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Identification of substances with a carcinogenic potential in spray-formulated engine/brake cleaners and lubricating products, available in the European Union (EU) – based on IARC and EU-harmonised classifications and QSAR predictions

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ABSTRACT

Spray-formulated engine/brake cleaners and lubricating agents are widely used to maintain machines. The occupational exposure to their aerosols is evident. To assess the carcinogenic potential of these products, we identified such products available in the European Union (EU). We built a database with CAS numbers of 1) mono-constituent substances, and 2) multi-constituent-substances, and unknown-or-variable-composition,-complex-reaction-products-and-biological-materials (multi-constituent/UVCBs). The compositions of multi-constituent/UVCBs were unravelled with European Chemicals Agency (ECHA) registration dossiers. To identify carcinogenic potentials, we searched for 1) International Agency for Research on Cancer (IARC) classification; 2) Harmonised classifications in Annex VI to the EU classification, labelling and packaging (CLP) Regulation; and 3) whether they had a Danish Environmental Protection Agency advisory CLP self-classification based on quantitative structure-activity relationships (QSARs) for genotoxicity and carcinogenicity in the Danish (Q)SAR Database. In 82 products, we identified 332 mono-constituent substances and 44 multi-constituent/UVCBs. Six substances were either IARC 1 or 2B classified. Twelve mono-constituent substances and 22 multi-constituent/UVCBs had harmonised classifications as Carcinogenic Category 1A, 1B or 2, while nine substances fulfilled the QSAR-based advisory self-classification algorithms for mutagenicity or carcinogenicity. At the product level, 39 products contained substances of carcinogenic concern by either IARC, harmonised classification or QSAR. We conclude that in the investigated EU marketed spray-formulated engine/brake cleaners and lubricants, 24 of 332 mono-constituent substances and 28 of 44 multi-constituent/UVCBs had a carcinogenic potential. At the product level, 39 of 82 contained substances with an identified carcinogenic potential. Regulators and manufacturers can use this determination of carcinogenic potential to decrease occupational risk.

1. Introduction

Cancer is a major cause of death, and limiting carcinogenic risk is of high concern. Workers employed in maintaining machines are exposed to substances that may have carcinogenic potential, e.g. hydrocarbons (IARC, 2012). Individuals working with engines have a four times higher risk for developing lung cancer compared to the general population, according to a study of cancer in 15 million workers in the Nordic countries (Pukkala et al., 2009). A study looking at the cancer risk for Danish seafarers evaluated the risk for 33.000 people based on their work title; seafarers compared to the general population had an increased cancer risk of 1.3 (i.e. 30% increase) for men and 1.1 for women. When the group was divided by work title, the engine-room crew of ships had an increased risk of 2.3, and the maintenance crew

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had an increased cancer risk of 4.2 (Kaerlev et al., 2005; Ugelvig Petersen et al., 2018).

Substances in machine maintenance shown to hold a carcinogenic potential include trichloroethylene, a degreaser for metal, identified as "carcinogenic to humans" by IARC (IARC, 2014). Moreover, oil products as well as polycyclic aromatic hydrocarbons (PAHs), and exhaust gases from diesel and gasoline were suggested as contributors to the increased cancer risk of Danish seamen (Kaerlev et al., 2005). Mineral oils are frequently used in engine cleaning and lubricant agents. 'Mineral oils, untreated or mildly treated' were classified as a Group 1 carcinogen by IARC (IARC, 2012), i.e. there is enough evidence to conclude that it can cause cancer in humans, while IARC back in 1984 wrote that 'more refined mineral oils' is "not classifiable as to its carcinogenicity to humans" (i.e. Group 3) (IARC, 1984).

One thing is that these products may hold a carcinogenic potential. Another is how high the exposure to the products is, as risk to the user is the product of hazard (carcinogenic potency) and exposure. Besides exposure via the skin, which may be substantial, inhalation is another important exposure pathway with potential transfer over the large surface area of the lungs. Thus, if the chemicals are formulated in spray form, the inhalation of aerosols will likely result in significant exposure for the workers. Such spray-formulated products for engine maintenance include cleaning agents (degreasers) and lubricating agents.

To limit exposure to potentially carcinogenic substances in sprays, we need to know their identity and the extent to which they are used. To address this issue, we retrieved the CAS numbers of each individual chemical substance by both covering mono-constituents and multi-constituent/UVCBs. We first evaluated the list for IARC and EU-harmonised classifications (Fig. 1); we then supplemented with the Danish Environmental Protection Agency (EPA) so-called advisory self-classifications (The advisory list for self-classification of hazardous substances) (EPA_Denmark, 2022; Wedebye et al., 2017), genotoxicity and carcinogenicity. The Danish EPA self-classifications are based on predictions from the Danish (Q)SAR Database from several QSAR models and following a weight-of-evidence (WoE) algorithm.

The justification for our application of these three approaches: 1) IARC is an important authority of the World Health Organisation (WHO); 2) Harmonised classifications is a system established in the EU to ensure adequate risk management of substances with known mutagenicity and/or carcinogenicity hazards, harmonised through classification and labelling based on assessments and regulatory adoption resulting in listing in Annex VI to the EU CLP Regulation. 3) Finally, we applied QSAR to identify possible additional substances with predicted carcinogenic potential based on the chemical structure. QSAR was used as a supplement for substances that had not been identified in the former two systems, e.g. if extensive animal tests or epidemiological studies had not investigated their carcinogenic potential in humans.

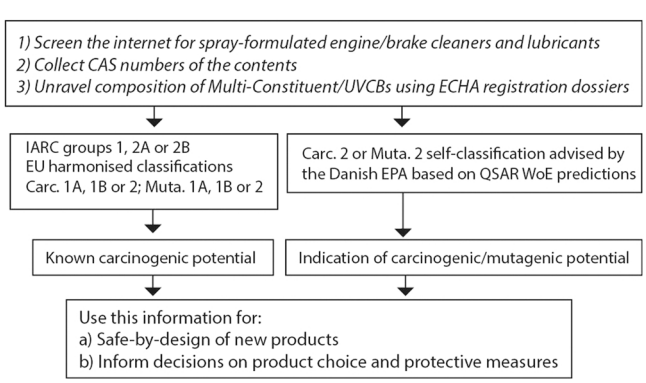

Fig. 1. Overview of the process of evaluating the carcinogenic potential of substances in spray-formulated engine/brake cleaners and lubricants.

2. Methods

2.1. Database of spray-formulated engine/brake cleaners and lubricating substances

An overview of the work process is provided in Fig. 1. We searched the internet for spray-formulated engine/brake cleaners and lubricants that could be purchased in the EU (or European Economic Area: EAA) using the Google search engine with combinations of the following words in English and Danish (Danish words not provided here): "greasing", "greaser", degreasing" "degreaser", "engine cleaner", "brake cleaner", "wheel/rim cleaner", in combination with "spray". The searches were mainly performed during the time period 1 March to 31 May 2020. Using information in Safety Data Sheets (SDSs) available on the internet, a list of CAS numbers was established in an Excel database (Supplemental File 1). The amount of each mono-constituent or multi-constituents/UVCBs in the products was noted only for substances with a carcinogenic potential determined by the approaches outlined in the next sections.

For multi-constituent substances/UVCBs, the CAS number of each known individual constituent was identified by inspection in the section "Compositions" of the registration dossier found on the ECHA portal. For example, the identity of the constituents in the multi-constituent/UVCB with CAS number 64742–47–8 was found using the "Compositions" in the Registration Dossier (https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/15375/1). The constituents that were part of multi-constituent/UVCBs are also included in the Excel database (Supplemental File 1). Notably, for some multi-constituent/UVCBs, composition information was not available in ECHA registration dossiers, and thus their constituents could not be identified. For some substances with multiple constituents, we could not retrieve information in ECHA registration dossiers on whether they were defined as multi-constituents or UVCBs. Yet, we still use the designation multi-constituent/UVCB. The purpose of the project was to characterise the overall extent of substances with a carcinogenic potential and not to point to specific products. Therefore the product names are omitted in this database. Instead, each product is given a number.

2.2. IARC classification and search for EU-harmonised classification as provided in Annex VI to CLP

All CAS numbers were screened using the IARC database (IARC, 2021), and we noted the classification in the Excel database (Supplemental File 1).

The Regulation on CLP is an EU implementation of the United Nations' Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (ECHA, 2022a, 2021). We investigated whether the mono-constituent substances or the multi-constituent/UVCBs, as well as the individual constituents of the multi-constituent/UVCBs, in our database, had harmonised carcinogenic or mutagenic classifications in Annex VI of the CLP regulation (Carc. 1A, Carc. 1B, Carc. 2, Muta. 1A, Muta. 1B or Muta. 2). We did this with the Annex VI Excel sheet in force from 1 May 2020 (Annex VI to CLP_ATP13) (ECHA, 2021), complying with the period when the database on spray-formulated engine/brake cleaners and lubricants was constructed. Note that in cases where we found that substances had IARC or EU CLP classification for carcinogenicity, we have not assessed whether the spray-formulated engine/brake cleaners and lubricating agent products should be classified according to the EU CLP criteria for mixtures (ECHA, 2019).

2.3. Danish EPA QSAR-based advisory self-classifications

QSARs are models, usually developed by machine-learning methods, by which potential toxicities of chemical structures can be predicted. The Danish (Q)SAR Database is a freely available online repository of pre-calculated predictions from several free, Danish Technical

University-developed and commercial QSAR models (National Food Institute, 2021). For many of the included endpoints, the same training sets are modelled in two or three QSAR systems, and so-called battery calls based on predictions from all systems are given. Battery calls are made on a majority vote where at least two of the three models agree and are in the applicability domain of the models.

The Danish (Q)SAR Database has formed the basis for the Danish EPA (Q)SAR-based advisory self-classifications of hazardous substances (EPA_Denmark, 2022). The applied (Q)SAR models and combinations of these into algorithms for generic assigning of so-called advisory self-classifications are documented in (Wedebye et al., 2017). The algorithms contain multiple QSAR models for genotoxicity and carcinogenicity included in the Danish (Q)SAR Database and are illustrated in Figs. 2 and 3. The algorithms were applied on REACH pre-registered substances contained in the Danish (Q)SAR Database and were known to be without any EU-harmonised classifications. It resulted in a list published on the Danish EPA homepage with more than 54,000 substances with an advisory self-classification for at least one of the included endpoints. Hereunder, 7323 received mutagenicity (Muta. 2), and 4788 (of which 2023 received Muta. 2) received carcinogenicity (Carc. 2) QSAR-based advisory self-classification. The Danish EPA advise using the advisory self-classifications together with other reliable information. If no other reliable information exists for a substance for the endpoints covered by the list, the Danish EPA recommends using the advisory self-classifications. In this project, we applied the advisory self-classifications as is, because it was outside the scope of the project to identify and assess possible other information. We used the Danish EPA advisory self-classifications to identify its overlap with substances in our database. Additionally we applied the algorithms ourselves to also screen substances not included in the list of selected substances in the Danish EPA project. We applied Danish EPA advisory self-classifications to screen for possible carcinogenicity or mutagenicity potential in cases where the substances did not have IARC or harmonised classifications. The resulting advisory classifications that are possible with the algorithms are Category 2 for mutagenicity (Muta. 2) or Category 2 for carcinogenicity (Carc. 2). It should be noted that if a substance did not receive an advisory self-classification for cancer or mutagenicity, it could either be because the models predicted the substance to be negative or because the substance was not in the defined so-called applicability domains of the applied models. Finally, as mutagenicity is a mechanism for carcinogenicity, we grouped mutagenic classification with the carcinogenic classification in the QSAR-based WoE predictions.

3. Results

3.1. Database contents

Most of the products in the database were from Danish retailers' web stores, but several products were found in web stores in other EU and EEA countries. Notably, nickel was found in spray-formulated lubricants, but only from web stores in the USA and Australia. Thus, these products were not included.

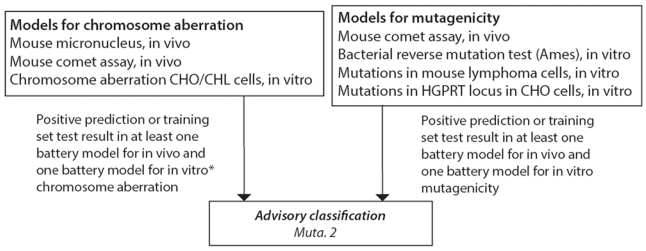

Fig. 2. Schematic diagram illustrating the QSAR models and algorithm applied to assign Danish EPA advisory self-classifications for mutagenicity. *The training set data were not used for the cancer and chromosomal aberrations in CHO cells models as these were proprietary information in the commercial models.

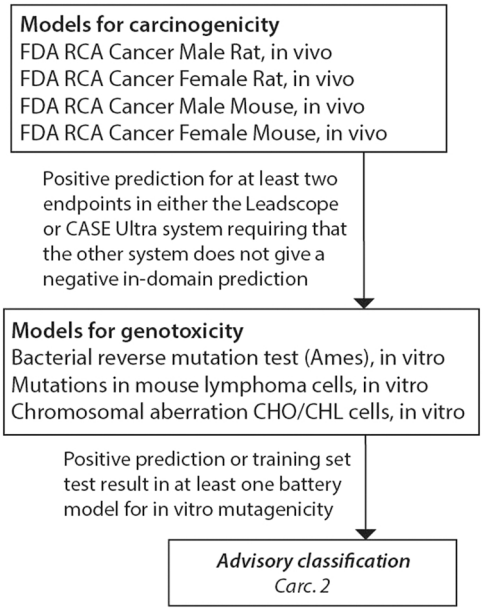

Fig. 3. Schematic diagram illustrating the QSAR models and algorithm applied to assign Danish EPA advisory classifications for carcinogenicity.

We identified 123 spray-formulated engine/brake cleaners and lubricating products available from EU websites. Of these, 82 had Safety Data Sheets (SDSs) readily available on the internet. The remaining products were discarded, based on the lack of direct access on the internet. In total, we identified 376 different CAS numbers; 88 were substances directly listed in the CAS number list in the SDS (14 inorganic elements and 74 organic molecules) (Fig. 4, Supplemental File 1). Forty-four multi-constituent/ UVCBs were identified, mostly including hydrocarbons (mineral oils). When these multi-constituent/UVCBs were unravelled for constituent CAS numbers using the ECHA registration dossiers, we identified 244 additional substances (illustrated in Fig. 4). The inorganic substances are listed in Table 1.

3.2. Overview of the carcinogenic potential of the substances

As shown in Fig. 5 (upper panel), only a few substances are classified as IARC 1 or 2B (we identified no Group 2A substances). One substance, diethanolamine (Group 2B), was listed directly in the SDS in one product, while two substances were IARC 1 and part of multi-constituent/ UVCBs and three substances were IARC 2B and part of multi-constituent/UVCBs (Fig. 5, substance identities provided in Table 2).

EU-harmonised classification identified two substances that are Carc. 2 and listed directly as ingredients, while 10 were Carc. 1A, 1B or 2 and

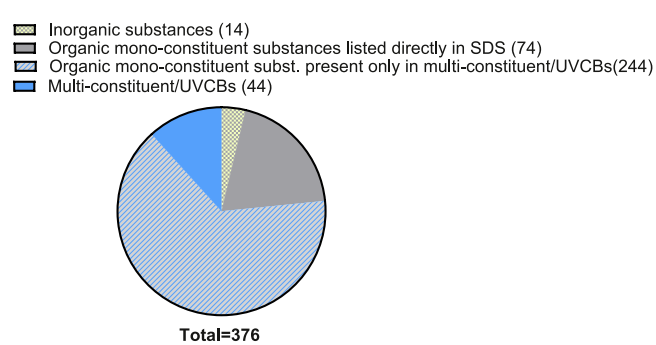

Fig. 4. Overview of the type of substances.

Table 1
Metals and other inorganic elements in the products *Nickel was identified in two products from outside the EU and thus not included in the current database.

Number of substances that were metals or other inorganic elements*	14 of 376 substances (3%)	Aluminium Ammonia Boron (nitride) Calcium dihydroxide Copper Lithium Magnesium (silicate) Molybdenum (disulphide) Phosphorodithioic acid Potassium (hydroxide) Sulphur Tungsten Zinc (sulphide) Zinc salts *
Number of products containing metals or other elements	18 of 82 products (22%)	n/a

substances in a multi-constituent/UVCB (Fig. 5). Notably, in the CLP regulation, there is also harmonised classification of the multi-constituent/UVCBs themselves: 5 multi-constituent/UVCBs had a harmonised classification Carc. 1A and 17 had a Carc. 1B, while 22 multi-constituent/UVCBs had no harmonised classification (Fig. 5). In total, 28 of 44 multi-constituent/UVCBs had a carcinogenic potential based on the 22 with direct harmonised classification and based on constituents with potential by either IARC, harmonised classification or QSAR. For the multi-constituent/UVCBs that themselves had either Carc. 1A or Carc. 1B, many were present in products at a content of over 50% (numbers given for each multi-constituent/UVCB in Table 2).

When we searched for the substances within our database in the Danish EPA QSAR-based advisory list for the self-classification of chemical substances (Fig. 5, lower panel), two substances had a QSAR-based Danish EPA advisory self-classification mutagenic or carcinogenic and were listed directly in the SDS. Seven substances that fulfilled the QSAR-based advisory self-classifications were part of multi-constituent/UVCBs. In addition, 229 substances were in the Danish (Q)SAR Database, but without a QSAR-based advisory self-classification for Muta.2 or Carc.2, and this could either be due to the QSAR models not predicting the substances to be (sufficiently) positive, or the substances could be outside the so-called applicability domains of the models. Moreover, 94 substances were not present in the Danish (Q)SAR Database. Those not found in the Danish (Q)SAR database included: 1) multi-constituent/UVCBs, 2) substances too small to be eligible for QSAR, 3) metals or other inorganic substances (Table 1). The database only contains organic molecules with two carbons or more (and only certain other atoms). Details of the QSAR-prioritised substances can be found in Table 2. One substance, 2-(1-methoxypropan-2-yloxy)propan-1-ol, was not pre-registered in REACH and thus not present in the screening list for the Danish EPA QSAR-based advisory list for self-classification of chemical substances (ECHA, 2022b). We manually ran the QSAR algorithms for advisory self-classification for this substance and found it to be Muta.2 (Table 2).

Figs. 6 and 7 show how much additional information was gained by supplementing IARC evaluations with harmonised classifications (9 substances) and QSAR predictions (9 substances) at the mono-constituent level (Fig. 6). At the multi-constituent/UVCB level (Fig. 7), 11 had a carcinogenic potential based on IARC, 16 additional ones based on harmonised classification, and one by QSAR (Fig. 7).

3.3. Overview of the carcinogenic potential at the product level

At the product level, Fig. 8 illustrates the number of products in

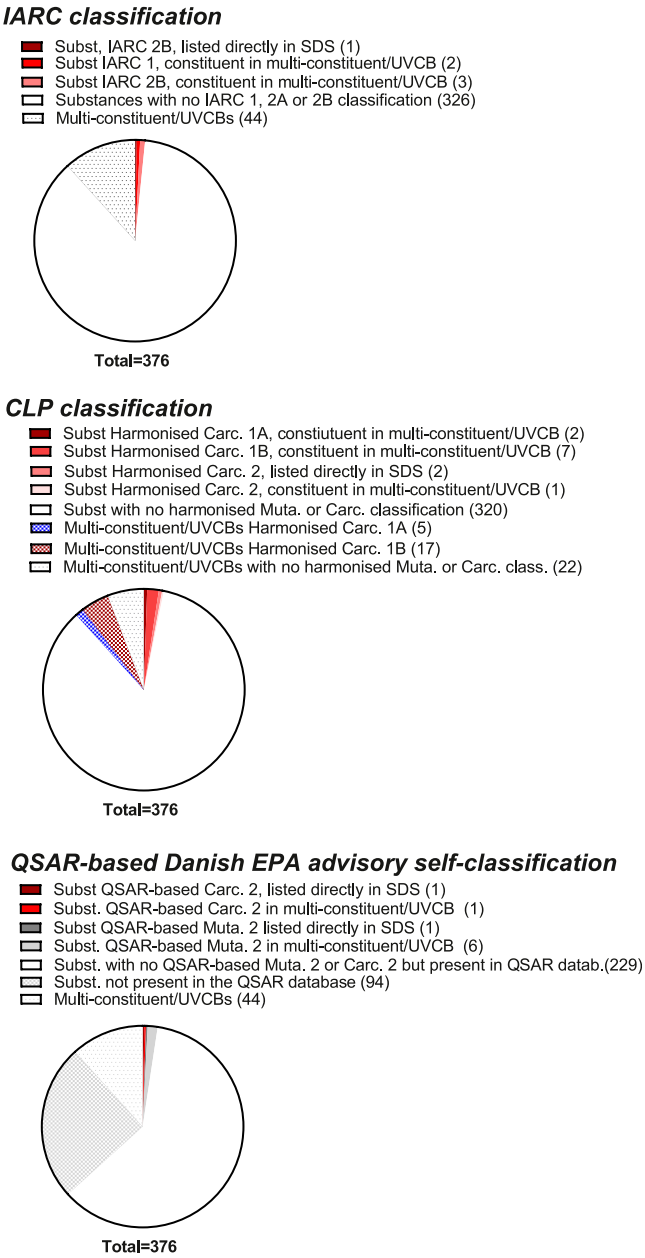

Fig. 5. The carcinogenic potential of ingredient substances as determined by IARC classification, EU-harmonised classification and QSAR-based advisory self-classification. Concerning harmonised classifications, none of the substances in our database were classified for mutagenicity, while not also classified for carcinogenicity. Thus, the mutagenicity classification is omitted from the pie chart.

different categories of concern. The first group comprises 31 products with either IARC 1 or 2B classified substances and seven products with harmonised classified Carc. substances that were not already IARC classified (IARC class 1 or 2B). One additional product has no IARC 1 or 2B substances or harmonised classified substances, but concern can be expressed for this product based on QSAR. A few products contain ingredients with no CAS number or for which the composition of multi-constituent/UVCBs cannot be unravelled because of limited information in ECHA registration dossiers (Fig. 8). Finally, there are products for which the composition is provided, and their reported composition does not contain substances that IARC classifies, have harmonised classification, or raise a concern based on QSAR. In the lower panels of Fig. 8, the results are divided into the two product categories 1) Engine/brake

Table 2
Overview of the substances evaluated to have carcinogenic potential.

Classification	Substance name/CAS number
IARC classifications	
Substances identified as IARC Group 1 (two substances)	*Constituents in multi-constituent/UVCB* Benzene / 71–43–2 Buta-1,3-diene / (1,3 butadiene) / 106–99–0 *
Substances identified as IARC Group 2A (none)	–
Substances identified as IARC Group 2B (four mono-constituent substances)	*Substances listed directly in SDS* Diethanolamine / 111–42–2 (concentration in one product 1–3%) *Constituents in a multi-constituent/UVCB* Ethylbenzene / 100–41–4 Cumene / 98–82–8 Naphtalene / 91–20–3
Substances identified as IARC Group 3 (seven mono-constituent substances)	*Substances listed directly in SDS* Toluene / 108–88–3 1,4-Dihydroxybenzene/ 123–31–9 Butylglycol / 2-butoxyethanol / 111–76–2 Xylene / 1330–20–7 Coumarin/91–64–5 *Constituents in a multi-constituent/UVCB* Propene / 115–07–1 Toluene / 108–88–3 Xylenes / various CAS numbers Pyrene / 129–00–0
EU-harmonised classifications	
Substances identified as Carc. 1A (two mono-constituent substances and five multi-constituent/UVCBs)	*Substances listed directly in SDS* None *Constituents in a multi-constituent/UVCB* Benzene71–43–2 Buta-1,3-diene / (1,3 butadiene) / 106–99–0 *Multi-constituent/UVCBs* Lubricating oils 74869–22–0 (5–15% in one product) Hydrocarbons, C3–4-rich, petroleum distillate 68512–91–4 (50–75% in two products) Hydrocarbons, C3–4 68476–40–4 (30–50% in two products) Hydrocarbons, C4 87741–01–3 (only listed as a constituent of one UVCB, 68476–85–7, in one product) Petroleum gases, liquefied 68476–85–7 (in four products at up to 30–60%)
Substances identified as Carc. 1B (seven mono-constituent substances and 16 multi-constituent/UVCBs)	*Substances listed directly in SDS* None *Constituents in a multi-constituent/UVCB* Benzo[*j*]fluoranthene 205–82–3 Benzo[*e*]acephenanthrylene 205–99–2 Benzo[*k*]fluoranthene 207–08–9 Chrysene 218–01–9 Benzo[def]chrysene 50–32–8 Dibenz[*a*,*h*]anthracene 53–70–3 Benz[*a*]anthracene 56–55–3 Multi-constituent/UVCBs Petrolatum8009–03–8 (only listed as a constituent of one UVCB, 8042–47–5, in one product) Hydrocarbons, C6-C7, n-alkanes, isoalkanes, cyclics, < 5% n-hexane 64742–49–0 (in 15 products at up to 50–100%) Distillates (petroleum), solvent-refined heavy paraffinic 64741–88–4 (1 product, per centage not reported) Distillates Petroleum Hydrotreated 64742–46–7 (1 product, per centage not reported) Hydrocarbons, C9-C11, n-alkanes, isoalkanes, cyclics, < 2% aromatics 64742–48–9 (11 products, up to 50–100%) Distillates (petroleum), hydrotreated heavy naphthenic 64742–52–5 (1 product, per centage not reported) Petroleum Base Oil 64742–53–6 (1 product, per centage not reported) Distillates (petroleum), hydrotreated heavy paraffinic 64742–54–7 (2 products, per centage not reported) Petroleum Base Oil 64742–56–9 (one product, per centage not reported) Distillates (petroleum), solvent-dewaxed heavy paraffinic 64742–65–0 Petroleum Base Oil 64742–71–8 (one product, per centage not reported) Naphtha (petroleum), hydrodesulfurised heavy 64742–82–1 (2 products at 1–1.5% and 40–50% Solvent-nafta (petroleum), slightly aromatic (benzene <0.1%) 64742–95–6 (two products 10–25% in both) Alkanes, C12–26-branched and linear 90622–53–0 (One product at 40–50%) Aromatic hydrocarbons, C890989–38–1 (only listed as a constituent of one UVCB, 64742–95–6, in one product) Naphtha (petroleum), hydrodesulfurised light, dearomatised 92045–53–9 (1 product at 20–50%) Distillates (petroleum), hydrotreated light paraffinic 64742–55–8 (1 product at 25–50%)
Substances identified as Carc. 2 (three mono-constituent substances)	*Substances listed directly in SDS* 1,4-Dihydroxybenzene 123–31–9 (<0.1% in one product) Dichloromethane 75–09–2 (50–70% in one product) *Constituents in a multi-constituent/UVCB* Naphthalene91–20–3
Substances identified as Muta. 1B (one mono-constituent substance and 11 multi-constituent/UVCBs)	*Constituent in a multi-constituent/UVCB* Buta-1,3-diene106–99–0 *Multi-constituent/UVCBs* Hydrocarbons, C9-C11, n-alkanes, isoalkanes, cycloalkanes 64742–48–9 Hydrocarbons, C7, n-alkanes, isoalkanes, cyclics 64742–49–0 Naphtha (petroleum), hydrodesulfurised heavy 64742–82–1 Solvent-nafta (petroleum), slightly aromatic (benzene <0.1%) 64742–95–6 Petroleum gases, liquefied 68476–85–7 Hydrocarbons, C3–4-rich, petroleum distillate 68512–91–4 Naphtha (petroleum), hydrodesulfurised light, dearomatised 92045–53–9 Benzo[def]chrysene 50–32–8 Hydrocarbons, C3–468476–40–4 Hydrocarbons, C4 87741–01–3 Aromatic hydrocarbons, C890989–38–1
Substances identified as Muta. 2 (two mono-constituent substances)	*Substances listed directly in SDS* 1,4-Dihydroxybenzene 123–31–9 (<0.1% in one product) *Constituents in a multi-constituent/UVCB* Chrysene 218–01–9
QSAR-based advisory CLP classifications	
Substances identified as Carc. 2 advisory classification (two mono-constituent substances)	*Substances listed directly in SDS* Coumarin / 2 H-1-benzopyran-2-one / 91–64–5 (<1% in one product) *Constituents in a multi-constituent/UVCB* Benzo[ghi]perylene / 191–24–2
Substances with Muta. 2 advisory classification (seven mono-constituent substances)	*Substances listed directly in SDS* Dimethoxymethan / 109–87–5 (80–95% in one product) *Constituents in a multi-constituent/UVCB* Fluoranthene 206–44–0 Fluorene / 86–73–7 2-(1-methoxypropan-2-yloxy)propan-1-ol / 55956–21–3 Indeno[1,2,3-cd]pyrene / 193–39–5

(*continued on next page*)

Table 2 (*continued*)

	Pyrene / 129–00–0
	4-vinyl-m-xylene / 2234–20–0

* Notably, ethanol 64–17–5 was identified in the database and is classified Group 1 by IARC as an ingredient in alcoholic beverages. Yet we have not included it in the table because of the inhalation route being considered here.

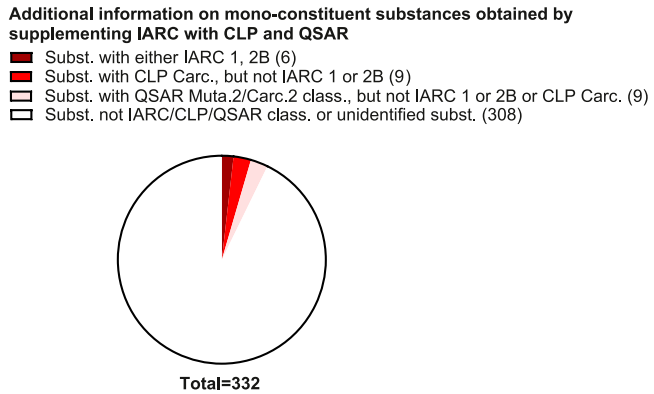

Fig. 6. Additional information on mono-constituent substances was obtained by supplementing IARC with harmonised classification and QSAR. The overlap between the different classifications illustrated how many additional substances were identified by starting with IARC and then a) adding harmonised classification and b) adding QSAR classification.

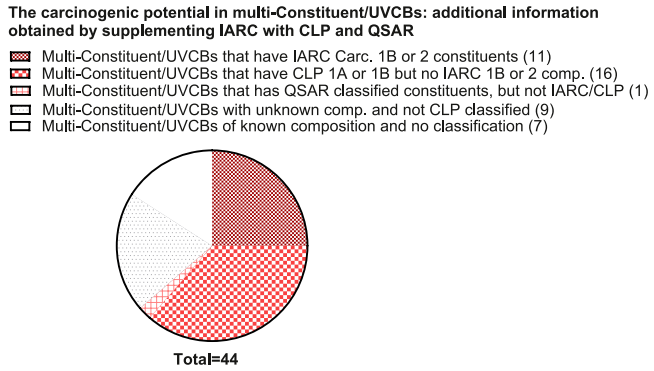

Fig. 7. The carcinogenic potential in multi-constituent/UVCBs: Additional information was obtained by supplementing IARC with harmonised classification and QSAR. The overlap between the different classifications illustrated how many additional substances were identified by starting with IARC and then a) adding harmonised classification and b) adding QSAR classification.

cleaners and 2) lubricants. For cleaners, 35% (17/48) have carcinogenic potential, with lubricants having a larger proportion, 56% (25/44).

4. Discussion

4.1. Fraction of the investigated substances with a carcinogenic potential

IARC classifications 1 and 2B were found for six substances. Harmonised classification pointed to 12 substances that were Carc. 1A, 1B or Carc. 2 and 22 multi-constituent/UVCBs (1A or 1B based on CAS numbers of these multi-constituent/UVCBs). QSAR pointed to nine substances with carcinogenic potential. Taking the overlap in substances identified by the three screening methods into account, this gives a total 24 of 376 substances that had a carcinogenic potential. Thus, the fraction of mono-constituent substances with a carcinogenic potential (compared with the total number of substances) is approximately 6%. In addition, we have another 6% when we look at multi-constituent/

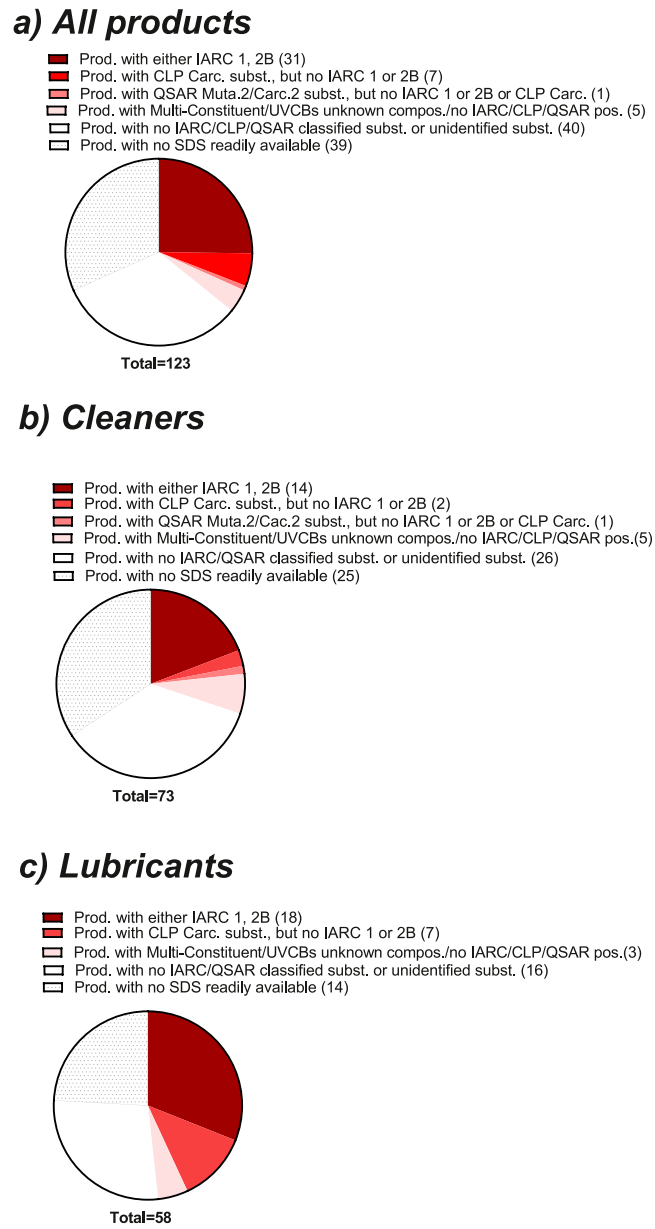

Fig. 8. Illustration of the number of products potentially containing mutagenic/carcinogenic substances. There may be substances of concern in the pink box (products with multi-constituent/UVCBs of unknown composition) as we were not able to unravel the composition of these CAS numbers. The two lower panels represent product groups. Notably, some products are counted twice as they are marketed as so-called multipurpose products being both cleaners and lubricants.

UVCBs based on EU-harmonised classification. Overall, if we look at the substance level, we find a smaller fraction with a carcinogenic potential than compared to the situation on the product level – this will be discussed below.

When we look at the substances with carcinogenic potential, the potential is mainly found in multi-constituents/UVCBs. Only five substances with carcinogenic potential are listed directly in the SDS (including one with Muta. 2 based on QSAR). At the same time, the other 19 are part of multi-constituent/UVCBs (22 multi-constituent/UVCBs are placed in Carc.-groups based on EU-harmonised classification). This finding suggests that most of the carcinogenic potential is found in multi-constituent/UVCBs, and that single substances with a carcinogenic potential have already been eliminated from products by historic

safe-by design decisions. For instance, we did not find trichloroethylene (an IARC 1 substance). It has a "Sunset date" of 21 April 2016 for authorised use (EU, 2013) and 1 March 2023 for the use of the substance in the production of spare parts as articles or as complex products for the repair of articles or complex products (ECHA, 2016). In addition, in recent years, changes have been made in the workplace to limit the use of solvents. For example, in Japan, the use of aromatic solvents fell over time (Ukai et al., 2014). Moreover, we note that nickel, classified IARC 2B, was only identified in spray products from outside the EU and thus not included in the database. Finally, the carcinogenic substance diethanolamine was found only in one product in our database, suggesting a very limited use.

The fact that multi-constituent/UVCBs hold a carcinogenic potential and are still used could reflect that it is difficult to obtain products that are effective cleaners (degreasers) and lubricating agents without these substances. Nonetheless, the question is whether one can choose the more refined mineral oils in the products and thus have lower carcinogenic potential. This point will be discussed further below, and is relevant taking into account that at the product level there is a substantial carcinogenic potential.

4.2. Carcinogenic potential at the product level

At the product level, a substantially larger fraction (48%) is potentially carcinogenic, as compared to the fraction seen at the substance level (6%) (plus 6% of the CAS numbers in the form of multi-constituent/UVCBs, based on EU-harmonised classification). This finding reflects that the substances with a carcinogenic potential are more frequently used in the products than those with no identified carcinogenic potential. It likely reflects the notion that the most biologically active substances are also those most efficient in cleaning (degreasing) or lubrication. On the product level, the extent of substances with IARC classification, harmonised classification or QSAR predicted carcinogenic potential is higher for lubricating agents (58%) than it is for cleaners (35%) (Fig. 8).

Notably, it is difficult to determine whether products with no identified carcinogenic potential indeed do not have such a potential or whether it has just not been detected. One challenge is the multi-constituent/UVCBs with no composition given in ECHA registration dossiers or with generic names with no CAS number provided. We also found that for some products, the main substances included in the name of the products were not provided as substances in the list of substances in the SDS – as was seen for several metals. Yet another challenge is that for a substantial number of products, i.e., 41 of 123 in the database, we could not readily retrieve an SDS on the internet. It is unclear if products sold by retailers who do not provide an SDS readily downloadable on the internet are marketing better or worse products in terms of carcinogenic potential. Also, we note that we did not look at whether the SDSs were in accordance with the regulation. For substances that had a carcinogenic potential, we returned to the SDSs and retrieved the concentrations in the products. For the 22 multi-constituent/UVCBs that themselves had either Carc. 1A or Carc. 1B harmonised classification, many were present in products at over 50% (numbers given for each multi-constituent/UVCB in Table 2). For the mono-constituent substances the concentrations were: diethanolamine (1–3%, 1 product), dichloromethane (50–70% 1 product), dimethoxymethan (80–95%, 1 product), 1,4-dihydroxybenzene (<0.1%, 1 product), and coumarin (<1%, 1 product). Overall, these numbers suggest that some products present ingredients with a carcinogenic potential in substantial amounts. This point is particularly seen for multi-constituents/UVCBs present in many products.

4.3. Reducing exposure to products with carcinogenic potential

4.3.1. Are there any hydrocarbon multi-constituent/UVCBs that do not contain substances with a carcinogenic potential?

Hydrocarbon mixtures are commonly included in many products. From a safe-by-design point of view, it would be desirable if we could state that one or more hydrocarbon mixtures were more safe than others to include in the products. Few hydrocarbon UVCBs did not contain any substances with carcinogenic potential, while many hydrocarbon UVCBs indeed had a carcinogenic potential. Based on this, it is questionable whether one can justify using specific UVCBs instead of others in a safe-by design approach – without further research. Nonetheless, one aspect reviewed by IARC is that some mineral oils that were unrefined or only mildly refined were IARC Group 1 (IARC, 2012), while more refined ones were IARC Group 3 (IARC, 1984). Notably, this statement dates back to 1984. Yet overall, based on considerations by IARC and the notion that refinement generally removes unwanted substances, one safe-by design measure to limit the carcinogenic potential of these products could be to consider more-refined hydrocarbon mixtures.

4.3.2. Avoiding future substances that hold a carcinogenic potential - the contribution of QSAR

While IARC and harmonised classification look into the already-existing human knowledge and experimental assays in animals and cells, QSAR infers the potential toxicity based on the chemical structure. QSAR can thus be used to assess the carcinogenic potential of substances, already before synthesis, and on many structures at a low cost. Thus, QSAR provides an opportunity to predict potential future long-term effects.

In the current overview looking at the substance level, the QSAR WoE algorithm identified nine substances that were not already classified as IARC 1 or 2 or had a harmonised classification as carcinogenic or mutagenic. Overall, QSAR contributed substantially to screening the carcinogenic potential of the substances in products. Although when looking at the product level, there was a substantial overlap between IARC/harmonised classification and QSAR predictions (Table 2), reflecting that other substances in the products already had an IARC or EU-harmonised classification. Nevertheless, the situation may be different when using this setup for product groups other than engine maintenance. For instance, we have previously demonstrated the value of QSAR in prioritising potential asthma-inducing substances (Hadrup et al., 2022a).

4.3.3. Avoiding exposure by not using spray-formulation

Besides controlling substances with a carcinogenic potential in the products, another option is to limit exposure by not formulating the products in spray form. This step will prevent aerosols from being inhaled. Some of the studied products indeed had alternative formulations from the retailer that could be applied in other ways, e.g., a paste. Choosing these products would already be a possibility for workers today to reduce exposure by inhalation, although with the caveat that gloves would be needed to avoid skin exposure. Yet one thing that we encountered through personal communication with mechanics is the widespread use of compressed air for cleaning engine parts – something that aerosolises surface-deposited grease and other substances, once again providing potential for occupational lung exposure.

4.4. Comparison with previous studies on exposure to engine/brake cleaners and lubricants

One review study from 2000 collected exposure information on some 17,000 hydrocarbon solvent exposure measurements in similar end-use products (painting and coating, printing, and adhesives). The authors found that reported hydrocarbon solvent exposures fell four-fold from 1960 to 1998 (Caldwell et al., 2000). We found no other investigations describing the exposure and risk characterisation in engine/brake

cleaners and lubricants. This point highlights the importance of the current work on carcinogenic hazard characterisation of spray-formulated engine/brake cleaners and lubricants.

4.5. Knowledge gaps, research recommendations and limitations of the study

In the current work, we identified a set of substances in spray-formulated engine/brake cleaners and lubricants with carcinogenic potential. A next step could be the collection of further data on their carcinogenic effect, e.g. whether they act by a threshold or non-threshold genotoxic mechanism, which again informs the risk assessment process. Further research into whether more refined hydrocarbon mixtures have lower carcinogenic potential would be useful to inform safe-by-design processes. Another research area is substances only identified by the QSAR algorithm, which need further in-depth study (literature search, IATA WoE, experimental testing and/or read-across) to assess whether they are carcinogenic. In addition, it is important to consider potential additive or even synergistic mixture effects of different ingredients in these products, which often contain numerous substances (Hadrup, 2014; Hadrup et al., 2016, 2015; Kortenkamp, 2007; Olmstead and LeBlanc, 2005). Finally, inorganic elements are not covered by QSAR, and for those readings, we rely on IARC evaluations and the toxicological literature. As an example of the latter, we recently published literature reviews of four of the metals present in the products in the current database, boron nitride, tungsten, molybdenum and lithium (Hadrup et al., 2022b, 2021).

5. Conclusion

This work provides an overview of the extent of genotoxic and carcinogenic substances in degreasers and lubricating spray-formulated products. We conclude that in the investigated EU marketed spray-formulated engine/brake cleaners and lubricants, 24 of 332 mono-constituent substances and 28 of 44 multi-constituent/UVCBs had a carcinogenic potential based on IARC, EU-harmonised classification, and QSAR. At the product level, 39 of 82 contained substances with an identified carcinogenic potential by either IARC, harmonised classification or QSAR, suggesting a carcinogenic potential in half of the products for which sufficient information on composition was available. These results can contribute to safe-by-design choices for manufacturers. Also, the data informs that precautions should be taken at the workplace to limit exposure to these agents. One possibility is to choose alternative application methods to spraying.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Niels Hadrup reports financial support was provided by The Danish Working Environment Research Fund.

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CRediT authorship contribution statement

Jorid B. Sørli: Conceptualization, Data curation, Writing – review & editing, Funding acquisition. **Marie Frederiksen:** Conceptualization, Data curation, Writing – review & editing, Funding acquisition. **Nikolai G. Nikolov:** Data curation, Methodology, Software, Writing – review & editing. **Eva B. Wedebye:** Data curation, Methodology, Software, Writing – review & editing. **Niels Hadrup:** Conceptualization, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tox.2022.153261.

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