the key events in the respiratory epithelium (hyperplasia, squamous metaplasia, hyaline degeneration, goblet cell hyperplasia) were of minimal severity or non-existent in this group. The key events were observed in approximately half of treated animals in all dose groups, whilst tumours were observed at all doses in males and at the mid and high doses in females.

The severity of the lesions in the respiratory epithelium did not increase with dose in either sex. This appears to be inconsistent with the exposure-related increased incidence of adenoma in males.

Despite evidence of the key events in low dose females, there were no reports of adenoma in these animals. The reason for the sex difference in the incidence of adenoma in the respiratory epithelium is unknown. However, in general, the results indicate that adenoma occurred at doses at which the key events were observed irrespective of the severity of the non-neoplastic lesions.

18 month NTP study in mice

Unlike in rats, nasal tumours were not reported in mice. The absence of nasal tumours could be considered inconsistent with the findings in rats. However, the non-neoplastic lesions reported in mice do not include all of the key events described in rat nasal tissue.

In the 18 month study histopathological examinations were performed on the nasal cavities of all mice. Therefore the lack of reports of some of the key events in mice (e.g. atrophy, hyaline degeneration and atypical hyperplasia in the olfactory epithelium) indicates that these effects were absent in mice rather than overlooked due to a limited study design. Therefore the data in mice support the assertion that the key events, listed in the tables in Section 7.9.4. are necessary precursors for tumorigenesis in nasal tissue. However, the reason for the absence of the key events in mice following exposure to naphthalene is unclear.

Short term inhalation studies in rats

The NTP does not appear to have conducted a 90 day study in rats (as they frequently do in their program) that would allow for a comparison between different durations of exposure in the same lab. Treatment-related non-neoplastic nasal lesions were observed at the lowest exposure level (2 ppm, equivalent to 10.5 mg/m^3) in a 90 day study in rats (Huntingdon Research Centre, 1993a). Similarly, non-neoplastic lesions were observed in the noses of rats at concentrations below 1 ppm (5.24 mg/m^3) in acute and subchronic studies (Dodd et al. 2010, Dodd et al. 2012). The NOAEC in the recent 90 day study was 0.52 mg/m^3. However, due to the short duration of these studies, the data do not inform on whether the non-neoplastic lesions would have progressed to tumours over time.

After short term exposure of rats to naphthalene by both inhalation and intraperitoneal injection, the incidence of the observed lesions correlated with formation of naphthalene-1,2-epoxide (Lee et al. 2005). This information supports the assertion that metabolism of naphthalene is involved in the carcinogenic MoA.

Antioxidant/Antielectrophilic response to metabolites

Cichocki et al. (2014) exposed F344 rats (both sexes) nose-only to 0, 1, 3, 10 or 30 ppm naphthalene vapour (equivalent to 0, 5.24, 15.7, 52.4 or 157 mg/m^3) for 4 or 6 hours. It is not clear how many animals were used. The study aimed to characterise the initial biochemical events in the olfactory and respiratory mucosa following exposure to naphthalene and to identify any sex-specific responses to the formation of electrophilic metabolites in the nasal passages that could explain the sex differences in the observed tumour incidences. Due to the nature of this study, the tissues were not examined histopathologically.

GSH levels in the respiratory/transitional and olfactory mucosa were significantly lower in all dose groups (both sexes) than in controls after both 4 and 6 hours of exposure to naphthalene. The decrease in GSH levels in comparison to controls was approximately 70% and 40% in the respiratory and olfactory epithelia, respectively and did not show any consistent difference between sexes.

Induction of genes indicative of oxidative stress was observed in the respiratory/ transitional and olfactory mucosa. In the olfactory mucosa, induction of the measured antioxidant genes (glutamyl cysteine ligase (catalytic subunit), NADPH quinone oxidase 1 and heme oxygenase 1) was greater in males than in females. The greater antioxidant response in males may contribute to the observed differences in tumour incidences in the olfactory mucosa. No such differences were reported in the respiratory/ transitional mucosa and therefore the results do not help to explain the sex differences in the tumour incidences observed in the respiratory epithelium.

7.9.6.3.1.4. Temporal association

Since there was no interim sacrifice in the 2 year NTP study in rats, it is not possible to evaluate whether the postulated key events preceded tumorigenesis in this particular study.

However, the acute (1 day), subacute (5 days) and subchronic (90 days) inhalation studies conducted by Dodd et al. (2010, 2012) and Lee et al. (2005) are useful in the examination of the temporal association between the key events and the tumours.

Olfactory epithelium

In rats, there is consistent evidence showing that adverse effects on the olfactory epithelium occur shortly after exposure to naphthalene. For example, necrosis of the olfactory epithelium was observed in F344 and Sprague Dawley rats exposed to a single 6 hour dose of naphthalene. Likewise, effects on the olfactory epithelium were reported after 4 hours of exposure to naphthalene (Lee et al. 2005). Exposure-dependent degeneration of the olfactory epithelium was also reported in both strains of rat in the 5 day study (Dodd et al. 2010).

In the 90 day study (Dodd et al. 2012), lesions of the olfactory epithelium including necrosis and degeneration of the olfactory epithelium in association with a prominent basal cell hyperplasia, were observed in F344 rats (both sexes) at 52.4 and 157 mg/m^3.

Respiratory epithelium

Similarly, effects on the respiratory epithelium were observed in rats after short exposures to naphthalene. Dodd et al. (2010) reported necrosis of the nasal respiratory epithelium in F344 and Sprague Dawley rats following an acute exposure (6 hours) to naphthalene. Mild hyperplasia and minimal squamous metaplasia in the respiratory epithelium were observed in rats exposed to naphthalene for 90 days (Dodd et al. 2012).

No tumours were reported in these short term studies. Therefore clear evidence is available to show that adverse effects including necrosis of the olfactory epithelium and hyperplasia of the respiratory epithelium occur prior to the formation of tumours in these tissues.

7.9.6.3.1.5. Strength, consistency, and specificity of association of tumour response with key events

Strength

In rats, the data show that nasal tumours occurred at sites at which cytotoxicity was observed, where there are high concentrations of naphthalene metabolising enzymes and GSH depletion, providing support for the postulated mode of action (Rhomberg et al. 2010).

The presence of tumours in the rat nose, where all of the key events were observed, is consistent with the absence of tumours in the mouse nose, where only some of the key events were reported.

More recent inhalation studies by Dodd et al. (2010, 2012) showed that non-neoplastic lesions occur at a lower dose (0.52 and 5.24 mg/m^3) and after a shorter duration (1 day, 5 days, 90 days) than tested in the NTP carcinogenicity studies. However, it is unknown whether exposure to naphthalene at this level would lead to carcinogenicity, given a longer duration of exposure.

Since there was no interim sacrifice in the NTP study, it is not possible to ascertain whether the non-neoplastic lesions occurred prior to the formation of tumours. However, the findings in the shorter duration studies support the assertion that the cytotoxicity does precede carcinogenicity.

Consistency

Treatment-related increases in the incidence of neuroblastoma in the olfactory epithelium and adenoma in the respiratory epithelium following inhalation exposure to naphthalene have been observed in both sexes of a single species (rats). Treatment-related tumours in the nasal tissue were not observed in mice.

In humans, there are reports of laryngeal cancer in four workers involved in the purification of naphthalene, as described in the ESR Review. However, since these workers were smokers and were co-exposed to coal tar volatiles, no reliable conclusions could be drawn from this information. Therefore no conclusive evidence is available to show that naphthalene causes such tumours in humans. The lack of case reports detailing the occurrence of tumours in the nasal tissue of humans exposed to naphthalene may suggest that the tumour types observed in rats are species-specific. However, the lack of reports could be due to the low number of workers exposed to naphthalene, the long latency period for tumorigenesis, or the possibility that naphthalene exposure does lead to these tumours in humans, but the cause of the tumours has not been not identified correctly, if at all. Therefore the absence of evidence of nasal tumours in humans exposed to naphthalene is not considered to negate the findings in rodents.

Cytotoxic non-neoplastic lesions have been observed consistently in rats and mice following inhalation exposure to naphthalene in studies ranging from 1 day to 2 years in duration (Dodd et al. 2010, 2012; Lee et al. 2005; NTP; 1992, 2000). The results of the biomonitoring study (Sucker et al. 2016) provide limited information about naphthalene's potential to irritate human nasal tissue.

Specificity

The tumours in the olfactory and respiratory epithelium occurred at sites where key cytotoxic events were observed and therefore there appears to be a large degree of specificity. However, some non-neoplastic lesions do not progress to carcinogenicity, for example tumours were not observed in the mouse nasal tissue despite observations of chronic inflammation, metaplasia of the olfactory epithelium and hyperplasia of the respiratory epithelium. The reason for the species difference is unclear.

7.9.6.3.1.6. Biological plausibility and coherence

Biological plausibility

Naphthalene is not considered to be mutagenic. The postulated MoA is consistent with the biologically plausible explanation that chronic inflammation (Vineis et al. 2010) and regenerative cell hyperplasia can result in carcinogenesis through a non-genotoxic MoA.

Coherence

Non-neoplastic nasal lesions have been reported in rats in numerous studies, showing that short- and long-term exposure to naphthalene by inhalation results in irritation to the

respiratory tract. The location of these lesions is consistent with the postulation that they are necessary precursors to naphthalene-induced tumours.

7.9.6.3.1.7. Other modes of action

A MoA involving genotoxicity caused by naphthalene metabolites (namely naphthalene-1,2-dioxide, 1,2-naphthoquinone and 1,4-naphthoquinone) has been proposed. However, in view of the negative results obtained in the *in vivo* genotoxicity studies, naphthalene was considered to be non-genotoxic by the authors of the ESR Review. The eMSCA agrees that the tumours observed in rodents are most likely to have arisen via a non-genotoxic mechanism.

7.9.6.3.1.8. Assessment of postulated mode of action

Naphthalene is not genotoxic. On consideration of the consistent evidence of non-neoplastic lesions occurring in the nasal tissue at low doses and only shortly after exposure to naphthalene, together with the fact that tumours in rodents were only observed at sites where cytotoxicity was observed, the eMSCA has a high level of confidence in the postulated cytotoxic mode of action. In the published literature, it is widely considered that the weight of evidence supports a mode of action involving cytotoxicity and regenerative hyperplasia (Bailey et al. 2015; Dodd et al. 2012; Rhomberg et al. 2010; SCOEL, 2010). There is also support for a dual mode of action, involving both cytotoxicity and genotoxicity (Bogen, 2008).

7.9.6.3.1.9. Uncertainties, inconsistencies, and data gaps

Tumour incidences

In the NTP study, adenomas were observed in 6, 8 and 15 rats at 52.4, 157 and 314 mg/m^3. However, degeneration, hyperplasia and metaplasia of the respiratory epithelium were not reported in 2/6, 2/8 and 3/15 (at 52.4, 157 and 314 mg/m^3, respectively) of the animals in which adenoma was observed. It has been postulated that non-neoplastic lesions may have been present in exposed rats, but these lesions may subsequently have been obliterated by the tumours (Bailey et al. 2015). The available data do not allow a firm conclusion on this postulation to be made. However, when taking all of the evidence into consideration, this inconsistency is not considered to reduce the confidence in the postulated MoA.

Despite observations of the key events in low dose male and female rats, neuroblastoma was not observed in low dose males and adenoma was not observed in low dose females. The study authors commented that the severity of the effects of the olfactory epithelium tended to increase with increased dose. Therefore, it is possible that the olfactory epithelial lesions at the low dose were not severe enough to progress neuroblastoma in males. However, the severity of the effects at the low dose was very similar in both sexes and therefore the reason for the absence of neuroblastoma and adenoma in low dose males and females, respectively, remains unclear.

In addition, it is unclear why only some of the key events were observed in the nasal tissue of mice following exposure to naphthalene. The species differences may indicate a greater inherent sensitivity of rats to the toxic effects of naphthalene on the nasal tissue.

Mode of Action/ Metabolism

Since there are similar levels of CYP2F in the nasal tissue of rats and mice, the reason for the absence of tumours in the mouse nose is uncertain. It has been suggested that tumour formation may require further metabolism of naphthalene (beyond the formation of the epoxide by CYP2F), and that this happens in the nasal passages of rats but not mice (Rhomberg et al. 2010). The same group postulated that fewer initiated cells may have progressed to tumours in mice compared to rats due to greater cytotoxicity in the nasal

cavity of mice. However, the group conceded that the results of the NTP study do not allow an assessment of this theory because almost 100% cytotoxicity was observed at all doses (Bailey et al. 2015). Cytotoxicity was indeed observed in a greater proportion of mice than in rats in the NTP studies (NTP 1992, 2000). However, at the top dose, cytotoxicity was observed in the olfactory epithelium of almost all rats and the lesions were more severe than in the nasal cavity of mice. Since these non-neoplastic lesions progressed to tumours in rats but not in mice, the eMSCA does not consider the postulation put forward by Bailey et al. (2015) to be plausible.

Another inconsistency is that CYP2F is present in the liver of both rats and mice, yet tumours, inflammation and regenerative hyperplasia have not been observed here. It was suggested that detoxification of naphthalene in the liver prevents GSH depletion and subsequent cytotoxicity (Rhomberg et al. 2010). However, following *in vitro* exposure of hepatocytes from rats and mice to naphthalene for 3 hours (Kedderis et al. 2014), a statistically significant and dose-dependent decrease in GSH levels was noted at ≥500µM naphthalene. After 24 hours in monoculture there was some recovery of GSH levels, although recovery was not complete. Although this study was conducted *in vitro*, it shows that naphthalene exposure can decrease GSH levels in rat hepatocytes. It is possible that although GSH levels decreased in hepatocytes *in vitro*, sufficient levels of GSH remain *in vivo* to preclude cytotoxicity. However, it is not possible to draw this conclusion with certainty based on the information available.

It has been proposed that the amounts and efficiencies of enzymes (CYP2F, GSH transferase, EH, DD and DNA repair enzymes) are different in different tissues in each species and that a disrupted balance of these enzymes could explain the species differences and site specific observations (Rhomberg et al. 2010).

7.9.6.3.1.10. Conclusion:

The eMSCA concurs with the conclusion in the ESR Review that the tumours observed in animal studies are likely to have arisen via a non-genotoxic mechanism. The available data are considered to be highly supportive of a cytotoxic MoA for naphthalene-induced carcinogenesis in the rat nasal cavity. Whilst there are some uncertainties, these are not considered to place doubt on the postulated MoA.

7.9.6.4. Human relevance

Having established the Mode of Action of naphthalene carcinogenesis in animals, the relevance of tumours to humans requires further consideration.

7.9.6.4.1. Physiology and Anatomy

Zhang and Kleinstreuer (2011) modelled the deposition of naphthalene in the human respiratory system using a computational fluid-particle dynamics (CFPD) simulation.

The simulations showed that the deposition fraction (DF) of naphthalene in the upper airways is approximately 25%. However this value can vary considerably depending on how absorbing the airways walls are. According to the study authors, a DF of 67% could arise if the walls of the airway perfectly absorbed naphthalene. Vapours that are not deposited in the upper airways travel deeper down the respiratory tract.

Notably, the authors reported a decrease in DF in the upper respiratory tract from 24% when exclusively breathing nasally, to 16% when exclusively breathing orally. This could be of particular importance when considering the relevance of the rodent data to humans. Since rats are obligate nasal breathers, the pattern of injury may not be a reflective of the situation in humans. It could reasonably be assumed that the DF in the upper respiratory tract would be higher in rats than in humans.

7.9.6.4.2. Route of exposure

In a combined inhalation/ intraperitoneal study (Lee et al. 2005), 6 male SD rats/ group were exposed to naphthalene by inhalation (17.8±2.6 mg/m^3 and 125±8.9 mg/m^3 for 4 hours). Three male SD rats/ group were exposed to naphthalene via intraperitoneal injection (0, 25, 50, 100 or 200 mg/kg). Olfactory epithelium lesions were noted following administration of naphthalene by both inhalation (at both concentrations) and intraperitoneal injection (from 100 mg/kg). This shows that the effects can arise following inhalation and systemic administration. However, the route of exposure was found to affect the pattern of adverse effects on the nasal passages of treated rats. After inhalation, the degree of injury correlated with the amount of airflow passing over a particular region of the nasal cavity. In contrast, the degree of injury was consistent throughout the nasal mucosa following systemic administration.

7.9.6.4.3. Kinetics

Buckpitt et al. (2013) investigated the metabolism of naphthalene and its metabolites in male rodents and rhesus monkeys (13 females and 6 males) using microsomal preparations from the respiratory tract. In this study, the maximum rate of naphthalene metabolism (V_{max}) in the rat olfactory epithelium was described as very high at 54 nmol/mg/min, which was four times greater than the V_{max} in microsomes from the rat respiratory nasal epithelium. Due to poor yields of microsomal proteins from non-human primates, the results from this species were more variable. However, in comparison to the rat, naphthalene was metabolised at a lower rate in non-human primates (approximately 5% of that observed in the rat nasal olfactory epithelium).

7.9.6.4.4. Metabolism – enzyme expression

At the Naphthalene State of the Science Symposium (NS3), the panel acknowledged that human enzyme CYP2F1 (which metabolises naphthalene to the epoxide) has been identified in human respiratory tissue (Bogen et al. 2008). CYP2F1 is 82% homologous to the mouse enzyme CYP2F2, but appears to be present in human respiratory tissue at much lower levels than the levels of CYP2F4 found in rat nasal tissue (Bailey et al. 2015).

The panel also noted that in rhesus macaques, CYP2F was found only in the nasal ethmoturbinates, and at levels 10-20 times lower than found in rodents (Bogen et al. 2008).

7.9.6.4.5. Rate of metabolism

It was noted by the panel, however, that the rate of metabolism by the human CYP2F1 is low (Bogen et al. 2008). This was supported by Rhomberg et al. (2010), who noted that *in vitro* data suggest that naphthalene metabolism occurs at a much lower rate in humans than in rodents.

7.9.6.4.6. Extent of metabolism

The results of a physiological-based pharmacokinetic model showed that naphthalene metabolism is approximately five times higher in the rat nose than in humans and therefore some doubts have been cast on the relevance of the rodent data for humans at typical human exposure concentrations (Bailey et al. 2015).

The dose-response relationship of naphthalene on GSH levels, ATP levels and cytotoxicity has been investigated *in vitro (*Kedderis et al. 2014). Cells from the lung, nasal respiratory epithelium and liver were isolated from male B6C3F1 mice, male F344 rats and human donors. Of particular interest are the results from the nasal epithelium in rats and humans. The respiratory epithelium was chosen because cells from the olfactory epithelium are difficult to isolate from humans.

Nasal respiratory epithelial cells were extracted from 2 men and 1 woman. It is unclear how many rodents were used in the study. Cell preparations from the nasal respiratory epithelium in humans (single cell suspension) and rodents (tissue explants) were exposed to naphthalene (0, 500, 1000 and 2000 µM) for 3 hours before aliquots were removed to measure ATP, LDH, GSH and protein levels. Cells were placed in monolayer cultures for 24 hours before the same parameters were measured again.

After 3 hours, significant decreases in GSH and ATP levels were observed in the rat respiratory epithelium at 2000 µM only. Levels recovered after 24 hours.

Statistically significant decreases in cell viability were not observed in rodent nasal respiratory epithelial cells following exposure to naphthalene.

After 3 hours, concentration-dependent decreases in cell viability, GSH levels and ATP levels were observed in human nasal respiratory epithelial cells. Some recovery from cytotoxicity was observed after 24 hours. At 500 µM, one of the three samples recovered completely after 24 hours in culture. In the remaining two samples, GSH and ATP levels recovered but cell viability did not. At 1000 µM, some recovery of ATP and GSH levels was noted in one sample after 24 hours. At 2000 µM, ATP and GSH levels remained low in all 3 samples.

Under the conditions of this study, naphthalene had a greater effect on cell viability, GSH levels and ATP levels in human cells *in vitro* than in rodent cells. This evidence suggests that the cytotoxicity observed *in vivo* in rats may be of relevance to humans.

7.9.6.4.8. Protein adducts

Although the available evidence suggests that initial metabolism of naphthalene is lower in monkeys and humans than in rats, DeStefano-Shields et al. (2009) found that covalently bound metabolites are formed at similar rates in the nasal epithelium of rhesus macaques and male SD rats.

Saeed et al. (2009) administered naphthalene (1200 or 500 nmol) and its metabolites (500 nmol of 1-naphthol, 1,2-dihydrodiolnaphthalene (1,2-DDN), 1,2-dihydroxynaphthalene (1,2-DHN) and 1,2-naphthoquinone) dermally to mice (4-5/group). In this study, 2 depurinating adducts (1,2-DHN-1-N3Ade and 1,2-DHN-1-N7Gua) were formed when 1,2-naphthoquinone and enzymically activated naphthalene, 1-naphthol, 1,2-DDN and 1,2-DHN reacted with DNA. In addition, the major stable adducts were formed by 1,2-naphthoquinone. Saeed et al. considered that the formation of these adducts is involved in the initiation of carcinogenesis. It is noted that this study applied naphthalene dermally and used mice rather than rats. However, combined with the information regarding the rate of formation of protein adducts in humans, the relevance of this mechanism to humans cannot be dismissed.

7.9.6.4.9. Metabolites

Kedderis et al. (2014) measured the levels of metabolites formed in nasal respiratory epithelial cells from rats, mice and humans following *in vitro* exposure to 500 µM naphthalene. The results are shown below.

Table 26: Levels of metabolites in the nasal respiratory epithelial cells following exposure to naphthalene; an extract from Kedderis et al. 2014

		Rats	Mice	Humans
Naphthalene metabolite (pmol)	Naphthalene dihydrodiol	6.6/28.8/5.4	23.1/18.8/0	0
	1,2-naphthoquinone GSH conjugate	0/0/95.6	0	0
	1,4-naphthoquinone GSH conjugate	0/9.3/20.6	11.2/0.5/0.4	0
	Naphthalene diolepoxide GSH conjugates	0	7.7/6.5/0	0
	Naphthalene diepoxide diGSH conjugate	0	0	0

The results appear to contrast the finding that naphthalene had a greater effect on cell viability, GSH levels and ATP levels in human cells than in rodent cells in this study. However, cell preparations from each species were also exposed to 1000 and 2000 µM naphthalene. At these concentrations, the decreases in GSH and ATP levels were more dramatic than at 500 µM but unfortunately, measurements of metabolites at these concentrations are not available. Therefore no firm conclusions can be drawn from this information.

7.9.6.4.10. Computational Fluid Dynamics Model

Campbell et al. (2014) investigated cross species dosimetry using a computational fluid dynamics-physiologically based pharmacokinetic (CFD-PBPK) model. The aim of the study was to extrapolate the (non-cancer) NOAELs from rats to humans and derive a human equivalent concentration (HEC). The HEC was defined in the report as 'the continuous exposure concentration in the human that would produce a tissue exposure at the site of toxicity equivalent to that at the NOAEL or LOAEL in the animal.' The study authors used a NOAEL of 0.1ppm (0.524 mg/m^3) from the 90 day rat study (Dodd et al. 2012).

The authors developed the model by extrapolating metabolic rates from rats and monkeys *in vitro* to *in vivo.* The model predicted a HEC of 0.12 ppm (0.63 mg/m^3) in the dorsal olfactory region. The study authors commented that, 'the metabolic capacity in the human is insufficient to produce the higher rates of metabolite production estimated for the rat.'

7.9.6.4.11. Conclusions by others on the human relevance of tumours

The relevance of the animal data to humans has been addressed by a number of authors.

In the absence of clarity regarding the relevance of positive animal bioassays to human health, the panel at the Naphthalene State of the Science Symposium (NS3) held in 2006 questioned the value of the available data for making regulatory decisions (North et al. 2008).

Rhomberg et al. (2010) were cautious about extrapolating the results observed at very high doses in animal bioassays to humans and commented that the lack of case reports of nasal tumours in humans suggested that naphthalene was not a causal factor.

The carcinogenic and genotoxic potential of naphthalene were evaluated by the Health Council of the Netherlands in 2012. The Health Council concurred with the assessment made by Rhomberg et al. (2010) and considered that carcinogenesis in rodents following naphthalene exposure is not relevant to humans.

Lewis (2012) reported on the human relevancy of animal carcinogenicity. After reviewing the available data, Lewis noted that no epidemiological data of workers exposed only to naphthalene are available. However, on the basis of differences in anatomy and metabolism in the upper respiratory tract of rats and humans, Lewis considered that the relevancy of the rat data to human health was somewhat questionable.

Bailey et al. (2015) considered that the data indicate that at typical human exposure levels, the low rate of naphthalene metabolism in humans would not deplete GSH to levels that would cause toxicity and tumours.

The anatomical and physiological differences alone were not considered sufficient by the ASTDR to eliminate concern for the possible human relevance of naphthalene-induced nasal lesions in rodents.

7.9.6.5. eMSCA Assessment of human relevance

7.9.6.5.1. Are the key events in the animal MoA plausible in humans?

For the MoA to be relevant to humans, a cytochrome P450 enzyme must be present in human nasal tissue in order for naphthalene to be metabolised. A CYP2F enzyme, with 82% homology to that found in mice, has been reported in humans (Bogen et al. 2008). Therefore, there is potential for initial metabolism of naphthalene to the epoxide in humans.

7.9.6.5.2. Taking into account kinetic and dynamic factors, are key events in the animal MoA plausible in humans?

Metabolism

The level of the CYP2F enzyme is 10-20 times lower in rhesus macaques than the levels of CYP2F in rodents. Furthermore, the human CYP2F is thought to metabolise naphthalene at a lower rate than the CYP2F isozyme expressed in rodents (Bogen et al. 2008, Bailey et al. 2015). In microsomal preparations, naphthalene and its metabolites were metabolised at a greater rate in rodents than in non-human primates (Buckpitt et al. 2013).

Although the available evidence suggests that initial metabolism of naphthalene is lower in monkeys and humans than in rats, DeStefano-Shields et al. (2009) found that covalently bound metabolites are formed at similar rates in the nasal epithelium of rhesus macaques and male SD rats.

In vitro, naphthalene has been shown to reduce cell viability and deplete GSH and ATP levels to a greater extent in human cells than in cells from rats and mice (Kedderis et al. 2014).

Physiology and Anatomy

Physiological differences between rats and humans may affect the relevance of the rat data. A computational fluid-particle dynamics simulation showed that the fraction of naphthalene deposited in the human upper respiratory tract decreased from 24% when exclusively breathing nasally, to 16% when exclusively breathing orally (Zhang and Kleinstreuer, 2011). Since rats are obligate nasal breathers, the output of this computational model could suggest that more naphthalene would be deposited in the upper airways of rats than in humans.

The pattern of airflow has been shown to affect the pattern of injury in the nasal cavity following exposure of rats to naphthalene by inhalation (Lee et al. 2005). Due to anatomical differences between the nasal cavities of humans and rodents, this finding could indicate that the pattern of injury in humans may differ from that observed in rats.

7.9.6.5.3. Conclusion

The presence of a CYP2F enzyme in humans indicates that there is a potential for naphthalene metabolism in humans. The anatomical, physiological and metabolic differences between rats and humans, including breathing route, anatomy of the nasal cavity and the likely lower rate of naphthalene metabolism in humans are noted. On the basis of these differences, it is possible that the consequences of naphthalene inhalation in humans will vary from those observed in the rat.

It is acknowledged that there is no evidence of nasal tumours resulting from naphthalene exposure in humans. However, the absence of case reports or other forms of epidemiological study of this issue cannot be considered to represent convincing evidence that the tumours observed in rats are not relevant to humans.

In mice receiving inhalation exposure to naphthalene, tumours were not observed in nasal tissue. However, it is not known whether the mouse or rat is a better model for the effects

of naphthalene inhalation exposure. Therefore the information available is not sufficient to conclude that the finding of nasal tumours in rats exposed to naphthalene by inhalation is not relevant for humans (albeit that humans might well be at least quantitatively less sensitive to such an effect).

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

This endpoint was not evaluated.

7.9.8. Hazard assessment of physico-chemical properties

Naphthalene is a solid with a relatively low vapour pressure but sublimes slowly at room temperature and has a characteristic odour. Naphthalene is not classified as flammable or explosive however it can be considered as capable of forming explosive mixtures with air in particulate or vapour form. Although not an oxidising agent itself naphthalene can be readily oxidised by other oxidising agents and undergoes a violent reaction with chromic oxide, CrO_3.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

In the LOUS (List of Undesirable Substances) Review (2014), the Danish Ministry of the Environment reviewed naphthalene. Denmark noted that the available data indicate the occupational levels of naphthalene are considerably below the current OEL of 50 mg/m^3. However, reference was made to Preuss et al. (2003), who suggested that the occupational threshold limit value for naphthalene should be set at 1.5 mg/m^3. Denmark considered that 1.5 mg/m^3 is an exposure level that can be realistically obtained and provided support to the conclusion of Preuss et al. (2003) on the basis that an increased incidence of nasal tumours were observed in the NTP study in rats at 50 mg/m^3 (the current OEL).

eMSCA DNEL Derivation

There is no information to suggest that short term peak exposures are relevant for nasal effects. Therefore, the eMSCA has derived a DNEL for long term inhalation exposure only.

Table 27: NOAEL and LOAEL values in rats after exposure to naphthalene by inhalation

Study duration Strain of rat	Concentrations (mg/m^3)	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Effects at LOAEL	Remarks
4 hour exposure, SD rats Lee et al. (2005)	17.8±2.6 and 125±8.9	None	17.8±2.6	Continuity of the olfactory mucosa was broken by areas of necrotic olfactory receptor cells Reduced volume of cytoplasm from sustentacular cells above the nuclei Vacuoles in the olfactory epithelium Patches of exfoliated	The concentrations in this study were much higher than those administered in other studies and therefore this study provides minimal information relevant to DNEL derivation.

				cells in the anterior part of the nasal passage	
6 hour exposure, F344 and SD rats Dodd et al. (2010)	0, 0.52, 1.57, 5.24, 52.4 and 157	None	0.52	Nasal olfactory epithelium necrosis in 2/5 SD males and 1/5 SD females.	Nasal olfactory epithelium necrosis was also observed in 1/5 SD female control. 0.52mg/m^3 is considered to be a conservative LOAEC.
5 day exposure (6h/d), F344 and SD rats Dodd et al. (2010)	0.52, 5.24 and 52.	None	0.52	Nasal olfactory epithelium degeneration in 2/10 SD females Nasopharyngeal goblet cell hyperplasia/hypertrophy in 1/10 F344 male and 1/10 F344 female	Nasal olfactory epithelium degeneration was also reported in 1/5 F344 female control. 0.52mg/m^3 is considered to be a conservative LOAEC.
90 days exposure (6h/d, 5d/week), F344 rats Dodd et al. (2012)	0, 0.52, 5.24, 52.4 and 157	0.52	5.24	Hyperplasia of the respiratory epithelium in 10/10 rats (graded as minimal)	
90 days exposure, (6h/d, 5d/week), F344 rats Meng et al. (2011)	0, 0.52, 5.24, 52.4 and 157	0.52	5.24	Minimal hyperplasia in the transitional/ respiratory epithelium.	Limited information about effects on the respiratory and olfactory epithelia is available due to the nature of the study.
2 year carcinogenicity study, F344 rats NTP (2000)	0, 50, 150 or 300	None	50	Olfactory epithelium: atypical hyperplasia, atrophy, chronic inflammation and hyaline degeneration in almost all animals (both sexes) and neuroblastoma in 2/49 females Respiratory epithelium:	The concentrations in this study were much higher than those administered in subsequent studies of shorter duration and therefore this study provides

				hyperplasia, squamous metaplasia, hyaline degeneration and goblet cell hyperplasia in 30-67% of animals (both sexes) and adenoma in 6/49 males Glandular hyperplasia in almost all animals (both sexes) Glandular squamous metaplasia in 3/49 males and 2/49 females	minimal information relevant to DNEL derivation

The NOAEC from the 90 day study was 0.52 mg/m^3 (Dodd et al. 2012). However, the next dose administered to rats in this study was 5.24 mg/m^3, where minimal hyperplasia was observed in the respiratory/transitional epithelium. Therefore, the true NOAEC may lie between 0.52 and 5.24 mg/m^3. However no further information is available to identity a more accurate NOAEC, and therefore a value of 0.52 mg/m^3 will be taken forward to calculate the DNEL.

Workers

NOAEC = 0.524 mg/m^3

The NOAEC was identified from a study where rats were exposed to naphthalene for 6h/day. The following calculation has been done to adjusting the NOAEC to account for exposures of 8h/day:

Inh 8h NOAEC = Inh 6h NOAEC x 6/8 x 0.67

= 0.524 x 6/8 x 0.67

= 0.26331 mg/m^3

As described in the section on 'relevance to humans', the rat is considered to be the most sensitive species for this effect and therefore a value of 1 has been assigned for the interspecies differences.

A standard assessment factor of 5 for workers has been used.

The eMSCA considers that the duration of exposure did not affect the NOAEC and therefore a value of one will be used for the extrapolation of a subchronic exposure to a chronic exposure.

On the whole, the quality of the database is good and therefore an assessment value of 1 is warranted.

Assessment factors: 1 for remaining interspecies differences

5 for workers

1 for subchronic to chronic

1 for quality of whole database

So DNEL = $\frac{0.26331}{1 \times 5 \times 1 \times 1}$ = **0.053 mg/m³**

Table 28

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Repeated dose toxicity (inhalation)	Inflammation of the respiratory/ olfactory epithelium	Dodd et al. (2012)	NOAEC = 0.524mg/m³	DNEL = 0.053 mg/m³	Since the carcinogenicity is considered to arise as a consequence of the cytotoxicity, this DNEL is considered to be protective against both repeated dose toxicity and carcinogenicity.

It is recognised that the DNEL derived from experimental animal data is considerably lower than current levels of exposure in the workplace. Given the lack of consistent evidence for inflammatory changes in nasal lavage and sputum samples taken from workers with daily exposure to levels of naphthalene over 100 times higher than this DNEL (Sucker et al., 2016) the eMSCA considers this is a very precautionary DNEL. Whilst it is possible to use the existing IOEL (50 mg/m³) to derive a DNEL for workers (Appendix R8-13 of ECHA's Guidance on Information Requirements and Chemical Safety Assessment) because of the uncertainties about the sustainability of the current IOELV this approach was not considered by the eMSCA.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

Haemolytic anaemia

Case reports of haemolytic anaemia in humans confirm that naphthalene presents a hazard to human health. However, there does not appear to be a suitable animal model that would allow a dose-response assessment to be made. The available data do not allow a NOAEL to be derived or a DNEL to be calculated. On the basis of the information available and using the estimation of 6 g of naphthalene as a lethal dose to humans, the eMSCA concurs with the conclusion in the ESR Review that values in the mg/kg range are considered to give rise to concern for acute haemolytic anaemia.

Inflammatory effects on the olfactory epithelium and Carcinogenicity

The eMSCA considered that the available data are highly supportive of a cytotoxic mode of action for naphthalene-induced carcinogenesis in the rat nasal cavity, whereby naphthalene is metabolised to cytotoxic (non-genotoxic) metabolites by a CYP enzyme in tumour-forming tissues including in the olfactory epithelium. Those metabolites are thought to be responsible for the inflammation and regenerative hyperplasia which precede carcinogenesis.

A DNEL of 0.053 mg/m³ has been derived for the non-neoplastic lesions. Since this value is considered to be protective for the non-neoplastic precursor lesions, it is also considered to be protective against carcinogenesis. Although no consistent effects on the nasal cavity

were observed in a recent bio-monitoring study, the relevance of nasal tumours to humans cannot be dismissed based on the available data. However, physiological, anatomical and metabolic differences between rodents and humans suggest that the rat is a conservative model.

On the basis of the current information the eMSCA does not consider additional classification is needed and agrees with the existing harmonised classification.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated. Endocrine disruption was not in the scope of this evaluation.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

Overview of sources of exposure to naphthalene

Naphthalene is a naturally occurring substance. It is ubiquitous in the environment, but at very low levels in pristine air. Price and Jaycock (2008) suggest levels of between 1 x 10^{-7} and 3 x 10^{-6} mg/m^3 (2 x 10^{-8} – 6 x 10^{-7} ppm based on the conversion factor of 1 ppm = 5.24 mg/m^3 reported in the ESR review).

Naphthalene occurs in pristine air because it is a product of the incomplete combustion of biomass. It has also been found to be produced naturally by certain species. There are reports that trace amounts of naphthalene are produced by magnolias (Azuma *et al*, 1996). The Formosan subterranean termite has been found to produce naphthalene, possibly as a repellant against predator species such as ants, poisonous fungi and nematode worms (Chen *et al*, 1998). Some strains of the endophytic fungus *Muscodor albus* also appear to produce naphthalene among a range of volatile organic compounds, and *Muscodor vitigenus* produces naphthalene almost exclusively (Daisy *et al*, 2002).

Higher levels are found in suburban and urban air due mainly to traffic pollution and there appears to be high spatial and temporal variability. Price and Jaycock (2008) suggest levels between 1 x 10^{-6} and 0.001 mg/m^3 (2 x 10^{-7} –1.9 x 10^{-4} ppm) would be typical for the United States of America (US) and there is no reason to think that levels would be substantially different in suburban and urban areas across Europe.

Other sources contributing to naphthalene levels in ambient air include emissions arising from the processing of coal, crude oil and natural gas, aluminium, iron and steel production, foundries and power plants as well as industrial processes that manufacture or use naphthalene as a raw ingredient (ECB, 2003). Indeed, naphthalene will be present anywhere that process generating PAHs as a result of combustion are in operation. In combustion processes that emit PAHs, it has been observed that naphthalene is the most abundant PAH. For example, it accounted for 58% of the total PAH emissions from a Danish asphalt factory (Danish EPA, 2015). Emissions also arise from the use of products made from petroleum refining streams such as asphalt, jet fuels and lubricants where naphthalene may be present as a minor component in these UVCB mixtures. Information cited by Price and Jaycock (2008) suggests that in fuels it may be present at between 0.0021 – 1.1% by weight with the highest level reported for jet fuel (JP-8) and in lubricating and motor oils at between 0.00005 and 0.25%. Automotive products containing naphthalene as a minor component include products available for consumers. Other products that may contain naphthalene as an impurity include carbon black. Levels of between 2.3 and 8.68 mg/kg naphthalene have been reported (Danish EPA, 2015).

Price and Jaycock (2008) separate industries where there is a potential for exposure to naphthalene into two categories. The low exposure category includes the refining and petroleum industries, asphalt (paving and roofing) and industries using pitch to

manufacture refractory materials or graphite electrodes. Here it is claimed, daily airborne exposure can be expected to be in the range 0.01 – 0.3 mg/m^3 (8-hr TWA). The high exposure category includes creosote production and use, workers exposed to jet fuels, coal tar and coke industries, production of naphthalene from coal tar and chemical industries using naphthalene as a raw material. Daily airborne exposures are estimated to be in the range of 0.1 – 3 mg/m^3 (8-hr TWA). Naphthalene was used as a biomarker to study inhalation and dermal exposure to JP-8 in air force maintenance personnel (Chao *et al*, 2006). Levels of naphthalene measured in the workers breathing zone over a 4-hour sampling period ranged from 0.0007 – 3.910 mg/m^3 (n= 83, geometric mean 0.61 mg/m^3). Dermal naphthalene levels, measured using a tape stripping process sampling pre-defined regions of the body, ranged from 0.0001 – 5.09 mg/m^2 (n= 85, geometric mean 0.0042 mg/m^3).

Naphthalene is found in indoor air. Price and Jaycock (2008) suggest typical levels are of the order of 0.0001 – 0.01 mg/m^3 (0.000019 – 0.0019 ppm) in US homes. Preuss *et al* (2003) quoted levels of 0.0007 – 0.014 mg/m^3 for German homes. To put these values into context, the odour threshold reported under additional physicochemical information on ECHA's dissemination site is 0.08 ppm[19]. Smoking, use of kerosene space heaters, wood stoves, vehicle emissions and stored petroleum products from attached garages, cooking and use of consumer products containing naphthalene (e.g. mothballs) all contribute. Although naphthalene containing mothballs are no longer used in the EU, many of the other sources are applicable to European homes. Cigarette smoke in particular has been identified as significant source with indoor naphthalene levels estimated to be approximately 10 times higher in the homes of smokers (average concentrations ranged from 0.0018 to 0.0095 mg/m^3) compared with non-smokers (average concentrations ranged from 0.00018 to 0.0017 mg/m^3) (Jia and Batterman, 2010). There is also information suggesting that low levels of naphthalene may be emitted from compact fluorescent light bulbs (Danish EPA, 2015). The Danish report cites tests performed by a German laboratory which found 12 of 14 light bulbs emitted naphthalene at a rate of 0.001 – 0.008 µg/bulb/hr. One outlier emitted naphthalene at a rate of 0.205 µg/bulb/hour.

In most of these situations, naphthalene is found as a vapour, but may also be present in the particuate phase (e.g. in cigarette smoke where naphthalene can be found bound to other particulate material). In indoor environments, naphthalene tends to partition to surfaces which prolongs the duration of exposure.

In addition to airborne and dermal exposure, there is a potential for dietary exposure. The ESR review reported low levels in a range of biota and foodstuffs (ECB, 2003). Cooking processes such as grilling, charbroiling and smoking have the potential to add to the naphthalene content in food (Price and Jaycock, 2008). In 2002, the US EPA estimated that the average daily intake of naphthalene for an adult was 0.041 - 0.237 µg/kd/day (Preuss *et al*, 2003).

Of these possible sources of exposure, the REACH registrations focus on the manufacture of naphthalene and identified uses for naphthalene itself. UVCB substances which may contain naphthalene as a component are covered by separate registrations and are not discussed in this evaluation. However, when deciding on the significance of the exposures estimated for naphthalene in REACH registrations it is important to take account of the existence of a wide range of additional possible sources all of which will contribute to the daily body burden received by an individual.

[19] https://echa.europa.eu/registration-dossier/-/registered-dossier/15924/4/24 (site accessed 11 October 2016)

7.12.1. Human health

The exposure assessments submitted by the registrants cover manufacture (including manufacture under strictly controlled conditions (SCC)), industrial use an intermediate (including use under SCC as a feedstock in the manufacture of other chemicals), industrial use to manufacture grinding wheels and its use to formulate smoke bombs/grenades for military use. Scenarios have also been provided covering military use of smoke bombs/grenades and service life of smoke bombs/grenades. No consumer uses have been identified and none of the registered uses are expected to lead to service life exposure for consumers.

7.12.1.1 Worker

The worker exposure assessments primarily rely on modelling calculations to estimate full shift exposure (mainly ECETOC TRA version 3 but ECETOC TRA version 2 has been used to assess exposure to naphthalene during use in the manufacture of grinding wheels). Short-term peak exposures have not been modelled and the eMSCA agrees with the registrants that this is not required for naphthalene.

Naphthalene is a subliming solid. In certain processes it is handled at elevated temperature 90°C or above to prevent the material solidifying in pipelines and vessels. Exposure will therefore predominantly be to vapour/fume. In order to generate exposure esimates using the TRA tool, the registrants have assumed that naphthalene will behave as a medium or high dustiness solid. Although this approach has not been formally implemented within the TRA tool, the tool developers reviewed the approach as part of the improvements introduced with version 3 (ECETOC, 2012). The tool developers concluded that this approach is likely to provide very precautionary estimates (ECETOC Technical Report 114, Appendix E). The eMSCA is therefore satisfied that the TRA tool has been used within its applicability domain.

7.12.1.1.1 Published measured data

There is very little information in the public domain on current worker exposure to naphthalene during REACH registered uses. Preuss *et al* (2003) published a collation of exposure measurements and biological monitoring results obtained from literature published in the preceeding 25 years. Although this paper includes some information relating to naphthalene distillation and the manufacture of phthalic anhydride, the original reports were published in the late 1990s. As such, the information may not be relevant to current working conditions and has not been taken into account in this evaluation. The paper does give an indication of industries where naphthalene may be generated as a process by-product. Recently, a study has been performed to measure exposure to naphthalene during the manufacture of abrasives (Sucker *et al*, 2016). This study is discussed below under the relevant scenario heading.

7.12.1.1.2 Manufacture including manufacture under SCC

Naphthalene is manufactured in predominantly closed processes. According to information provided in 2007 for the risk reduction strategy document, sites are often highly automated with machines and robots undertaking jobs such as packaging naphthalene granules/flakes into bags. Although much of the manufacturing process takes place under strictly controlled conditions (SCC), the registrants state that the process to solidify naphthalene to produce flake/granules does not meet the requirements for SCC. The following discussion relates to manufacturing processes that are not performed under SCC at all stages of the process.

The PROCs selected by registrants to describe manufacture include PROCs 1, 2, 3, 8a, 8b and 15. The greatest potential for worker exposure occurs during sampling, tanker filling, granulation, packaging and maintenance activities. Sampling and tanker loading tasks may occur up to eight times per day. Exposure will therefore arise as a series of short, but potentially high, peaks and will be to both particulate and vapour, although the latter is

likely to be the greatest contributor to exposure. High peak exposures may also arise during the manual handling which may occur during granulation and packaging.

When the ESR RRS was prepared, the majority of EU production sites appeared to rely more on personal protective equipment (PPE) than containment to limit worker exposure during activities such as sampling. The PPE described in the risk reduction strategy included overalls, safety shoes, safety goggles and CAT II tested chemical resistant disposable gloves (nitrile-rubber) or leather gloves. CAT II gloves are designed to protect against intermediate risks in accordance with the Personal Protective Equipment Directive (89/686/EEC). Where respiratory protective equipment (RPE) was used this took the form of safety goggles fitted with a dust respirator (particle filter FFP3) or masks fitted with organic filters. Protection factors were not reported. Only one site had implemented containment (closed boxes with LEV) around sampling points. At this site, breathing apparatus with multi filter was required during vaccum cleaning, with maintenance at the flaker drum requiring air-fed breathing apparatus.

From the information provided in REACH registrations it is not clear if this information is still applicable. The eMSCA has been told informally that Cat III gloves are now used in many cases. Cat III gloves are designed to be used for irreversible or mortal risks. In addition to the indepentent testing and certification necessary for the gloves to carry a CE mark which must be performed for Cat II gloves, the quality assurance system must be independently checked[20].

In relation to other risk management measures, one registrant reported a need to use RPE (confirming to EN 140 fitted with type A filter, protection factor not reported) during sampling from production equipment located outdoors. Gloves, overalls and eye protection were also required. This registrant also reported a need to use RPE (described as before), gloves and eye protection as a secondary measure for material transfers covered by PROC 8b where containment or LEV is fitted at fill points. Other registrants did not provide this level of detail in their CSRs. The exposure calculations did not take account of the use of LEV or RPE, even for transfers covered by PROC 8a where a high potential for exposure may be expected. The only risk management measures identified were gloves for activities covered by PROCs 8a and 8b and some requirements for general ventilation for transfers taking place indoors. This does not mean that a higher level of control has not been implemented in practice. It could simply reflect the case that the registrants have identified the minimum RMMs required to maintain 8-hr TWA exposure below their DNEL.

A specific assessment has not been provided in REACH registrations for routine cleaning and maintenance. These activities have the potential to produce high exposures and may require different risk management measures to those required for other activities associated with naphthalene manufacture. In this situation, it may be appropriate to consider cleaning and maintenance as a separate contributing scenario. According to version 3.0 of the Information Requirements and Chemical Safety Assessment Guidance (IR & CSA) Guidance, Chapter R.14, section R14.5.1, exposure assessments should include a contributing scenario describing conditions for periodic cleaning and maintenance if such activities are not already covered in one or more of the other contributing scenarios.

Note to registrants: To ensure that it is transparent in the exposure scenario how all relevant work activities are covered, it is helpful to either include a specific contributing scenario for routine cleaning and maintenance activities or indicate which of the already chosen contributing scenarios apply to these activities.

[20] http://www.ansell.eu/industrial/pdf/en-guide/EN%20Guide_EN.pdf. From 21 April 2018, Directive 89/686/EEC will be repealed by the new Regulation (EU) 2016/425 of the European Parliament and of the Council of 9 March 2016 on personal protective equipment.

Inhalation

To provide context to the exposure information provided in registrations, it is helpful to look back at the information provided for the ESR review and risk reduction strategy and this will be done for each exposure scenario. The exposure data for manufacture that was submitted for the ESR review came from various tar distillation plants operated by one EU producer.

Table 29: Occupational exposure to naphthalene during tar distillation (various plants throughout Europe) as reported in the ESR review (ECB, 2003)

Plant area	**Range (mg/m^3)***
Crystallisation	0.1 to 0.8
Laboratory	0.40
Tank car loading with coal tar products	0.76 to 4.8
Coal tar distillation	0.16

* The number of samples was not reported

These results were stated to be representative, to derive from personal sampling and reflect 8-hour TWA exposure. A further value of 6.3 mg/m^3 (assumed to represent an 8-hr TWA) was reported as the highest value recorded. This was taken forward to the risk characterisation. For the ESR RRS, a small number of additional measurements (collected between 2003 and 2007) were provided from 3 of the seven manufacturing sites in operation in the EU at that time. The new measurements appear to be consistent with the data reported in the ESR RAR. However, the contextual information accompanying the new data was incomplete so the original exposure estimate from the ESR RAR was used for the risk reduction strategy.

Moving forward to the REACH registrations, although early versions of CSRs included measured data, most registrants have updated and now rely solely on modelled estimates to characterise exposure during manufacture (ECETOC TRA V3). The measured data was collected between 2007 and 2010 and is stated to represent a typical European manufacturing operation. The samples were taken during normal operating conditions and included a mixture of personal and static, vapour and dust measurements. Unfortunately sampling duration was not reported so it is not possible to obtain time weighted averages from the most recent measured data and it cannot be used for the risk characterisation.

The risk characterisation provided by the registrants is based on modelled data and the eMSCA will also use modelled data for its assessment.

Dermal

Dermal exposure can occur during the production of naphthalene, when operators come into contact with surfaces contaminated from splashing or condensed vapour, or as a result of direct contact onto the skin. As processing predominantly takes place in closed systems, dermal exposure will primarily occur during activities such as sampling and the uncoupling of pipes or cleaning of occasional spills. This was characterised in the ESR RAR as "direct handling with incidental contact" and it was assumed that operators wore gloves. Dermal exposure was predicted to be within the range 0 – 0.1 mg/cm^2/day but thought likely to be at the lower end for most activities. The upper end of the range was thought to reflect exposure during maintenance activities. This assessment was not changed when the risk reduction strategy was prepared.

The modelled dermal exposure estimates reported in registrations suggest dermal exposure may be an order of magnitude higher. Not all calculations assumed the use of gloves (glove use was taken into consideration for PROCs 8a and 8b) and this is one

possible source of overprediction since the use of gloves may be more widespread than has been assumed for the purposes of REACH exposure calculations. There is also the possibility that the use of estimates for a medium/high dustiness solid results in overprediction.

Recommendations from the risk reduction strategy

The ESR RRS concluded that containment should be implemented where possible and that the PPE being used, in particular the use of CAT II gloves was not suitable for naphthalene since this is regarded as a high hazard substance whereas CAT II gloves are tested for medium hazard substances. It was also recommended that an industry code of good practice should be drawn up. It appears that Cat III gloves are now used. The PROC codes selected to describe manufacture suggest that this takes place in predominantly closed systems. It is not known if there is scope for further containment around the transfers described by PROC 8a. The eMSCA has no information about whether or not a code of good practice has been developed.

Conclusions about exposure during manufacture

Several sources of uncertainty have been identified in relation to the inhalation and dermal exposure estimates presented in registrations. The eMSCA does not expect that the modelled estimates which are being used for the risk characterisation underestimate potential exposure. However, it is not possible to determine if there is any substantial overestimation given the uncertainty. It is also not clear if the recommendation for greater use of containment has been implemented to the fullest extent possible. The eMSCA will therefore assume that the modelled estimates are representative of the exposures likely to arise where naphthalene is not manufactured under SCC and that the parameters chosen to calculate these estimates reflect current operating conditions and risk management measures.

7.12.1.1.3 Use as an intermediate including use as feedstock in the manufacture of other substances under SCC

Two scenarios have been submitted to cover the use of naphthalene to manufacture other substances. These are use as a feedstock in the manufacture of other substances under SCC and use as an intermediate.

Use as a feedstock in the manufacture of other substance under SCC is described with PROCs 2, 3, 8b and 15. No exposure estimates have been provided for this scenario but registrants have provided a description of the SCC that are applied. Since no exposure assessment has been provided, this scenario will not be discussed further. The following discussion relates to use as an intermediate where SCC are not implemented at all stages of the process.

The PROCs selected by the registrants to describe this use include PROCs 1, 2, 3, 4, 8a, 8b, 9 and 15.

Most of the information available for the ESR RAR and RRS came from a UK site using naphthalene to manufacture phthalic anhydride and it was assumed that the working conditions would be similar for other intermediate uses since these also take place in closed plant. For the ESR RRS, additional sites provided information about the controls that were in use. As is the case for manufacture, the main opportunities for exposure arise during sampling and maintenance. Exposure may also occur during delivery where a small amount of naphthalene is run off (to remove possible contaminants) prior to connecting to the storage tank. The pattern of exposure is therefore likely to be to a series of short but potentially high peaks.

The risk management measures that were used for these tasks included gloves (where reported these were described as "Cat II tested ABCD" – the letters denote the chemical classes which the gloves have been tested with), safety helmets, goggles, respirators (where reported the type was described as A1P1 representing a low capacity/efficiency

filter suitable for organic vapours and particulates) and safety boots. Two sites also referred to the use of LEV but did not give information on the processes where it was applied. Where periodic maintenance is performed and workers need to enter vessels to scrape out solidified naphthalene, air line breathing apparatus and gloves are worn.

It is not possible to see if the situation has changed since REACH entered into force based on the information provided in REACH registrations. The exposure calculations do not take account of the use of RPE or LEV. There are requirements for gloves to be worn for activities covered by PROCs 4, 8a, 8b and 9 and general ventilation for PROCs 4, 8a and 8b where these processes take place indoors. As noted previously, this may reflect the case that the registrants have identified the minimum RMMs required to maintain 8-hr TWA exposure below their DNEL rather than present an accurate picture of current operating conditions and risk management practices.

Inhalation

The exposure data that was submitted for the ESR RAR (see table 30) came from a personal air sampling exercise undertaken in 1994. It was considered that occupational exposure during the manufacture of other substances would be similar to these data for phthalic anhydride.

Table 30: Occupational exposure to naphthalene during its use in the manufacture of phthalic anhydride as reported in the ESR RAR (ECB, 2003)

Task	Result (mg/m^3)*	8-hour TWA (mg/m^3)
Process operator	0.38	0.57
Charge hand	0.22	0.33
Process operator	0.62	0.93
Charge hand	1.30	2.00

* Results represent single data points for a 12-hour shift

For the ESR review, the maximum value of 2 mg/m^3 was used as the basis for the risk characterisation. For the ESR RRS, a small number of additional measurements (collected between 2003 and 2007) were provided none of which exceeded the value used for the risk characterisation in the ESR RAR. No new measured data have been submitted in REACH registrations, hence the risk characterisation will rely on modelled data. The modelled estimates (generated using ECETOC V3) imply that exposures to naphthalene during its use as an intermediate will be very similar to exposures during manufacture and the parameters used to generate modelled estimates are the same. Given that this use of naphthalene is performed under very similar conditions to manufacture, the eMSCA identifies the same uncertainties in relation to these modelled estimates.

Dermal

Dermal exposure can occur as a result of contact with contaminated surfaces due to splashing or condensed vapour or as a result of direct skin contact during sampling and the uncoupling of pipes. As for manufacture, this was characterised in the ESR RAR as "direct handling with incidental contact" and it was assumed that operators wore gloves. Dermal exposure was predicted to be within the range 0 – 0.1 mg/cm^2/day but thought likely to be at the lower end for most activities. The upper end of the range may reflect exposure during maintenance activities. This assessment was not changed when the risk reduction strategy was prepared.

The modelled dermal exposure estimates reported in registrations suggest dermal exposure may be an order of magnitude higher. Not all calculations assumed the use of gloves (glove use is taken into account for PROCs 4, 8a, 8b and 9) and this is one possible

source of overprediction since the use of gloves may be more widespread than has been assumed for the purposes of risk characterisation calculations. There is also the possibility that the use of estimates for a medium/high dustiness solid results in overprediction.

Recommendations made in the risk reduction strategy

The recommendations made in the ESR RRS document are very similar to those for manufacture. These include greater use of enclosures around sampling points and greater use of LEV to capture releases at source. Questions were raised about the suitability of CAT II gloves and there was a recommendation for industry to develop good practice guidance. It is not clear how widely these recommendations have been implemented based on the information presented in the CSRs.

Conclusions about exposure during use as an intermediate

The conclusions for use as an intermediate are the same as those for manufacture. Several sources of uncertainty have been identified in relation to the inhalation and dermal exposure estimates presented in registrations. The eMSCA does not expect that the modelled estimates which are being used for the risk characterisation underestimate potential exposure. However, it is not possible to determine if there is any substantial overestimation given the uncertainty. It is also not clear if the recommendations from the risk reduction strategy for greater use of engineering controls such as containment and LEV have been implemented. The eMSCA will therefore assume that the modelled estimates are representative of the exposures likey to arise during use as an intermediate where SCC are not applied at all stages of the process and that the parameters chosen to calculate these estimates reflect current operating conditions and risk management measures.

7.12.1.1.4 Use of naphthalene in the abrasive industry

Napthalene is used as a pore forming agent in the production of inorganic bonded abrasive tools (grinding wheels). The registrants have described this process using PROCs 5 and 14. Sized granules of crystalline naphthalene are blended with other components such as grit and binders. The proportion of naphthalene in these blends ranges from 5 – 40% by volume. The blends are then cold pressed to give the required shape/density and dried to remove excess moisture. Pressing typically takes 1-2 minutes and involves pressures of up to 14 – 35 MPa (2,000 – 5,000 pounds per square inch (psi)). The grinding wheels are then stored on drying racks (in chamber dryers or vacuum driers) at temperatures of 50 – 150°C for several hours (up to 45 hours may be needed in some cases to ensure crack free drying) to allow the naphthalene to volatilise out of the wheel leaving behind pores. Naphthalene removal may also be carried out using steam recovery where the wheels are placed inside an oven and steam injected. In this process, the driven off naphthalene is carried on the steam and recovered from the subsequent condensate. Finally, the wheels are placed inside a kiln at around 1,200°C (range 850 – 1,300°C) to "cure" in a process that can take between 40 and 120 hours depending on the size of the grinding wheel. The curing process means that finished grinding wheels do not contain any residual naphthalene.

Information provided in early versions of CSRs suggested that typically LEV is applied where dust generation or vapour release is expected. However, assessments were also provided to cover situations where LEV is not in use. Air conditioning may also be in operation to limit the build up of volatilised naphthalene in work areas. No RPE is worn for routine tasks but may be required for maintenance activities where there is the potential for exposure to excessive levels of dust/vapour. Gloves are worn, the registrants identify the glove materials and thicknesses that are required depending on the duration of activities. Organisational measures that are in place include training, regular cleaning, the use of dedicated storage areas and it is reported that periodic medical surveys are undertaken.

Inhalation

A recent report by Sucker *et al* (2016) provides comprehensive information about exposure to naphthalene in abrasives manufacture including a description of the operational conditions and risk management measures that were in place at the time the samples were collected (between July and October 2014 from 5 abrasive manufacturing sites located in Germany and Austria). It is assumed that these sites are representative for other abrasive manufacturing sites across the EU. At each site, sampling took place on Thursday of the week that health investigations were also performed (see section 7.9.8 for details). Both personal and static measurements were made. Personal monitoring included 15-minute samples collected onto Tenax® TA tubes (these detect substances in the vapour phase) and 4 - 5.5 hour samples collected via the GGP-Mini sampling head (designed to simultaneously sample vapour and particulate fractions). Static monitoring was performed in areas where naphthalene exposure was expected to occur. Sampling devices were located at a height of approximately 1.5 m and included up to 8 hour sampling using the GGP-Mini sampling head to record the vapour and particulate phase and silica gel tubes which will record only the vapour phase. The limits of detection/quantification were not reported.

Exposures during the production of grinding wheels will be to both naphthalene particulate and naphthalene vapour. During early stages of the process, sieving, weighing, blending and pressing particulate exposure is likely to dominate as the naphthalene blends are transferred to and from storage / transfer containers and scooped in smaller quantities to weigh scales and moulds. Typically the components of the grinding wheels are prepared and mixed in the same working hall as the moulding and pressing operations. Typically materials are weighed manually, only one site used automated filling of blending machines from storage tanks. Prior to blending, grinding wheel components are sieved either through an automated vibrating screen or manually. Typically LEV is used to limit emissions during sieving and it is stated that most sites have fitted LEV to the blending machines to capture emissions during filling. Where blending involves the addition of binders that result in wetting of the blend, this will help to reduce dust formation. Lids on blending machines are closed during blending, though in some cases may be opened to add ingredients during the blending process. On completion of the blending process, the mixture is collected in a container. It is not clear what controls are in use to limit the release of naphthalene during this transfer. A magazine article published in 2014, includes photographs illustrating the blending and sieving stages (Sawodny, 2014). These show an apparently open transfer of powder from the blender to the sieve without LEV. The worker is wearing a close fitting half mask designed to capture particulates but not vapours, cotton overalls, eye protection and gloves. These illustrations are stated by the registrants to be representative for these activities.

After each batch has been mixed, blenders are cleaned with a hand brush or by "blowing out". Quantities of up to 150 kg may be blended at a time. Preparation of batches, blending and emptying and cleaning the blender typically takes 15 minutes and 6 – 12 blending operations may be performed in each blender per shift. In addition to the use of LEV, mechanically enhanced room ventilation was fitted in the production hall at one site. Others relied on natural ventilation in working areas via opening of gates and ridge turrets.

Blended formulations are typically weighed manually into the moulding and pressing machines but some use of automated feeding was reported. Sometimes blended formulations may be sieved again. The report stated that LEV was sometimes available at weighing stations and some moulding and pressing machines had LEV fitted, but in many cases no LEV was installed.

After the pressing process is completed, residual formulation is swept off the machines with hand brushes. Moulds are cleaned out using hand brushes or by "blowing out". The quantities used per abrasive item range from a few grams to around 15 kg and pressing cycles vary from 2-3 minutes up to around 15 minutes per cycle. Between 15 and 100 abrasive items are produced each shift.

Final processing of the abrasives includes the use of grinding and polishing machines. Sometimes water is used as a dust suppressant but dry processing also occurs. Most machines incorporate LEV. Occasionally closed systems with cooling lubricants are used. Although there should be no exposure to naphthalene from the abrasives at this stage, workstations were sometimes located in areas where naphthalene was handled.

Workers wear respiratory protective equipment (RPE) during mixing and sieving of dusty blends. Sawodny (2014) shows a worker wearing a close fitting but not sealed half mask of a type that is designed to capture particulates but not vapours. This type of RPE does not seem to be consistent with the RPE recommended by the registrants in their guidance for safe use. The worker is also wearing cotton overalls, eye protection and gloves. The emMSCA has been informed that gloves are typically worn when blends containing naphthalene are handled.

Exposure measurements were aggregated across all sites and were stratified according to task and potential for direct exposure to naphthalene. Personal exposure measurements are summarised in table 31.

Table 31: Personal short-term and full-shift exposure*

Working area	**Short-term mg/m³ (15-minute TWA)****		**Full shift mg/m³ (8-hour TWA)**	
	Arithmetic Mean ± SD	**Median (range)**	**Arithmetic Mean ± SD**	**Median (range)**
Direct exposure				
Mixing/sieving (n=11)	15.92 ± 18.41	11.64 (3.47 – 69.6)	8.05 ± 2.96	7.48 (3.62 – 11.58)
Pressing/moulding (n= 14)	6.17 ± 4.39	6.41 (0.23 – 12.83)	4.89 ± 3.68	4.72 (0.36 – 11.16)
Indirect exposure				
Post-processing/finishing (n=12)	0.8 ± 0.75	0.60 (0.2 – 3.05)	0.57 ± 0.23	0.52 (0.2 – 0.96)
No or rare exposure				
Finshing/packing (n=13) (spatially separated)	0.12 ± 0.05	0.12 (0.04 – 0.2)	0.17 ± 0.1	0.13 (0.06 – 0.36)
Office (n=10) (spatially separated)	0.05 ± 0.04	0.05 (0.01 – 0.13)	0.33 ± 0.39	0.14 (0.05 – 1.05)

* The LOD for the sampling and analysis procedure was not reported and no information was provided on the procedure to deal with non-detects in the statistical analysis. The eMSCA also noted some discrepancies between the tabulated exposure data and the data that was presented in scatter plots by Sucker *et al*. This table is based on the tabulated data.

**The device used to collect short-term samples is designed to sample the vapour phase and hence these values may underestimate short-term worker exposure in situations such as sieving and mixing where particulate aerosols may be generated in addition to vapour. However, no differences were observed between static sampling devices designed to collect vapour only or vapour and particulate suggesting that any underestimation may be small.

For areas where direct exposure to naphthalene may occur, no distinction was made between measurements taken where LEV was and was not in operation.

The highest short-term naphthalene concentrations for directly exposed workers were obtained for sieving of pure naphthalene. The data set included 4 short-term measurements that exceeded 50 mg/m^3 demonstrating that high peak exposures can occur during this activity. Sucker *et al* (2016) also commented that the lowest naphthalene concentrations measured for mixing and for moulding/pressing were for workstations

located close to an open window. The mean full shift exposure for workers engaged in mixing where the workstation was adjacent to an open window (3.62 mg/m^3, 8-hr TWA) was approximately half of the value for workers situated at mixing stations elsewhere (7.75 mg/m^3, 8-hr TWA). The maximum short term exposure in the "window" group (4.93 mg/m^3, 15-minute TWA) was almost ten times lower than mixers located away from windows (41.83 mg/m^3, 15-minute TWA). The high short term exposures observed during sieving and observation that working next to an open window is associated with significantly lower exposures suggests that where LEV was used, it may not have been working effectively. Use of dry hand brushing and "blowing out" (which implies the use of compressed air or similar to blow away contaminants) mixing vessels and moulds, if this is done, could also have contributed to the high transient peaks and higher concentrations away from windows. Dry hand brushing and use of compressed air are not consistent with good occupational hygiene practice for a hazardous substance and alternative ways of cleaning equipment should be considered.

Working areas with potential bystander exposure included e.g. the turning shop, the post- and final processing where this was located in the same area as other production stages, the firing kilns and storage silos.

The remaining two groups include workers engaged in finishing/packing activities where this is physically separated from other production stages and office staff. At some sites, office and planning areas were situated within the production areas and managers and quality control staff spent some of their time in areas with naphthalene exposure. Elsewhere, offices were located separately and employees would only rarely enter production areas (less than 30 minutes per day or 3 hours per week). It is assumed that the office measurements do not include data from sites where the office is located within the production area. The exposures measured for bystanders and office workers suggest airborne exposures for these groups will rarely exceed 1 mg/m^3. This is still in the same region as the high industry exposure category reported by Price and Jaycock (2010).

The measurements reported by Sucker *et al* (2016) appear to be consistent with the measurements reported in registrations and the information made available for the ESR RAR. For the ESR RAR, measured data were provided for one EU site manufacturing grinding wheels. The data set consisted of two personal vapour measurements collected on separate occasions. Exposures were 2.9 and 5.4 mg/m^3 8-hour TWA. This plant had fitted LEV to the mixers, although mainly to control dust evolving during mixing and not during material transfer to and from vessels. Due to the limitations (e.g. unidentified exposure location, sample period, low number of samples, exposure period etc) in the industry data set, modelled (using EASE) data was used to generate exposure estimates for the risk characterisation. The following estimates were used for the risk characterisation:

- Inhalation (with LEV): 1.4 – 3.1 mg/m^3 (0.27 – 0.59 ppm)
- Inhalation (without LEV): 6.9 – 20 mg/m^3 (1.32 – 3.81 ppm)

Early versions of CSRs report measured data collected from 3 EU sites. The data were split into the following activities:

- Weighing, sieving and mixing (n = 9)
- Forming and pressing (n = 10)
- Storage, drying and firing (n = 10)

The measurements apparently included both personal and static measurements. Workers wore gloves, eye protection and protective overalls. In some cases mechanically assisted ventilation or LEV was in place, but most samples were taken in areas where LEV was not in use.

Taking all of the available information together, it is the eMSCA's opinion that 10 mg/m^3 (8hr TWA) can be taken as a reasonable worst case exposure for airborne exposure to

naphthalene during abrasive manufacture. This is the number that the eMSCA will use in its risk characterisation. The eMSCA has noted evidence that current working practices and ineffective LEV may have contributed to the high expsoures reported for workers engaged in activities with potential direct contact with naphthalene. It is also noted that the samples were collected during the summer and early autumn when ambient temperatures were high and this could have increased volatilisation of naphthalene from powdered blends compared with the levels of volatilisation that could occur during periods of lower ambient temperature. These factors will be taken into consideration in the risk characterisation.

As an observation, in addition to the measured data provided in early versions of CSRs, modelled exposure estimates (ECETOC TRA V2) were submitted to complement the measured data. It was assumed that naphthalene behaved as a medium dustiness solid and calculations were performed both with and without LEV. Interestingly, the modelled estimates are below the "average" values obtained from the measured data provided in early versions of CSRs and are below the lower end of the ranges estimated using the EASE tool in the ESR RAR suggesting that the assumption that naphthalene behaves as a medium dustiness solid may be inaccurate for this scenario. The previous EASE estimates correspond more closely with the measured data.

Dermal

Dermal exposure to naphthalene is likely during the manufacture of grinding wheels from handling the blends and from contaminated surfaces. This work involves considerable dermal contact with the dry blends and unfinished wheels. For the ESR RAR, this was characterised as "direct handling with extensive contact, where extensive refers to greater than ten significant contacts in a shift". This results in a prediction of 1 to 5 mg/cm^2/day. Since operators will for most of the time be in contact with blends containing only 30% naphthalene the prediction was reduced to to 0.3 to 1.5 mg/cm^2/day.

Estimates generated using the ECETOC TRA tool version 2 suggested potential dermal exposures to be an order of magnitude higher than the range identified in the ESR RAR. The registrants applied a linear reduction to the initial estimates to take account of the assumption that blends may contain up to 40% naphthalene. Even with this reduction, the registrants are using values 3-4 times higher than those used in the ESR RAR. The values that are being used by the registrants may overestimate dermal exposure given that information provided to the eMSCA by abrasive manufacturers indicates that blends typically contain only 10-13% naphthalene.

The eMSCA used the ECETOC TRA tool version 3 to generate dermal exposure estimates. The model prediction is not affected by the degree of dustiness assumed. It is assumed that workers wear gloves with 80% effectiveness. For a mixture containing >25% naphthalene and for the situation where LEV is not in use, the following exposures are estimated:

- PROC 5 2.74 mg/kg/day
- PROC 14 0.69 mg/kg/day

The eMSCA will take these values forward to the risk characterisation.

If it is assumed that LEV is in operation and this is taken into account for dermal exposure, these estimates are reduced by a factor of 10. This reduction is not considered relevant for naphthalene since the tasks likely to give rise to the greatest dermal exposure (manual sieving and brushing out mixing vessels and moulds) involve direct dermal contact.

Biological monitoring data

Sucker *et al* (2016) performed analyses of urine samples for 1-naphthol and 2-naphthol as biological markers of exposure. Pre- and post-shift urine spot samples were collected from exposed workers each day of the week that the health investigations took place. In

addition, post-shift samples were collected from reference subjects (those expected to have no or rare naphthalene exposure) on Monday and Thursday. Samples were analysed according to the method published by the MAK Commission (see table 32). The limit of quantification for the method was stated to be 1 µg/L. Since smoking may contribute to naphthalene metabolite levels, smoking status was objectively verified by quantifying urinary cotinine levels using a value of 100 µg/L to distinguish between smokers and non-smokers.

Table 32: Biomonitoring results

	Pre shift µg/L				**Post shift µg/L**			
	Mean (range)	**Median (25-75%ile)**	**95%**	**Number > BAR**	**Mean (range)**	**Median (25-75%ile)**	**95%**	**Number > BAR**
Direct naphthalene exposure (n=27)								
Monday	239 (6-1543)	156 (35-259)	958	20	1228 (38-4715)	767 (222-1886)	3540	27
Thursday	968 (33-6139)	612 (179-1317)	2512	26	1909 (37-7438)	1569 (765-2650)	4869	27
Indirect naphthalene exposure (n=26)*								
Monday	25 (1-102)	16 (17-30)	85	6	36 (10-58)	36 (27-47)	55	3
Thursday	35 (10–55)	41 (18-52)	54	3	70 (4-199)	51 (19-121)	162	16
No or rare naphthalene exposure (n=10)								
Monday	9 (2-18)	7 (3-14)	18	0	n/a			
Thursday	n/a				15 (0-65)	10 (4-17)	46	1

* Samples were collected from 26 workers, pre-shift on Monday and post-shift on Thursday. Initially 20 in this group were assessed as having no or rare exposure and so samples were only taken on Monday morning and Thursday evening. Six workers from this group were sampled throughout the week.

When interpreting biological monitoring data it is helpful to establish some points of reference. A Biologischer Arbeitsstoffreferenzwert (BAR) of 35 µg total urinary 1- and 2-naphthol/L urine has been established by the German Research Foundation (Deutsche Forschubgsgemeinschaft, DFG). This is the 95th percentile of levels from people who do not smoke and are not occupationally exposed to naphthalene. Results at or below this level in people with potential occupational exposure suggest that their exposure at work is not making a significant contribution to exposure from other sources. Other biomonitoring studies quoted by Preuss *et* al (2003) reported urinary 1-naphthol levels ranging from <1 – 30.5 µg/L and 2-naphthol levels ranging from <0.5 – 12.9 µg/L in non-smokers. Sucker *et al* (2016) calculated a total urinary 1- and 2- naphthol level corresponding to exposure at the recently established German AGW value of 0.5 mg/m^3. Based on the data they collected from this group of workers they estimated this would be around 97 µg/L or 86 µg/g creatinine. They also estimated that the urinary concentration corresponding to the IOELV value of 50 mg/m^3 would be 22000 µg/L or 12500 µg/g creatinine.

Very few samples were below the LOD. In workers with no or rare exposure at work, levels generally remain below the BAR throughout the week. In workers with indirect exposure, although there was a trend for levels to increase through the week, levels remained close to or below the BAR in pre-shift samples. It was only in post-shift samples collected later in the week that levels started to rise above levels deemed to correspond to exposure at the German AGW value.

A different picture was found for workers with direct exposure. In this group, most workers had levels of urinary 1- and 2-naphthols in excess of the BAR at the start of the working week and in many cases the levels at the start of the week were also higher than levels

deemed to correspond to exposure at the AGW value. Workers with the highest levels exceeded this value by 10 – 15 fold indicating that several workers from this group are maintaining a raised body burden of naphthalene from one week to the next. Across the shift and through the week, urinary levels showed clear increases from the levels recorded at the start of the week. In end of shift samples, urinary levels for the majority of directly workers exceeded levels deemed to correspond to exposure at the AGW value. The highest urinary 1- and 2-naphthol level of 10127 µg/L was reported for a post-shift sample collected from a directly exposed worker on Tuesday (mid-week results were reported in Sucker *et al* (2016) but have not been presented in table 32 above).

These biological monitoring results show that under current working practices at these sites, there is a potential for significant exposure to naphthalene for directly exposed workers (i.e. those engaged in mixing/sieving and pressing/moulding). The observation that several of the directly exposed workers start the week with body burdens well above levels deemed to correspond to exposure at the AGW value is a concern. Additional controls and improvements in working practices should be implemented to reduce the body burdens that workers are receiving. Given that the photographs in Sawodny (2014) apparently show representative working conditions, it may be useful to consider if exposure to naphthalene in the vapour phase is making a greater contribution to worker exposure than has been assumed. It may be useful to reconsider the way inhalation exposures are managed.

Recommendations made in the risk reduction strategy

Concerns were raised in the risk reduction strategy that even if LEV was implemented across the sector, this might not be sufficient to reduce exposures to levels that would be considered acceptable. It was recommended that new exposure information should be generated and this has been done. Companies were also advised to pursue substitution as far as possible. Although the tonnages of naphthalene that are currently reported to go to this use are of the order of several hundred tonnes per annum, information provided informally by the abrasive industry during the evaluation indicates that some companies have successfully replaced naphthalene.

Conclusions about use to manufacture abrasives

Allthough improvements have been made in response to the ESR RRS, the new exposure data and accompanying contextual information suggests that additional improvements may be required.

It is evident from the biological monitoring data that the body burdens attained during the working week are sufficiently high that they cannot be cleared over the weekend. Assuming gloves are worn when blends containing naphthalene are handled, the high body burdens will have occurred as a result of inhalation exposure. The activities contributing the greatest to airborne naphthalene levels are sieving and mixing. For these activities, short-term (15-minute TWA) peaks of around 70 mg/m^3 have been reported with full shift (8-hr TWA) values averaging 8.05 ± 2.96 mg/m^3. Practices which could contribute to high transient peaks include manual weighing and sieving of dry particulate material with ineffective or no LEV, inadequate enclosures around filling points, briefly opening lids on blending machines during mixing to add ingredients and the use of dry hand brushing and "blowing out" (which the eMSCA assumes refers to the use of compressed air to blow particulate out of moulds). It is also possible that dermal exposure may be contributing to total body burdens if suitable procedures are not in place to manage glove use.

Naphthalene is a hazardous substance and it is a concern that the body burdens attained during the working week by directly exposed workers cannot be cleared from the body over the weekend.

The eMSCA therefore recommends that working practices in this sector should be reviewed. Clear information needs to be provided in the exposure scenario about the correct risk management measures that should be used, including information about appropriate

methods for routine cleaning. Downstream users need to ensure that they fully comply with the exposure scenario.

Note to registrants: In the light of the new information about the exposures and body burdens that can be attained under current working practices, registrants are advised to work with the abrasives sector to develop good practice guidelines for the use of naphthalene. Exposure scenarios should be updated so that safe working practices are documented unambiguously. Particular attention should be paid to the methods specified for routine cleaning of mixing vessels and moulds during production. It may also be useful to consider developing additional communication tools e.g. posters/videos which can be used by downstream users in worker training programmes.

7.12.1.1.5 Formulation of smoke bombs/grenades (military use), military use (including reloading) and service life.

Although the ESR RAR reported use of naphthalene in pyrotechnics which included pyrotechnics used for special effects in the film industry, this source of exposure was not specifically discussed in either the ESR RAR orrisk reduction strategy. The only exposure information about this use therefore derives from modelled data (ECETOC TRA V3) submitted in registrations and the scenario has been specifically limited to military use.

The life cycle for smoke bombs/grenades containing naphthalene has been divided into three scenarios. The PROCs selected for these scenarios include:

- Formulation: PROCs 4, 5, 8a, 9, 14, 15 and 19 (activities may take place indoors or outdoors).
- Military use (including reloading): PROCs 5, 8a and 9 (activities may take place indoors or outdoors).
- Service life: PROC 21 (outdoors only).

For formulation it is assumed that naphthalene may be handled as the substance itself and it is characterised as a high dustiness solid. For the scenarios covering military use and service life it is assumed that naphthalene is present at up to 25% in a solid in solid mixture. For military use it is assumed the mixture has a high dustiness, for service life it is assumed the mixture has a low dustiness. Gloves are required for all activities with the exception of service life where no gloves are required. No other risk management measures have been identified. Since the eMSCA does not have any further information about these uses, it will assume that the exposure estimates reported in CSRs are representative of the exposures likey to arise during formulation, military use and service life of smoke bombs/grenades. The eMSCA notes that in the case of PROCs 4, 5 and 8a, the registrants found it necessary to limit the duration of exposure, in some cases to less than 1 hour per day, in order to achieve RCRs < 1. The exposure value calculated by the ECETOC TRA tool is based on the assumption that there is no further exposure to naphthalene during the working day. If this pattern of work is not typical for the downstream user it may be necessary to apply additional controls to ensure adequate control.

Notes to registrants: To ensure that companies receiving exposure scenarios including tasks assessed on a reduced duration basis implement sufficient measures to protect their workers, clarification should be provided with the scenario that the RMMs identified apply where the worker does not have further exposure to naphthalene during the shift.

In the light of the new information about the exposures and body burdens that can be attained under working practices adopted during the manufacture of abrasives, registrants are advised to reconsider the measures that are recommended for formulation and for reloading of smoke bombs/grenades. Based on the PROC codes selected for this scenario, the eMSCA identifies similarities with the activities performed during the manufacture of abrasives and is concerned that no measures have been identified in the exposure scenarios for formulation and for reloading of smoke bombs that will limit the release of naphthalene into the workroom air. Workers experiencing daily exposure at the levels of naphthalene estimated for this scenario are likely to accrue body burdens that will carry

across to the next working week. It is recommended that working practices are reviewed and the exposure scenario is updated to include controls that will limit the release of naphthalene to air. Attention should be paid to the methods specified for routine cleaning during production to avoid the use of methods that allow dust to become airborne which will unnecessarily raise airborne levels of contamination throughout the workroom. It may also be useful to consider developing additional communication tools which can be used by downstream users in worker training programmes.

7.12.1.1.6 Overall conclusions for worker exposure

This evaluation focusses on the manufacture and uses of naphthalene covered by naphthalene registrations. This does not cover all potential sources of exposure to naphthalene from REACH registered substances since exposure to naphthalene may occur where this substance is a constituent of UVCB mixtures covered by other registrations. Workplace exposure will also arise where there is combustion of carbonaceous material and from activities such as tar and asphalt laying e.g. roofing and road repair. Workers performing activities covered in REACH registrations for naphthalene and other substances containing naphthalene will also be exposed to naphthalene from non-work related sources. Table 33 provides a summary of the exposure information discussed in this evaluation.

Table 33: Summary of exposure to naphthalene.

Source	Inhalation		Dermal (mg/kg/day)
	Low end of range (mg/m³)	High end of range (mg/m³)	
Sources not covered in naphthalene registrations			
Pristine air	1X10-7	3X 10-6	n/a
Suburban air	1X10-6	0.001	n/a
Indoor air (non –smoker)	0.0001	0.0017	n/a
Indoor air (smoker)	0.0018	0.01	n/a
Industrial exposure (lower exposure industries)	0.01	0.3	n/a
Odour threshold		0.42	n/a
Industrial exposure (higher exposure industries)	0.1	3	n/a
Exposure conclusions for uses covered in REACH registrations			
Manufacture		eMSCA relying on modelled data from registration	eMSCA relying on modelled data from registration
Use as an intermediate		eMSCA relying on modelled data from registration	eMSCA relying on modelled data from registration
Manufacture of abrasives		10 (8-hr TWA)	PROC 5 2.74 PROC 14 0.69
Formulation and use of smoke bombs/grenades		eMSCA relying on modelled data from registration	eMSCA relying on modelled data from registration

n/a not available

Based on information obtained during the evaluation, it can be concluded that improvements have been implemented in response to the ESR RRS. However, the new exposure data for abrasive manufacture indicates that the current working practices are not reducing worker exposure sufficiently to enable in workers carrying out tasks with direct exposure to naphthalene to clear the body burden of naphthalene accrued during the working week before starting work the next week. Additional improvements should be made, in particular to the methods used to limit inhalation exposure. It would be useful to check working practices and corresponding exposure levels at sites formulating and reloading smoke bombs. The lack of measures to limit the release of naphthalene to the workroom air during these acivities may result in these workers maintaining a residual body burden of naphthalene from one week to the next if they work with naphthalene on a daily basis.

For its risk characterisation, the eMSCA will use the modelled estimates generated by the registrants for scenarios covering manufacture, use as an intermediate and formulation of smoke bombs/grenades. For manufacture of abrasives, the eMSCA will take 10 mg/m^3 (8-hr TWA) as a reasonable worst case for inhalation exposure and will use its own modelled exposure estimates for dermal exposure (see table 33). Since a DNEL has not been derived for biological monitoring data this data will not be used to perform a quantitative risk characterisation. However, the findings will be taken into consideration.

7.12.1.2 Consumer

No consumer uses have been identified for naphthalene in REACH registrations and it seems likely that the consumer uses that were identified in the ESR review have largely ceased with the possible exception of cases where consumers purchase products directly from non-EU suppliers.

Consumer exposure to naphthalene is still possible if consumers use products containing naphthalene that are covered by other REACH registrations e.g. substances covered by the C_{10}-C_{12} aromatic hydrocarbon solvents category. Additional background exposure for the general population will also occur from a wide range of possible sources and this may exceed consumer exposure from substances that are covered by REACH registrations. These sources of exposure have not been quantified as part of this evaluation.

7.12.2. Environment

Not evaluated.

7.12.3. Combined exposure assessment

Registrants either refer to the combined exposure assessments published in the ESR report or provide an assessment that only addresses combined exposure to emissions to the environment arising from the exposure scenairos covered in REACH registrations. These environmental emissions are minor and do not make a significant additional contribution to daily exposure from other sources. The Registrants are not required to quantify exposures arising from other potential sources of background exposure or exposure arising from uses of other substances and products that may contain naphthalene but are not covered in REACH registrations for naphthalene.

Given the ubiquitous nature of these sources it is likely that the exposure predictions arrived at in REACH registrations will underestimate total daily exposure for workers and the general population. The eMSCA does not have enough information on the potential scale of these additional sources to characterise risks in a meaningful way. However, this is identified as a source of uncertainty for the risk characterisation.

7.13. Risk characterisation

Human Health

The lead health concerns for naphthalene are haemolytic anaemia and carcinogenicity. Now and in the future, (potential) exposures in the workplace are the principal exposure scenarios of concern.

Evidence from humans drives the concern for haemolytic anaemia since the main experimental species (rats, mice and rabbits) do not appear to be a suitable model for this effect. In humans, the occurrence of haemolytic anaemia has been reported in at least 30 individuals, typically following single or repeated oral intake of naphthalene mothballs but also following inhalation and dermal exposure to naphthalene from clothing. Individuals who are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD) may be more susceptible to the haemolytic effects of naphthalene than others in the general population. Owing to the circumstances surrounding the poisoning incidents, it is not possible to determine the doses involved and the nature of the dose-response relationship cannot be identified. It is therefore not possible to calculate a derived no effect level (DNEL) for this effect and perform a quantitiative risk characterisation. At the time of the ESR review, an investigation was performed into the feasibility of conducting a workplace survey to look for signs of haemolytic anaemia. However, it was determined that the only suitable population for such a study (the workforce of a mothball manufacturing plant was identified because they were exposed to high levels of naphthalene without confounding exposures) was too small to draw meaningful conclusions. No further information was therefore requested and it was concluded in the ESR RAR that body burdens in the mg/kg range may be of concern for haemolytic anaemia.

Very little new information has emerged since the ESR review to shed further light on a no-effect level for haemolytic anaemia in humans. In the light of this continuing uncertainty, the conclusion that body burdens in the mg/kg range may be of concern remains. It is also the case that there is no evidence to clarify whether or not naphthalene exposed workers currently experience haemolytic anaemia; if they do, then one can infer from the absence of reports that the degree of effect is not sufficient to prevent them from attending work.

The concern for carcinogenicity is driven by experimental evidence, particularly from studies in rats. In long-term repeated exposure studies, nasal tumours have been observed at levels that also caused non-neoplastic inflammatory changes and it appears likely that inflammation is a necessary precursor for the tumours. The ESR review concluded that the tumours observed in animal studies are likely to have arisen via a non-genotoxic mechanism and this conclusion has been upheld by the mode of action (MoA) analysis performed during this evaluation (see section 7.9.6.3.1).

The postulated mode of action (MoA) for the nasal tumours in rats proposes that naphthalene is metabolised to cytotoxic metabolites by a CYP (CYP2F) enzyme in tumour-forming tissues. Those metabolites are responsible for the inflammation and regenerative hyperplasia which precede carcinogenesis. The presence of a CYP2F enzyme in humans indicates that there is a potential for naphthalene metabolism in humans. The anatomical, physiological and metabolic differences between rats and humans, including breathing route, anatomy of the nasal cavity and (based on findings from *in vitro* studies) the likely lower rate of naphthalene metabolism in humans are noted. On the basis of these differences, it is possible that the pattern of effects observed in humans will vary from those observed in the rat.

There is no evidence of nasal tumours resulting from naphthalene exposure in humans. However, the absence of case reports or other forms of epidemiological study of this issue cannot be considered to represent convincing evidence that the tumours observed in rats are not relevant to humans.

In mice receiving inhalation exposure to naphthalene, tumours were not observed in nasal tissue. However, it is not known whether the mouse or rat is a better model for effects of naphthalene inhalation exposure. Therefore, the total information available is not sufficient to conclude that the finding of nadal tumours in rats exposed to naphthalene by inhalation is not relevant for humans (albeit that humans might well be at least quantitatively less sensitive to such an effect). The current Carc Cat. 2 classification is based on this perspective.

In setting their long-term inhalation DNEL of 25 mg/m^3 (8-hr TWA), the registrants chose to rely on information obtained from an unpublished survey of workers at 12 European abrasives producers, conducted in 2010. Few details from this survey were provided in the registration. Company doctors are reported to have never observed blood anomalies or haemolytic anaemia or other occupational health effects in workers, some of whom had been employed for up to 40 years. However, the registrants have not provided sufficient information about the endpoints that were assessed in medical examinations of these workers, nor the frequency of examinations, to understand how comprehensive these assessments were. It is claimed that workers were regularly exposed to levels approaching 25 mg/m^3 (8-hr TWA). However, no information has been provided to confirm the levels of exposure these workers were subjected to in their daily work and a more recent study in this sector (Sucker *et al*, 2016) reported a maximum personal 8-hr TWA value of 11.58 mg/m^3 (see table 31). The registrants have therefore not provided sufficient evidence to demonstrate that their DNEL will be protective of worker's health and the eMSCA considered alternative routes by which an appropriate and robust DNEL can be derived.

If the conventional DNEL setting approach is followed, in the absence of reliable dose response data from humans, a suitable starting point should be selected from studies in animals. The no-observed adverse effect concentration (NOAEC) from the 90-day inhalation study by Dodd *et al* (2012) of 0.52 mg/m^3 provides such a starting point. At the next dose administered to rats in this study, 5.24 mg/m^3, only minimal hyperplasia was observed in the respiratory/transitional epithelium suggesting the true no-effect concentration might lie somewhere between 0.52 and 5.24 mg/m^3. However, since no further information is available to identify a more accurate no-effect concentration, it would be necessary use the value of 0.52 mg/m^3 as the starting point which, if the conventional assessment factors are applied, leads to a worker, long-term inhalation DNEL of 0.053 mg/m^3.

However, a recent workplace study (Sucker *et al*, 2016) found no consistent evidence for nasal inflammation in workers occupationally exposed to levels up to 10 mg/m^3 (8-hour time weighted average (TWA)) naphthalene. In this study, a battery of tests were performed to look for signs of nasal inflammation and adverse effects on olfactory function. Endoscopic examinations of nasal tissues revealed that slight to moderate inflammation was present in participants from the high exposed, moderately exposed and reference groups (which had daily naphthalene exposures of 6.97±3.10 mg/m^3 (arithmetic mean±standard deviation), 0.66±0.27 mg/m^3 and 0.15±0.10 mg/m^3 respectively). A comparison of readings taken on Monday and Thursday revealed an increase in endoscopy examination scores (suggesting more severe inflammation) in some individuals from each group and a decrease in scores (suggesting less severe inflammation) from other individuals, with a greater tendency (statistically significant) for scores to increase (Monday – Thursday) in moderately and high exposed workers compared with the reference group. However, there were no differences between the moderate and high exposed groups, despite the 10-fold higher naphthalene exposure in the high exposed group. No consistent changes were observed in biomarkers for inflammation in nasal lavage or sputum samples from the exposed and reference groups. Also, where statistical differences were observed between the exposed and reference groups, there was often a high degree of overlap in the range of results (for example, for total endoscope scores, the Thursday readings ranged from 0-13 in the high exposed group, from 3-13 in the moderately exposed group and from 0-9 in the reference group). Complicating the analysis is the fact that both exposure groups were also exposed to inhalable and respirable dusts including ceramic grain and silica which could have contributed to the observed nasal inflammation. It is therefore

difficult to determine what role naphthalene might have played in any nasal effects observed in these workers. Overall, there was no indication of a substantial effect of naphthalene inhalation on nasal irritation, with exposures up to about 7 mg/m^3. On this basis, a DNEL of 0.053 mg/m^3 will be a very precautionary value given the lack of consistent evidence for inflammatory changes associated with naphthalene in workers with daily exposure to levels of naphthalene over 100 times higher than this DNEL.

It is also worth noting that the DNEL is at the low end of the range of exposures recorded for office workers that are spatially separated from areas where naphthalene is in use (exposures for these office workers ranged from 0.05 – 1.05 mg/m^3 (8-hr TWA) (see table 31)). This suggests that if exposures are to be maintained below this DNEL, it is likely that there would need to be a major redesign of the sites where the data for Sucker et al were collected and potentially other sites using naphthalene. Requiring the downstream use chain for naphthalene registrants to adopt this DNEL would also set higher standards of control for these sites compared with sites where exposure to naphthalene arises because it is a component in a substance of unknown or variable composition (UVCB) or generated as a process by-product. For example, Price and Jaycock (2008) suggested exposure to naphthalene can be expected to be in the range 0.01 – 0.3 mg/m^3 (8-hr TWA) for refining and petroleum industries, asphalt (paving and roofing) and industries using pitch to manufacture refractory materials or graphite electrodes. For these reasons the eMSCA does not think that a DNEL of 0.053 mg/m^3 provides a workable reference point from which to derive a control strategy for naphthalene.

Due to the lack of understanding of the most appropriate experimental models for the effects of naphthalene in humans, the eMSCA does not consider that requiring further experimental studies is an appropriate course of action. Instead, the eMSCA proposes that an EU-wide OEL will be the most appropriate way to manage risks. Setting an EU-wide limit value would not only target the sectors of use that have been covered by this evaluation, but would also target other sectors where exposure to naphthalene arises because it is a component in a UVCB or because it is generated as a process by-product. It would ensure that consistent standards of control are adopted wherever there is occupational exposure to naphthalene and that these standards apply across all EU-territories.

The current EU-wide Indicative Occupational Exposure Limit Value (IOELV) of 50 mg/m^3 (8-hr TWA) was introduced via the first Indicative Limit Value Directive (91/322/EEC) and was directly transposed into the current system via the second IOELV Directive (2006/15/EC). Although the IOELV has been reviewed by the Scientific Committee on Occupational Exposure Limits (SCOEL, 2010), the review took place at a time when potentially relevant experimental studies were ongoing. SCOEL therefore declined to recommend a limit value pending publication of this data.

The studies SCOEL were waiting for have now been published along with a new workplace study (Sucker et al, 2016) and all of the new evidence has been considered in this evaluation. Since the IOELV is twice as high as the registrants' DNEL of 25 mg/m^3 (8-hr TWA) and five times higher than the levels in air measured by Sucker et al, (2016) for directly exposed workers (up to around 10 mg/m^3) the eMSCA concludes that the IOELV is not providing any incentive for employers to improve workplace control. The current IOELV should therefore be revised.

In considering what number should be adopted for the OEL, it will be useful to understand the levels in air that are achievable with the currently applied controls and working practices. REACH registrations only describe the registrants' recommended risk management measures but do not provide clarity about the measures currently implemented by downstream users and the associated levels of exposure.

A key piece of information to take into account in setting the OEL is the biological monitoring data obtained by Sucker et al, summarised in table 12. This showed that the majority of non-smoking workers carrying out tasks involving direct exposure to naphthalene at levels of up to 10 mg/m^3 (8-hr TWA) do not appear to clear the body burden

of naphthalene accrued during the working week over the weekend. The 95th percentile levels of unriary 1- and 2-napthol in directly exposed workers in pre-shift samples on Monday was 958 µg/L compared with 85 µg/L in workers with indirect exposure and 18 µg/L in workers with no or rare exposure. Although Sucker *et al* did not measure body burdens, the potential body burden corresponding to the exposures estimated for the grinding wheel scenario can be calculated. If it is assumed that an average worker weighs 70 kg and inhales 10 m^3 air per shift, and that there is 100% absorption by the inhalation route, the body burden accrued by the end of the week may be around 2.8 mg/kg (this value is based on an estimated elimination constant (k_{el}) of 0.5/day derived by the regsitrants from the biomonitoring data presented by Sucker et al and does not take a possible contribution from dermal exposure into account). This value should be considered commensurate with the "low mg/kg" range identified in the ESR RAR as potentially of concern for the possibility of producing haemolytic anaemia. There was no evidence in this study that maintaining an elevated body burden of naphthalene was evidently detrimental to the health of the workers studied. However, significant uncertainties apply: the study focussed on examinations of the nasal passages, markers for haemolytic anaemia and G6PD deficiency were not investigated; there is uncertainty surrounding the dose-response relationship for haemolytic anaemia, particularly taking into account that around 4% of the European population may have the G6PD deficiency making them more susceptible to naphthalene induced haemolytic anaemia; and there is uncertainty surrounding the dose-response relationship for nasal inflammation, with the possibility that such inflammation could have the potential to progress to nasal tumour development in humans. The eMSCA argues that, with all these uncertainties, it seems sensible to aim to limit exposure to levels that do not cause workers to retain a residual body burden of naphthalene from one week to the next.

The high urinary 1- and 2-napthol levels measured by Sucker *et al* (2016) could potentially have arisen as a result of either inhalation or dermal exposure or a combination of the two. The eMSCA has been informed that it is standard practice for these workers to wear gloves if there is the potential for direct skin contact with naphthalene. Assuming that appropriate gloves are being worn and suitable management systems are in place to ensure the gloves are used correctly, this directs attention towards inhalation as being the main route of exposure.

The conclusion is therefore reached that airborne exposures to naphthalene should be kept below 10 mg/m^3 (8-hr TWA).

To ensure body burdens are kept within acceptable levels, it is not clear how far below 10 mg/m^3 it is necessary to reduce airborne exposure. Ideally this decision should be informed by additional information linking measured airborne exposures with biological levels across a range of sectors where there is the potential for exposure to naphthalene. Such an extensive survey will require the voluntary participation of a wide range of companies and workers and it seems unrealistic to place this as a requirement on the REACH registrants of naphthalene. This is therefore identified as a recommendation from this evaluation.

It also seems appropriate to reflect on the potential exposures associated with the current operating conditions and risk management measures identified in the naphthalene REACH exposure scenarios.

For the manufacture of naphthalene and the use of naphthalene as a feedstock/ intermediate, worst case modelled estimates for PROCs 4, 8a, 8b and 9 suggest airborne exposure may exceed 10 mg/m^3 if a worker performs these tasks exclusively for the entire shift. It is possible that worker exposure has been overestimated, for example a higher level of containment may be implemented than has been assumed in the exposure calculations and the time workers spend working directly with naphthalene may be much less than has been assumed. Unless more details are provided in registrations about the way processes are currently operated it will not be possible to refine these worst case estimates.

The information provided in registrations and from Sucker *et al* about exposure to naphthalene during the manufacture of abrasives suggests that additional control measures should be implemented to further limit the release of naphthalene to air during activities involving direct handling of naphthalene i.e. weighing, mixing, sieving, pressing and moulding (see section 7.12.1.1.4 for details).

Very little information is available about the formulation, military use and service life of naphthalene containing smoke bombs/grenades. This is another sector where naphthalene exposures may be sufficiently high that workers retain a residual body burden from one week to the next. Further information should be obtained to clarify working practices in this sector. Decisions can then be taken about the need (or not) to implement additional control measures e.g. containment or LEV to limit the release of naphthalene particulate and vapour to air.

In summary, in addition to the conclusion that the existing EU-wide OEL for naphthalene should be revised, the following recommendations are made:

- To ensure that it is transparent in the exposure scenario how all relevant work activities are covered, either a specific contributing scenario for routine cleaning and maintenance activities should be provided or registrants should indicate which of the already chosen contributing scenarios apply to these activities. Registrants should update registrations with this information without undue delay.

- To allow authorities to better understand the current operating conditions and any risk management measures that are used, and to put the exposure estimates into context, all registrants should provide additional descriptions of the the tasks/activities that are performed and the risk management measures that are applied for all uses covered in their CSRs. Registrants are recommended to update registrations with this information without undue delay.

- All sectors of industry where there is a potential for exposure to levels of naphthalene that could approach or exceed 10 mg/m^3 (8-hr TWA) should consider gathering information on levels in air and corresponding biological levels under current working conditions. Where there is evidence that body burdens in workers regularly exceed background levels at the start of the working week, operating conditions and risk management measures should be re-examined. The Biologischer Arbeitsstoffreferenzwert (BAR) of 35 µg total urinary 1- and 2-naphthol/L urine established by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) may be a useful benchmark to use for this assessment. If it appears necessary to reduce worker exposure, additional controls should be implemented in accordance with the hierarchy of control described in the Chemical Agents Directive (98/24/EC). In addition to the sectors covered in this evaluation, it may also be useful to investigate exposure to naphthalene in other sectors such as those where UVCB mixtures are used which contain naphthalene as an impurity and sectors where naphthalene is emitted as a process by-product.

7.14. Additional information

UK CA literature search for human health

To ensure that the dossier included all relevant publications, the eMSCA performed a literature review on naphthalene (human health effects and human exposure). The strategy for the review was to search for naphthalene and its synonyms in conjunction with defined key words that are specific to the areas identified as a concern in the CoRAP. Two databases were employed which cover many areas of science (Pubmed and Toxnet).

The following search terms were adopted:

naphthalene or albocarbon or dezodorator or "moth flakes" or naphthaline or "tar camphor" or "white tar" or "NSC 37565" or "202-049-5" or "91-20-3"

in combination with

irritat* or irritant* or sensiti* or hypersensiti* or expose* or exposure* or exposing or breath* or respir* or inhale* or inhalation or allerg* or toxic* or intoxic* or poison* or disease* or illness* or morbid* or mortalit* or neurodegen* or neurotoxic* or neurobehavio* or "nervous system*" or neuropatholog* or brain or derma* or cancer* or carcinogen* or carcinoma* or reproduct* or reprotox* or fertilit* or mutagen* or mutat*or genotoxic* or gene or genes or genetic* or immunotoxic* or immune* or immuni*or hepato* or terato* or cell or cells or cytotox* or metabolis* or "endocrine disrupt*"

or

expose* or exposure* or exposing or work* or consumer* or domestic or monitor* or surveillance or occupation* or paraoccupation* or ["1-naphthol"]

7.15. References

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7.16. Abbreviations

%	Percentage
°C	degrees Celsius
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASTDR	Agency for Toxic Substances and Disease Registry
ATH	Atypical tubule hyperplasia
ATP	Adenosine Triphosphate
bw	bodyweight
BAR	Biologischer Arbeitsstoffreferenzwert
CC16	Club cell protein 16
CFPD	Computational Fluid-Particle Dynamics
CLP	Classification, labelling and packaging (of substances and mixtures)
cm	Centimetre
CoRAP	Community Rolling Action Plan
CPN	Chronic progressive nephropathy
CSR	Chemical Safety Report
CYP	Cytochrome P450
d	Day
DD	Dihydrodiol dehydrogenase
DF	Deposition Fraction
DNA	Deoxyribonucleic acid
DMEL	Derived Minimal Effect Level
DNEL	Derived No Effect Level
DSD	Dangerous Substances Directive
EC	European Commission
ECETOC TRA	European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment
ECHA	European Chemicals Agency
EH	Epoxide hydrolase
eMSCA	evaluating Member State Competent Authority
EPA	Environmental Protection Agency
ES	Exposure Scenario
ESR	Existing substances regulation
EU	European Union
g	Gramme
G6PD	Glucose-6-phosphate dehydrogenase
GC	Gas chromatography

GC/FID	Gas chromatography – Flame Ionisation Detection
GC/MS	Gas chromatography – mass spectrometry
GLP	Good laboratory practice
GSH	Glutathione
HEC	Human Equivalent Concentration
hPa	Hectopascal
HPV	High production volume
IARC	International Agency for Research on Cancer
IL-6	Interleukin 6
IL-8	Interleukin 8
ILV	Indicative limit value
IOELV	Indicative occupational exposure limit
IPA	Institut für Prävention und Arbeitsmedizin der Deutschen Gesetzlichen Unfallversicherung
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union of Pure and Applied Chemistry
kg	Kilogram
kJ	Kilojoule
km	Kilometre
K_{ow}	Octanol-water partition coefficient
kPa	Kilopascal
L	Litre
LDH	Lactate dehydrogenase
LEV	Local Exhaust Ventillation
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LOD	Limit of detection
Log	Logarithmic value
LOQ	Limit of quantitation
m	Metre(s)
m^3	cubic metres
M	Molar
MS	Mass spectrometry
m/z	Mass to charge ratio
µg	Microgram
µM	micromoles
MoA	Mode of Action

mg	Milligram
min	Minute
mL	Millilitre
MMP-9	Matrix metalloproteinase-9
mol	Mole
MPa	Mega pascal
MSCA	Member State Competent Authority
MTD	Maximum Tolerated Dose
NADPH	Nicotinamide adenine dinucleotide phosphate
nm	Nanometre
nmol	nanomoles
NOAEL	No observed adverse effect level
NOEC	No-observed effect concentration
NOEL	No observed effect level
NTP	National Toxicology Program
OC	Operational condition
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational exposure limit
p	Statistical probability
Pa	Pascal
PBPK	Physiologically based pharmacokinetic
PC	Product category
pKa	Acid dissociation constant
pg	Picogramme
PP	5-phenyl-1-pentyne
ppb	Parts per billion
PPE	Personal Protective Equipment
ppm	Parts per million
PROC	Process Category
psi	Pounds per square inch
QSAR	Quantitative structure-activity relationship
r^2	Correlation coefficient
RAR	Risk assessment report
RCR	Risk characterisation ratio
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (EU Regulation No. 1907/2006)
RMM	Risk Management Measures
RPE	Respiratory protective equipment
RRS	Risk reduction strategy

SCC	Strictly controlled conditions
SCOEL	Scientific Committee on Occupational Exposure Limits
SD	Sprague Dawley
t	Tonne
TEDX	Endocrine Disruption Exchange
TIMP-1	Tissue inhibitor of metalloproteinase
TG	Test Guideline
TWA	Time-weighted average
UK	United Kingdom
US	United States
UV	Ultraviolet
UVCB	Substances of unknown or variable composition, complex reaction products and biological materials
V_{max}	maximum rate of reaction
WHO	World Health Organisation
wt.	Weight