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Author manuscript
Environ Res. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:
Environ Res. 2019 February ; 169: 163–172. doi:10.1016/j.envres.2018.10.018.

Evaluation of potential carcinogenicity of organic chemicals in synthetic turf crumb rubber

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Abstract

Currently, there are > 11,000 synthetic turf athletic fields in the United States and > 13,000 in Europe. Concerns have been raised about exposure to carcinogenic chemicals resulting from contact with synthetic turf fields, particularly the infill material ("crumb rubber"), which is commonly fabricated from recycled tires. However, exposure data are scant, and the limited existing exposure studies have focused on a small subset of crumb rubber components. Our objective was to evaluate the carcinogenic potential of a broad range of chemical components of crumb rubber infill using computational toxicology and regulatory agency classifications from the United States Environmental Protection Agency (US EPA) and European Chemicals Agency (ECHA) to inform future exposure studies and risk analyses. Through a literature review, we identified 306 chemical constituents of crumb rubber infill from 20 publications. Utilizing ADMET Predictor™ , a computational program to predict carcinogenicity and genotoxicity, 197 of the identified 306 chemicals met our *a priori* carcinogenicity criteria. Of these, 52 chemicals were also classified as known, presumed or suspected carcinogens by the US EPA and ECHA. Of the remaining 109 chemicals which were not predicted to be carcinogenic by our computational

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Author contributions
ANP, SSF, (data acquisition, analysis, and interpretation), ANP, NCD (study design), ANP, DT (preparation of manuscript, and critical revision of the manuscript), NCD, CHJ (data interpretation and critical revision of the manuscript), SHIH (regulatory data analysis, Cytoscape analysis and critical revision of the manuscript) VV (study design, data interpretation, critical revision of the manuscript, and study supervision).
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Conflict of interest
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toxicology analysis, only 6 chemicals were classified as presumed or suspected human carcinogens by US EPA or ECHA. Importantly, the majority of crumb rubber constituents were not listed in the US EPA (n = 207) and ECHA (n = 262) databases, likely due to an absence of evaluation or insufficient information for a reliable carcinogenicity classification. By employing a cancer hazard scoring system to the chemicals which were predicted and classified by the computational analysis and government databases, several high priority carcinogens were identified, including benzene, benzidine, benzo(a)pyrene, trichloroethylene and vinyl chloride. Our findings demonstrate that computational toxicology assessment in conjunction with government classifications can be used to prioritize hazardous chemicals for future exposure monitoring studies for users of synthetic turf fields. This approach could be extended to other compounds or toxicity endpoints.

Keywords

Carcinogenicity; Computational toxicology; Crumb rubber; Regulatory classification; Synthetic turf

1. Introduction

Synthetic turf is a ground surfacing material designed to imitate both the appearance and function of natural grass (Cheng et al., 2014). Within the sports world, synthetic turf gained popularity in 1966 when it was used in the Astrodome Stadium in Houston, Texas (Marsili et al., 2014). Since then, over 11,000 synthetic turf fields have been installed in the United States (US) (McCarthy and Berkowitz, 2008). In Europe, there are currently over 13,000 synthetic turf fields, a number predicted to increase to approximately 21,000 by the year 2020 (ECHA, 2016). Synthetic turf fields have several advantages over natural grass fields. They do not require irrigation, fertilizers, or pesticide application, which saves water, labor, time, and reduces the likelihood that certain potentially toxic chemicals will be introduced into the environment (Cheng et al., 2014; Claudio, 2008). In addition, synthetic turf fields can be used more frequently because they do not become muddy after precipitation and do not require waiting periods between uses to facilitate repair and recovery (Claudio, 2008). Although synthetic turf installation costs substantially more than natural grass, the overall longterm expenses are lower (Huber, 2006).

Despite these practical advantages, there have been growing concerns about the safety of synthetic turf fields, particularly the infill materials. All synthetic turf fields share the same basic composition, i.e., polyethylene synthetic grass fibers, infill, and carpet backing (Cheng et al., 2014). Crumb rubber is commonly used as the infill material and is mainly produced by fragmentation of scrap vehicle tires (Cheng et al., 2014). It consists of rubber polymer (40–60%), reinforcing agents (e.g., carbon black) (20–35%), aromatic extender oil (≤ 28%), vulcanization additives, antioxidants, antiozonants, and processing aids, such as plasticizers and softeners (Li et al., 2010; Wik and Dave, 2009). The proportional contributions of each constituent depend on the source from which the crumb rubber is manufactured (Cheng et al., 2014). Some of the specific chemicals measured in crumb rubber include polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), semi-volatile organic

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compounds (SVOCs), and metals, such as zinc and lead (Marsili et al., 2014). The focus of concern has been on the crumb rubber infill due to its ubiquitous use, exposure potential, and components which may exert effects that are deleterious to human health.

Human exposure to crumb rubber-derived chemicals may occur through inhalation, ingestion, and/or dermal contact. The dominant route by which the various chemicals in crumb rubber enter the human body will depend, in part, upon each compound's physicochemical properties. For example, semi-volatile compounds, such as PAHs, are more likely to be absorbed *via* inhalation given their off-gassing capabilities (especially during high temperatures). By contrast, metals may be more readily absorbed *via* unintentional ingestion of crumb rubber particles (Zhang et al., 2008). The exposure route may also be influenced by the characteristics and behaviors of the player, such as age, type of sport played, use of gloves and mouth guards, and field position (Hibbert et al., 2017). For example, younger players may have more hand-to-mouth contact than older players; soccer goalkeepers may have more skin-to-field contact than other positions. To date, exposure measurement studies of crumb rubber-derived chemicals have been quite limited.

The magnitude of exposure to chemicals from crumb rubber likely depends on several factors. The age of the infill layer can affect the concentration of chemicals found within crumb rubber, which is of relevance because 900–1000 new synthetic turf fields are established annually in the US (McCarthy and Berkowitz, 2008). Newer synthetic turf fields have higher levels of PAHs and benzothiazole in crumb rubber samples than in those collected from older synthetic turf fields (Zhang et al., 2008; Li et al., 2010). Indoor exposures are presumed to be higher and are greatly influenced by room-ventilation rates (Marsili et al., 2014). Release and transport of chemicals found in the crumb rubber infill layer of synthetic turf fields located outdoors will be affected by wind parameters, such as direction, velocity, and turbulence (MacIntosh and Spengler, 2000), as well as ambient temperature. Specifically, at an outdoor air temperature of 25 °C, the surfaces of synthetic turf fields can reach as high as 60°C, a temperature at which crumb rubber can release semi-volatile organics into the surrounding air (Marsili et al., 2014). If the surface of a synthetic turf field does not reach a temperature of 25 °C, the release of crumb rubber chemicals into the surrounding air can be linked to other mechanisms, such as wind erosion (Marsili et al., 2014).

Over the past several years, public health concerns have been raised regarding the potential adverse health effects in humans exposed to the crumb rubber infill component of synthetic turf fields, e.g., hematopoietic cancers among adolescent goalkeepers (Bleyer, 2017). The limited number of risk assessments that have been conducted do not currently support a significant health risk from playing on synthetic turf fields; however, exposure monitoring data are sparse, and no epidemiologic studies have been conducted to date (US EPA, 2016a, 2016b). Consequently, in February 2016, the Centers for Disease Control and Prevention/ Agency for Toxic Substances and Disease Registry, the US Consumers Product Safety Commission, and the US Environmental Protection Agency (EPA) announced the *Federal Research Action Plan on Recycled Tire Crumb Used on Playing Fields and Playgrounds* (US EPA, 2016b). Other agencies, such as the National Institute of Environmental Health Sciences, the US Department of Defense, and California's Office of Environmental Health

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Hazard Assessment, committed to assist with this crumb rubber research enterprise (US EPA, 2016b). While awaiting results from these large-scale, comprehensive exposure studies, screening-level toxicologic assessments can help prioritize chemicals which may be emitted from the fields for more in-depth exposure and risk assessment.

Therefore, the overarching purpose of this analysis is to provide an assessment of the carcinogenic potential of a broad range of crumb rubber synthetic turf infill constituents using interrogation of regulatory agency classifications. The specific objectives are to (1) identify chemicals present in crumb rubber infill based on a comprehensive literature review, (2) predict potential carcinogenicity using computational toxicology methods, (3) evaluate the carcinogenic hazards of each chemical according to government regulatory agency databases and (4) prioritize the carcinogens by applying hazard scores.

2. Methods

2.1. Identification of synthetic turf crumb rubber constituents

We conducted a literature review as part of a substance review at the National Toxicology Program related to potential health effects from exposure to crumb rubber in synthetic turf fields. First, all articles referenced in the report by the US EPA's *Tire Crumb and Synthetic Turf Field Literature and Report List as of Nov. 2015* (US EPA, 2016c) were included. Additionally, we conducted a search in PubMed using the following query: "(artificial-turf[tiab] OR synthetic-turf[tiab] OR artificial-grass[tiab] OR synthetic-grass[tiab] OR AstroTurf[tiab] OR chemgrass[tiab] OR "Everlast Turf"[tiab] OR FieldTurf[tiab] OR "Perfect Turf[tiab] OR PlayersTurf[tiab] OR "Tiger Turf"[tiab]) OR (artificial-field*[tiab] OR synthetic-field*[tiab] OR artificial-surface*[tiab]) OR ((rubber[tiab] OR tire[tiab]) AND (crumb[tiab] OR granuled[tiab] OR granulat*[tiab] OR pellet*[tiab] OR scrap[tiab] OR waste[tiab] OR mulch[tiab] OR infill[tiab] OR recycled[tiab]))." These papers were screened against our inclusion criteria, i.e., measurement of crumb-rubber derived compounds in the crumb rubber itself, analysis of crumb rubber leachate or volatilization, measurements in crumb rubber recycling facilities, or in environmental samples collected at synthetic fields. The relevant publications are summarized in Table 1. We abstracted chemical names and compiled a list of crumb rubber chemical constituents. Although metals have been detected in crumb rubber, we focused our screening assessment on organic chemicals because metals have unique redox complexities which are not accounted for in the ADMET Predictor™ and thus could not be entered into the predictive software for interpretation. A flow chart describing the steps involved in this study is presented in Fig. 1.

2.2. Computational toxicology predictions of potential carcinogenicity

The chemicals identified during the systematic literature review were compiled in the form of the simplified molecular-input line-entry system (SMILES) chemical structure notation and entered into ADMET Predictor™ (version 7.2, Simulations Plus, Lancaster, CA). ADMET Predictor™ can be used to predict various physicochemical, absorption/permeability, metabolism, excretion, and toxicity endpoints for each identified chemical within crumb rubber infill. Because of our focus on carcinogenic potential, we directed our efforts with the "Chronic Carcinogenicity and Mutagenicity" models of the Toxicity

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Module, which included four model types drawing upon a total of 13 individual models: (i) one quantitative prediction model for carcinogenicity built from *in vivo* rat studies, (ii) one quantitative prediction model for carcinogenicity built from *in vivo* mouse studies, (iii) one qualitative prediction model for *in vitro* chromosomal aberrations, and (iv) one compilation of ten qualitative prediction models developed from *in vitro* Ames assay data (with and without S9 metabolic activation). The two computational models for carcinogenicity were developed and validated by Simulations Plus using curated data from Environmental Protection Agency's DSSTox program (Carcinogenic Potency Database (CPDB)) which includes more than 5000 chronic, long term carcinogenesis bioassays reported in over 1200 manuscripts (e.g., > 400 Technical Reports from the National Toxicology Program and National Cancer Institute). These models predict the TD_{50} value in units of mg/kg/day within rats or mice orally exposed to substances over the course of their lifetimes. Likewise, eleven genotoxicity models developed and validated by Simulations Plus utilizing publicly-available datasets. Validation data for these computation models can be found on the Simulations Plus website (https://www.simulations-plus.com/software/admetpredictor/toxicity/). We set *a priori* thresholds for each of these four model types. Chemicals meeting any of the following threshold criteria were considered to have carcinogenic potential (SimulationsPlus, 2017). A description of all "Chronic Carcinogenicity and Mutagenicity" models as well as their pre-specified screening thresholds are as follows:

(i) and (ii) The two quantitative *in vivo* carcinogenicity models, referred to as TOX_BRM_Rat and TOX_BRM_Mouse, predict the median toxic dose (mg/kg/day) at which toxicity occurs in 50% of cases (TD_{50}) of specific chemicals in rats and mice, respectively. The TD_{50} is the chronic dose of a chemical given orally to rodents that gives rise to tumors in 50% of the population at the end of their lifespan. Chemicals with a TD_{50} value prediction of less than or equal to 100 mg/kg/day met the threshold for the TOX_BRM_Rat model and/or the TOX_BRM_Mouse model.

(iii)TOX_CABR, an *in vitro* model, assesses the genotoxic potential of chemicals. This modeling software classifies whether chemicals may cause a chromosome aberration based upon their 2D structures. A chemical given a "toxic" prediction met this model threshold.

(iv)TOX_MUT* artificial neural network ensembles (ANNE) were developed from experimental *in vitro* data for one test for chromosomal aberrations and ten qualitative models that evaluate Ames Mutagenicity in five separate strains of *Salmonella* (five with, and five without liver S9 metabolic activation). The Ames Test, also known as the Bacterial reverse mutation test is a measurement of the mutagenic capability of chemical compounds (Eastmond et al., 2009). "Positive" labels are assigned to chemicals predicted to be mutagenic by the modeling software. As a conservative threshold, we arbitrarily assigned chemicals as being mutagenic if they were positive in the chromosomal aberrations test or at least one of the ten Ames assays in TOX_MUT*ANNE.

2.3. Evaluation of regulatory authority carcinogenicity databases

For each chemical constituent, we searched the US EPA Integrated Risk Information System (IRIS, www.epa.gov/IRIS) and the European Chemicals Agency harmonized classification and labelling of hazardous substances (ECHA, https://echa.europa.eu/information-on-

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chemicals/annex-vi-to-clp) databases to identify documented carcinogenic classification for each chemical. ECHA is based on United Nations Globally Harmonized System for Classification and Labelling of Chemicals (United Nations Globally Harmonized System for Classification and Labelling of Chemicals, 2017). The various descriptors used by the regulatory authorities (i.e., US EPA and ECHA) to categorize chemicals as carcinogens are shown in Table 2. In the present study, we recategorized ECHA and US EPA classifications into "known human carcinogen", "presumed human carcinogen" or "suspected human carcinogen" (Table 2).

2.4. Chemical prioritization and data visualization using cytoscape

To prioritize chemicals for future exposure assessment, a numerical cancer hazard scoring was assigned to either ADMET Predictor™ -based prediction or classification by US EPA and ECHA. A numerical score of 20, 16 and 12 were applied to known, presumed and suspected human carcinogens, respectively, per previously published methods (Shin et al., 2014; Inayat-Hussain et al., 2018). A hazard score assigned to a chemical was based on the most stringent classification from either US EPA or ECHA. Any chemical classified by the US EPA or ECHA and concomitantly classified as a predicted carcinogen based on ADMET Predictor™ was assigned an additional hazard score of 10. These data were then analyzed using Cytoscape, an open-source software platform for integration, analysis and visualization of networked data (Shannon et al., 2003) to graphically represent the carcinogens and their relationship with the source of classification, i.e., ADMET Predictor™ , US EPA or ECHA. The color intensity of the chemical nodes code for the cancer hazard score such that darkest nodes are chemicals of highest concern due to higher cumulative cancer hazard scores.

3. Results

Our literature search yielded 43 articles, of which 20 met our inclusion criteria (Table 1). In these studies, conducted primarily in the US and Europe, crumb rubber constituents were analyzed through direct chemical extraction, air sampling (i.e., off-gassing, volatilization), or in leachate (water or other fluid passing over crumb rubber, facilitating release of chemicals into the liquid). Within these publications, we identified 306 organic chemicals that were associated with crumb rubber infill. These compounds spanned several chemical classes, including PAHs, nitrosamines, furans, organochlorines, antioxidants and plasticizers.

An overall summary of the data is presented in Fig. 2. One hundred and ninety-seven of the 306 chemicals met the assigned thresholds and therefore were predicted as having carcinogenic potential by ADMET Predictor™ (listed in Table 3); the remaining 109 chemicals did not meet the assigned thresholds and therefore were not predicted as carcinogenic by this computational program (Supplemental Table 1). The categorization of the classifications found in the US EPA and ECHA databases relative to the ADMET predictions are presented in Fig. 2. This analysis revealed that 61% and 80% of the ADMET predicted carcinogens were not listed in the US EPA and ECHA databases, respectively.

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Forty-five of the 197 chemicals predicted to be carcinogenic by ADMET Predictor™ were also classified by US EPA as known, presumed or suspected carcinogens. Five chemicals, benzene, benzidine, benzo(a) pyrene, trichloroethene and vinyl chloride, were classified as known human carcinogens, 28 were classified as presumed carcinogens and 12 as suspected (i.e. possible or suggestive evidence of) carcinogens. Thirty chemicals predicted as carcinogens based on ADMET Predictor™ were considered not classifiable by the US EPA due to inadequate information. Only one chemical, 2-butoxyethanol, predicted to be carcinogenic by the ADMET Predictor™ was classified as not likely to be carcinogenic to humans by the US EPA.

In comparison, only 39 of 197 ADMET predicted chemicals were classified as known, presumed or suspected carcinogens by the ECHA. Of these, three (benzene, benzidine and vinyl chloride) were classified as known human carcinogens, while 18 chemicals were classified as presumed carcinogens and the remaining 18 chemicals as suspected carcinogens.

There were 109 chemicals from our literature search that did not meet the criteria as predicted carcinogens based on ADMET Predictor™ . As shown in Fig. 2, only a small percentage of these chemicals were classified as presumed or suspected carcinogens by the US EPA or ECHA. For example, bis(2-ethylhexyl) phthalate, hexachlorobenzene, and pentacholorophenol were classified by the US EPA as presumed carcinogens while isophorone was a suspected carcinogen. Hexachlorocyclopentadiene was the only chemical which had evidence for non-carcinogenicity in humans and therefore was not classified by the US EPA. It is pertinent to note that 86% and 95% chemicals of these 109 chemicals were not listed in the US EPA and ECHA databases, respectively.

Network graphs based on the cancer hazard scores were created using Cytoscape to allow visualization of the relationships between the 58 chemicals classified as carcinogenic by the US EPA or ECHA (Fig. 3). Of these, 52 chemicals also had evidence of carcinogenicity based on the ADMET Predictor™ . Five carcinogens, benzene, benzidine, benzo(a) pyrene, trichloroethylene and vinyl chloride, showed the highest hazard scores (darkest nodes), indicating they were consistently classified by all three sources, i.e., ADMET Predictor™ , EPA and ECHA. As such, these are chemicals that should be of high priority for exposure assessment. Most of the ADMET Predictor™ -identified carcinogens were mutually classified by EPA and ECHA (as shown by nodes in the middle section of the figure), while some were classified singly by either EPA or ECHA (as shown by nodes on the upper and right side of the figure, respectively). Specifically, bis (2-ethylhexyl) phthalate was identified by the US EPA (but not by the ECHA), whereas 1, 3 butadiene 2-methyl (generally known as isoprene) and 1,4 dichlorobenzene were classified by the ECHA (but not by the US EPA). Isophorone, hexachlorobenzene and pentachlorophenol were classified by both EPA and ECHA but not predicted to be carcinogenic by ADMET Predictor™ . Chemicals exhibiting discordance among some of the classifications/predictions might be considered lower priority chemicals for future assessment. Benzene, benzidine, and trichloroethylene were confirmed by Simulations Plus to be part of the computational model training set structures for rat TD_{50} determinations, while benzidine, benzo(a)pyrene, and trichloroethylene were confirmed training compounds for mouse TD_{50} determinations.

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4. Discussion

There has been a growing concern about the health risks posed by the chemicals found in synthetic turf (Simcox et al., 2011; Peterson et al., 2018; Celeiro et al., 2018). Users of synthetic turf fields engage in activities that would potentially promote exposure to crumb rubber infill chemicals, such as increased ventilation during exercise, hand-to-mouth contact, and abrasions through falls during competitive sports. Repeated exposure to chemicals, such as the predicted carcinogens in this study or others, could be expected to increase cancer risk.

The conflicting opinions on the potential health risks of chemicals (including carcinogens) found in synthetic turf was reviewed by Watterson (2017). The author noted that although several studies have shown little risk to athletes ands children, several of the studies suffered from significant uncertainties, especially in relation to the exposure data and the range of substances monitored. Our findings demonstrate that computational toxicology assessment in conjunction with government classifications can be used to identify and prioritize hazardous chemicals to be examined in future exposure studies for users of synthetic turf fields.

A recent evaluation was conducted by the ECHA on the possible health risks of recycled rubber granules used as infill in synthetic turf sports fields (ECHA, 2017). The ECHA screened more than 200 substances found in the US EPA list (Thomas, 2016) and classified 20 chemicals (including PAHs and phthalates) as known and presumed carcinogens, mutagens or toxic to reproduction (CMRs; categories 1A or 1B). Based on our study, there were 21 predicted carcinogens which were also classified as known or presumed carcinogens. In addition, two presumed carcinogens were identified by the US EPA or ECHA from our list of chemicals which were not predicted to be a carcinogen by our computational toxicology assessment, ADMET Predictor™ . This highlights a potential limitation of the ADMET Predictor™ . Specifically, this software provides results that are not 100% concordant with EPA and ECHA evaluations. As such, where EPA and/or ECHA data are available, they should take precedence over the ADMET Predictor™ . However, in the absence of government data, the present results provide support for the use of the ADMET Predictor™ software to guide future chemical evaluation or exposure assessments.

It is noteworthy that in Europe, products (*i.e.,* “articles”) containing one or more of PAHs at concentrations greater than or equal to 0.0001% are restricted from being placed on the market for the public (ECHA, 2017). From a human health risk assessment perspective, chemicals known or presumed to be carcinogens have higher priorities for future exposure assessment. Our data lend support to the hazard identification process of carcinogens found in crumb rubber infill. In addition, application of hazard scores based on the most stringent classification to the carcinogens by either the US EPA or ECHA provides an opportunity to prioritize chemicals which should be of greater concern versus those of lesser concern.

Our study highlights a vacuum in our knowledge about the carcinogenic properties of many chemicals in crumb rubber infill. Specifically, there were 207 chemicals identified in our literature search that did not have any cancer classification in the US EPA database.

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Similarly, 262 chemicals were not found in the ECHA database. It is not possible to comment whether these chemicals have carcinogenic properties; additional information evaluating the carcinogenic potential (or lack thereof) of these chemicals in *in vitro* or *in vivo* studies would address this critical knowledge gap. In the interim, we would advocate that the ADMET Predictor™ software may provide valuable guidance for future evaluations by government agencies. While we appreciate the fact that the majority of chemical structures for established carcinogens were available in the development and validation of these computational models within ADMET-Predictor™ , the fact that known carcinogens were readily identified with this approach further enhances our confidence in the potential utility of this rapid approach for prioritization. Moreover, during computational model development, reference data were split into training and validation sets with overall $R^2 > 0.7$, which increased confidence towards the extension of these models to the broader chemical structure diversity of crumb rubber constituents. As with all models, it is important to understanding of the domain of applicability of these types of models as our molecular understanding of chemical-induced carcinogenicity evolves.

Our study focused on understanding the cancer hazards of rubber infill chemicals in synthetic turf. However, it is entirely conceivable that the chemicals identified in our literature review may carry other health hazards that could be shorter-term or more acute in nature. Indeed, several of the chemicals identified in our literature search appear to have other health risks. For example, 1,3 dichloropropene, a presumed carcinogen (according to US EPA) is also classified as a skin sensitizer by ECHA, while phenol (no carcinogen classification) and hexachlorobutadiene (suspected human carcinogen according to US EPA) are both classified as corrosive to skin by ECHA. A recent assessment on the possible health risks of recycled rubber granules used as infill in synthetic turf sports fields by ECHA also revealed several skin sensitizers including formaldehyde and benzothiazole-2-thiol (2-mercaptobenzothiazole) (ECHA, 2017). Such actions should also be considered for synthetic turf because minor superficial skin injuries obtained by players on a field may be further aggravated by synthetic turf-derived skin irritants or corrosive chemicals (van den Eijnde et al., 2014). Similar concerns may be raised regarding the potential for respiratory sensitization caused by inhalation of VOCs or SVOCs from rubber infill, particularly when the synthetic turf temperatures increase.

5. Conclusions

The crumb rubber infill of artificial turf fields contains or emits chemicals that can affect human physiology. Of the 306 chemicals associated with crumb rubber infill from publications, application of an *in silico* computational program predicted 197 carcinogens. Of these, a total of 52 had been classified as carcinogens by the US EPA and/or the ECHA. Of the 109 chemicals which were not predicted to be carcinogenic using the ADMET Predictor™ , only four were classified as carcinogens by the US EPA and only five chemicals by ECHA. These results demonstrate that *in silico* carcinogenic prediction is modestly robust and should be considered as a tool for prioritizing carcinogen studies by government bodies under circumstances in which no carcinogenic data is available or conflicting carcinogenic classifications have been obtained. Further prioritization by application of hazard scores in conjunction with Cytoscape visualization revealed chemicals that we propose should be of high priority for future exposure assessments. The results of the present study underscore the need for human exposure studies that investigate the likelihood of users of synthetic turf fields being exposed to the chemicals identified in our study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work is supported in part by the intramural program of the National Toxicology Program in the Health Sciences (NIEHS) in the United States. Dr. Inayat-Hussain would like to thank the Bureau of Educational and Cultural Affairs (ECA) of the US Department of State and the Malaysian-American Commission on Educational Exchange (MACEE) for the Fulbright Visiting Scholar Program at Yale School of Public Health. Dr. Abee L Boyles (NIEHS) is gratefully acknowledged for her contribution in data analysis and study design.

Appendix A.: Supporting information

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.envres.2018.10.018.

Abbreviations:

ANNE	Artificial Neural Network Ensembles
EPA	Environmental Protection Agency
ECHA	European Chemicals Agency
PAHs	polycyclic aromatic hydrocarbons
SVOCs	semivolatile organic compounds
VOCs	volatile organic compounds
US	United States

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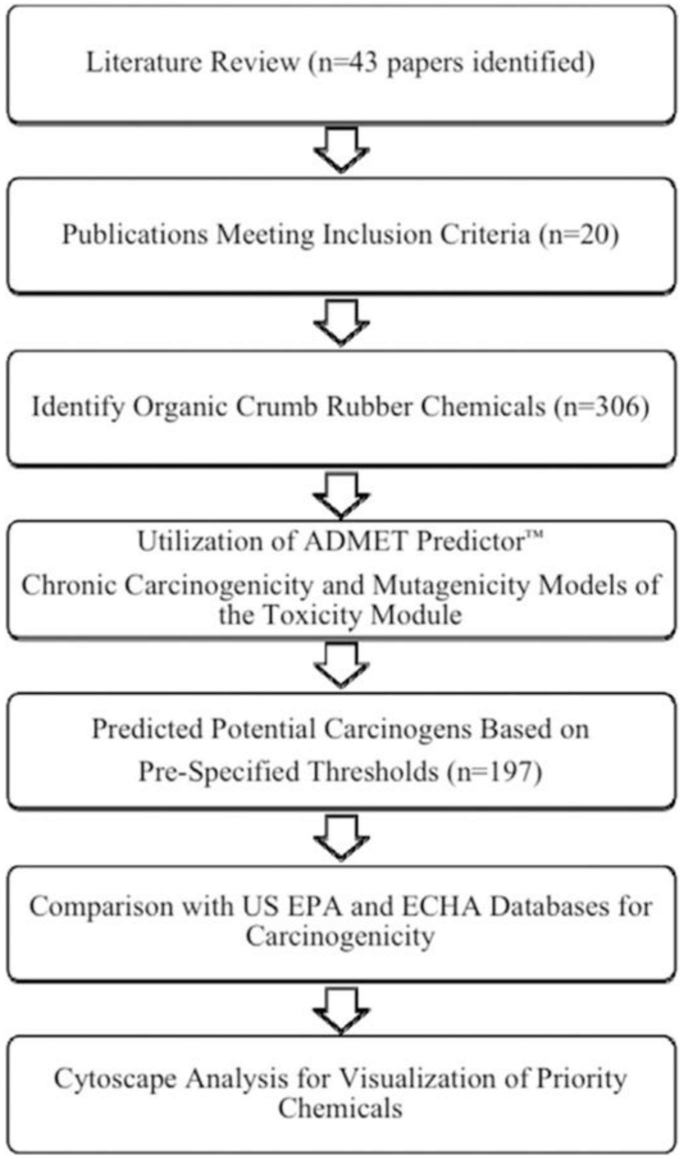

Fig. 1.
Overview of the study design and results.

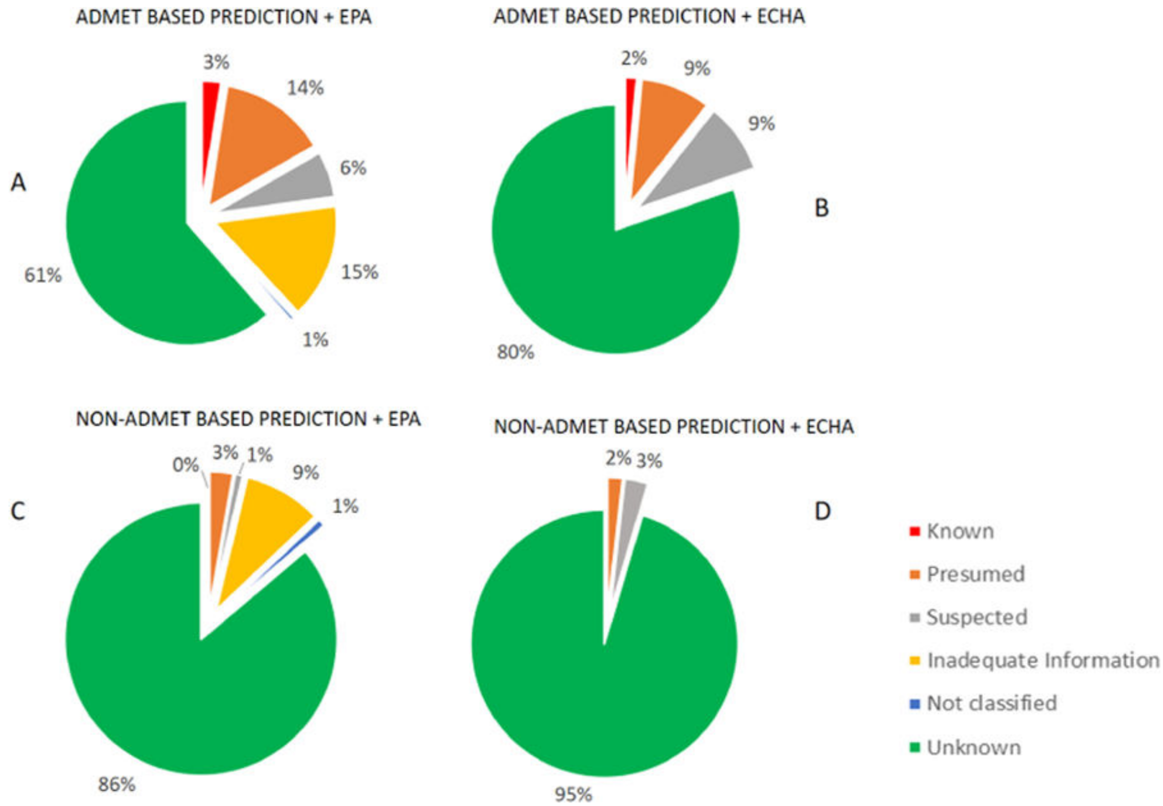

Fig. 2. Overview of carcinogenic classification of chemicals from the literature review.

Panels A and B describe the EPA and ECHA carcinogenic classifications respectively on chemicals which were predicted to be carcinogens based on ADMET Predictor™ (n = 197). Panels C and D represent EPA and ECHA carcinogenic classifications respectively on chemicals which were not predicted to be carcinogenic based on ADMET Predictor™ (n = 109).

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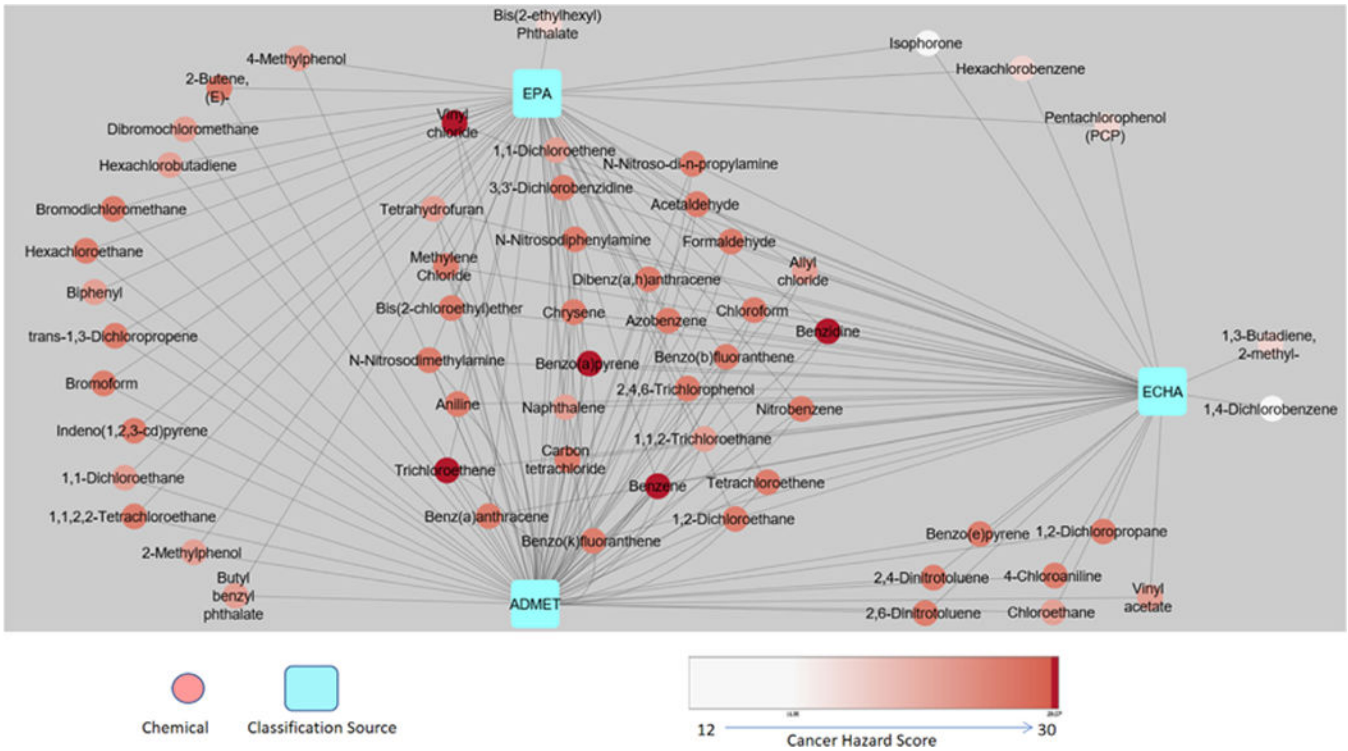

Fig. 3. Visualization of carcinogenic chemicals by Cytoscape.

The three sources, ADMET (ADMET Predictor™ computational predictions), EPA and ECHA, were linked by lines based on classification similarity. The node color intensity shows the cancer hazard score between 12 and 30 where chemicals with the highest color intensity are due to higher scores.

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Table 1

Studies evaluating chemicals present in or emitted from crumb rubber.

Author	**Study location**	**Study type**		
		Direct chemical analysis of crumb rubber	**Air sampling of volatilization from crumb rubber**	**Leachate of crumb rubber**
Bocca et al. (2009)	Italy	X		X
Cheng et al. (2014)	Lyon, France; Connecticut US; Sittard, Netherlands; New York, US			X
Connecticut (2010)	Connecticut, US		X	X
Dye et al. (2006)	Oslo, Norway; Fredrikstad, Norway		X	
Ginsberg et al. (2011)	Connecticut, US		X	
Highsmith et al. (2009)	Georgia, US; North Carolina, US; Ohio, US; Nevada, US	X	X	
Kim et al. (2012)	Seoul, Korea	X		
Li et al. (2010)	Connecticut, US		X	X
Lim and Walker (2009)	New York, US		X	X
Marsili et al. (2014)	Tuscany and Lazio, Italy	X	X	
Mattina et al. (2007)	Connecticut, US		X	X
Pavilonis et al. (2014)	New Jersey, US	X		
Ruffino et al. (2013)	Turin, Italy	X	X	
Schiliro et al. (2013)	Torino, Italy		X	
Selbes et al. (2015)	South Carolina, US	X		X
Simcox et al. (2011)	Connecticut, US	X	X	
Vetrano, Ritter (2009)	New York, US	X	X	
Vidair (2010)	California, US		X	
Zhang et al. (2008)	New York, US	X		

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Table 2

Description of the US EPA and ECHA classifications for carcinogenicity.

Descriptors in present study	EPA Guidelines for Carcinogen Risk Assessment		ECHA
	1986	2005	
Known Human Carcinogen	A Human Carcinogen	Carcinogenic to Humans	1A Known Human Carcinogenic Potential
Presumed Human Carcinogen	B1, B2 Probable Human Carcinogen	Likely to Be Carcinogenic to Humans	1B Presumed Human Carcinogenic Potential
Suspected Human Carcinogen	C Possible Human Carcinogen	Suggestive Evidence for Carcinogenic Potential	2 Suspected Human Carcinogen
	D Not classifiable as to Human Carcinogenicity	Inadequate Evidence to Assess Carcinogenic Potential	
	E Evidence of Noncarcinogenicity in Humans	Not Likely to Be Carcinogenic to Humans	

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Table 3

US EPA and ECHA cancer classifications of chemicals linked to artificial turf with predicted carcinogenicity by ADMET Predictor™ (n=197).

CASRN [a]	Chemical name	US EPA cancer classification [b]	ECHA cancer classification [b]
71556	1,1,1-Trichloroethane	Inadequate information	–
79345	1,1,2,2-Tetrachloroethane	Likely to be carcinogenic	–
79005	1,1,2-Trichloroethane	Possible human carcinogen	Suspected human carcinogen
75343	1,1-Dichloroethane	Possible human carcinogen	–
75354	1,1-Dichloroethene	Possible human carcinogen	Suspected human carcinogen
95636	1,2,4-Trimethylbenzene	Inadequate information	–
107062	1,2-Dichloroethane	Probable human carcinogen	Presumed human carcinogen
78875	1,2-Dichloropropane	–	Presumed human carcinogen
108678	1,3,5-Trimethylbenzene	–	–
504609	1,3-Pentadiene	–	–
793248	1,4-Benzenediamine, N-(1,3-dimethylbutyl)-N'-phenyl-	–	–
101724	1,4-Benzenediamine, N-(1-methylethyl)-N'-phenyl-	–	–
591935	1,4-Pentadiene	–	–
111320	1-Butanol, 4-methoxy-	–	–
27799833	1H-Benzotriazol-5-amine, 1-methyl-	–	–
107982	1-Methoxy-2-propanol	–	–
872504	1-Methyl-2-pyrrolidinone	–	–
90120	1-Methylnaphthalene	–	–
673325	1-Propynylbenzene	–	–
1551322	2 Ethyltetrahydrothiopene	–	–
112345	2-(2-Butoxyethoxy)ethanol	–	–
124174	2-(2-Butoxyethoxy)ethanol acetate	–	–
934349	2(3H)-Benzothiazolone	–	–
5469169	2(3H)-Furanone, dihydro-4-hydroxy-	–	–
108601	2,2'-Oxybis(1-Chloropropane)	–	–
3910358	2,3-Dihydro-1,1,3-trimethyl-3-phenyl-1H-indene	–	–
95954	2,4,5-Trichlorophenol	–	–
88062	2,4,6-Trichlorophenol	Probable human carcinogen	Suspected human carcinogen

CASRN [a]	Chemical name	US EPA cancer classification [b]	ECHA cancer classification [b]
120832	2,4-Dichlorophenol	–	–
105679	2,4-Dimethylphenol	–	–
51285	2,4-Dinitrophenol	–	–
121142	2,4-Dinitrotoluene	–	Presumed human carcinogen
581420	2,6-Dimethylnaphthalene	–	–
606202	2,6-Dinitrotoluene	–	Presumed human carcinogen
78933	2-Butanone	Inadequate information	–
624646	2-Butene, (E)-	Likely to be carcinogenic	–
111762	2-Butoxyethanol	Not likely to be carcinogenic to humans	–
1613496	2-Butyltetrathydrothiopene	–	–
110758	2-Chloroethyl vinyl ether	–	–
1321659	2-Chloronaphthalene	–	–
95578	2-Chlorophenol	–	–
3693229	2-Dibenzofuranamine	–	–
19780111	2-Dodecen-1-yl succinic anhydride	–	–
591786	2-Hexanone	–	–
928949	2-Hexen-1-ol, (Z)-	–	–
119368	2-Hydroxybenzoic acid methyl ester	–	–
149304	2-Mercaptobenzothiazole	–	–
120752	2-Methylbenzothiazole	–	–
91576	2-Methylnaphthalene	Inadequate information	–
2531842	2-Methylphenanthrene	–	–
95487	2-Methylphenol	Possible human carcinogen	–
88744	2-Nitroaniline	–	–
88755	2-Nitrophenol	–	–
91941	3,3’-Dichlorobenzidine	Probable human carcinogen	Presumed human carcinogen
4106665	3-Dibenzofuranamine	–	–
1848404	3H-Indazol-3-one, 1,2-dihydro-2-methyl-	–	–
832713	3-Methylphenanthrene	–	–
99092	3-Nitroaniline	–	–
104552	3-Phenyl-2-propenal	–	–

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CASRN [a]	Chemical name	US EPA cancer classification [b]	ECHA cancer classification [b]
99898	4-(1-Methylethyl)phenol	–	–
534521	4,6-Dinitro-2-methylphenol	–	–
101553	4-Bromophenyl phenyl ether	Not Classifiable as Human Carcinogen	–
59507	4-Chloro-3-methylphenol	–	–
106478	4-Chloroaniline	–	Presumed human carcinogen
7005723	4-Chlorophenyl phenyl ether	–	–
106434	4-Chlorotoluene	–	–
50548431	4-Dibenzofuranamine	–	–
622968	4-Ethyltoluene	–	–
108101	4-Methyl-2-pentanone	Inadequate information	–
106445	4-Methylphenol	Possible human carcinogen	–
100016	4-Nitroaniline	–	–
100027	4-Nitrophenol	–	–
781431	9,10-Dimethylanthracene	–	–
83329	Acenaphthene	–	–
208968	Acenaphthylene	Not Classifiable as Human Carcinogen	–
75070	Acetaldehyde	Probable human carcinogen	Suspected human carcinogen
141786	Acetic acid ethyl ester	–	–
75058	Acetonitrile	Not Classifiable as Human Carcinogen	–
98862	Acetophenone	Not Classifiable as Human Carcinogen	–
107051	Allyl chloride	Possible human carcinogen	Suspected human carcinogen
62533	Aniline	Probable human carcinogen	Suspected human carcinogen
191264	Anthanthrene	Not Classifiable as Human Carcinogen	–
120127	Anthracene	Not Classifiable as Human Carcinogen	–
613127	Anthracene, 2–methyl-	–	–
779022	Anthracene, 9-methyl-	–	–
103333	Azobenzene	Probable human carcinogen	Presumed human carcinogen
56553	Benz(a)anthracene	Probable human carcinogen	Presumed human carcinogen
101677	Benzenamine, 4-octyl-N-(4-octylphenyl)-	–	–
71432	Benzene	Human carcinogen	Known human carcinogen
611143	Benzene, 1-ethyl-2-methyl-	–	–

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CASRN [a]	Chemical name	US EPA cancer classification [b]	ECHA cancer classification [b]
620144	Benzene, 1-ethyl-3-methyl-	–	–
104461	Benzene, 1-methoxy-4-(1-propenyl)-	–	–
21573364	Benzene, 2-methoxy-1,3,4-trimethyl-	–	–
53957349	Benzenemethanol, ar-ethenyl-	–	–
1678257	Benzenesulfonanilide	–	–
92875	Benzidine	Human carcinogen	Known human carcinogen
203338	Benzo(a)fluoranthene	–	–
50328	Benzo(a)pyrene	Carcinogenic to humans	Presumed human carcinogen
205992	Benzo(b)fluoranthene	Probable human carcinogen	Presumed human carcinogen
243174	Benzo(b)fluorene	–	–
16587476	Benzo(b)thiophene, 6-methyl-	–	–
192972	Benzo(e)pyrene	–	Presumed human carcinogen
191242	Benzo(g,h,i)perylene	Not Classifiable as Human Carcinogen	–
203123	Benzo(ghi)fluoranthene	–	–
207089	Benzo(k)fluoranthene	Probable human carcinogen	Presumed human carcinogen
65850	Benzoic Acid	Not Classifiable as Human Carcinogen	–
93890	Benzoic acid ethylester	–	–
95169	Benzothiazole	–	–
615225	Benzothiazole, 2-(methylthio)-	–	–
100516	Benzyl alcohol	–	–
92524	Biphenyl	Suggestive evidence of carcinogenic potential	–
111911	Bis(2-chloroethoxy)methane	Not Classifiable as Human Carcinogen	–
111444	Bis(2-chloroethyl)ether	Probable human carcinogen	Suspected human carcinogen
75274	Bromodichloromethane	Probable human carcinogen	–
75252	Bromoform	Probable human carcinogen	–
74839	Bromomethane	Not Classifiable as Human Carcinogen	–
123728	Butanal	–	–
106978	Butane	–	–
106650	Butanedioic acid dimethylester	–	–
109217	Butanoic acid butylester	–	–

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CASRN [a]	Chemical name	US EPA cancer classification [b]	ECHA cancer classification [b]
85687	Butyl benzyl phthalate	Possible human carcinogen	–
86748	Carbazole	–	–
75150	Carbon disulfide	–	–
56235	Carbon tetrachloride	Likely to be carcinogenic	Suspected human carcinogen
108907	Chlorobenzene	Not Classifiable as Human Carcinogen	–
75003	Chloroethane	–	Suspected human carcinogen
67663	Chloroform	Probable human carcinogen	Suspected human carcinogen
74873	Chloromethane	Not Classifiable as Human Carcinogen	Suspected human carcinogen
218019	Chrysene	Probable human carcinogen	Presumed human carcinogen
291645	Cycloheptane	–	–
101837	Cyclohexanamine, N-cyclohexyl	–	–
110827	Cyclohexane	Inadequate Information	–
1122823	Cyclohexane, isothiocyanato-	–	–
108941	Cyclohexanone	–	–
287923	Cyclopentane	–	–
62337933	Cyclopropane, 1-chloro-2-ethenyl-1-methy	–	–
112312	Decanal	–	–
1740198	Dehydroabietic acid	–	–
53703	Dibenz(a,h)anthracene	Probable human carcinogen	Presumed human carcinogen
132649	Dibenzofuran	Not Classifiable as Human Carcinogen	–
132650	Dibenzothiophene	–	–
124481	Dibromochloromethane	Possible human carcinogen	–
75718	Dichlorodifluoromethane	–	–
131113	Dimethyl phthalate	Not Classifiable as Human Carcinogen	–
64175	Ethanol	–	–
100414	Ethylbenzene	Not Classifiable as Human Carcinogen	–
206440	Fluoranthene	Not Classifiable as Human Carcinogen	–
86737	Fluorene	Not Classifiable as Human Carcinogen	–
50000	Formaldehyde	Probable human carcinogen	Presumed human carcinogen
75694	Freon 11	–	–
87683	Hexachlorobutadiene	Possible human carcinogen	–

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CASRN [a]	Chemical name	US EPA cancer classification [b]	ECHA cancer classification [b]
67721	Hexachloroethane	Likely to be carcinogenic	–
66251	Hexanal	–	–
627930	Hexanedioic acid dimethylester	–	–
29812791	Hydroxylamine, O-decyl-	–	–
193395	Indeno(1,2,3-cd)pyrene	Probable human carcinogen	–
25155151	Isopropyltoluene	–	–
462953	Methane, diethoxy-Cyclohexane	–	–
1783251	Methanimidamide, N,N-dimethyl-N'-phenyl-	–	–
32469866	Methyl 2alpha -D-xylofuranoside	–	–
108872	Methylcyclohexane	–	–
75092	Methylene Chloride	Likely to be carcinogenic	Suspected human carcinogen
108383	m-Xylene	Inadequate Information	–
91203	Naphthalene	Possible human carcinogen	Suspected human carcinogen
98953	Nitrobenzene	Likely to be carcinogenic	Suspected human carcinogen
75525	Nitromethane	–	–
62759	N-Nitrosodimethylamine	Probable human carcinogen	Presumed human carcinogen
621647	N-Nitroso-di-n-propylamine	Probable human carcinogen	Presumed human carcinogen
86306	N-Nitrosodiphenylamine	Probable human carcinogen	Suspected human carcinogen
124196	Nonanal	–	–
1120076	Nonanamide	–	–
103651	n-Propylbenzene	–	–
95476	o-Xylene	–	–
1119295	Pentanamide, 4-methyl-	–	–
109660	Pentane	–	–
1119400	Pentanedioic acid dimethylester	–	–
198550	Perylene	–	–
85018	Phenanthrene	Not Classifiable as Human Carcinogen	–
108952	Phenol	Not Classifiable as Human Carcinogen	–
85416	Phthalimide	–	–
106423	p-Xylene	Inadequate Information	–
129000	Pyrene	Not Classifiable as Human Carcinogen	–

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CASRN [a]	Chemical name	US EPA cancer classification [b]	ECHA cancer classification [b]
2381217	Pyrene, 1-methyl-	–	–
100425	Styrene	–	–
127184	Tetrachloroethene	Likely to be carcinogenic	Suspected human carcinogen
2425549	Tetradecane, 1-chloro-	–	–
109999	Tetrahydrofuran	Suggestive evidence of carcinogenic potential	Suspected human carcinogen
108883	Toluene	Inadequate Information	–
156605	trans-1,2-Dichloroethene	Inadequate Information	–
542756	trans-1,3-Dichloropropene	Probable human carcinogen	–
79016	Trichloroethene	Carcinogenic to humans	Presumed human carcinogen
76131	Trichlorotrifluoroethane	–	–
6846500	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	–	–
108054	Vinyl acetate	–	Suspected human carcinogen
75014	Vinyl chloride	Human carcinogen	Known human carcinogen
111400	Benzamide, N-N-diethyl-3-methyl-	–	–
598254	1,2-Butadiene, 3-methyl-	–	–

CASRN, chemical abstract registry number; ECHA, European Chemicals Agency; USEPA, United States Environmental Protection Agency

[a] Differences in classification descriptors reflect the 1986 EPA Hazard Assessment Guidelines versus 2005 EPA Carcinogen Risk Assessment Guidelines.

[b] "-" indicates no information available"

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