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# Epistemology of contaminants of emerging concern and literature meta-analysis

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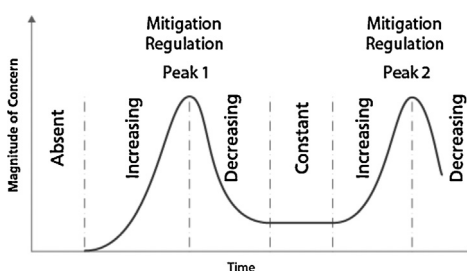
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### HIGHLIGHTS

- Meta-analysis of 143,000 papers reveals common pattern of emergence of contaminants.
- CECs emerge from obscurity to height of concern over a period of  $14.1 \pm 3.6$  years.
- It typically takes  $14.5 \pm 4.5$  years for a CEC to descend from the peak of concern to a new, lower baseline level.
- Regulatory actions are shown to play an important role in managing concern over contaminants.

### GRAPHICAL ABSTRACT



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### ABSTRACT

A meta-analysis was conducted to inform the epistemology, or theory of knowledge, of contaminants of emerging concern (CECs). The CEC terminology acknowledges the existence of harmful environmental agents whose identities, occurrences, hazards, and effects are not sufficiently understood. Here, data on publishing activity were analyzed for 12 CECs, revealing a common pattern of emergence, suitable for identifying past years of peak concern and forecasting future ones: dichlorodiphenyltrichloroethane (DDT; 1972, 2008), trichloroacetic acid (TCAA; 1972, 2009), nitrosodimethylamine (1984), methyl *tert*-butyl ether (2001), trichloroethylene (2005), perchlorate (2006), 1,4-dioxane (2009), prions (2009), triclocarban (2010), triclosan (2012), nanomaterials (by 2016), and microplastics ( $2022 \pm 4$ ). CECs were found to emerge from obscurity to the height of concern in  $14.1 \pm 3.6$  years, and subside to a new baseline level of concern in  $14.5 \pm 4.5$  years. CECs can emerge more than once (e.g., TCAA, DDT) and the multifactorial process of emergence may be driven by inception of novel scientific methods (e.g., ion chromatography, mass spectrometry and nanometrology), scientific paradigm shifts (discovery of infectious proteins), and the development, marketing and mass consumption of novel products (antimicrobial personal care products, microplastics and nanomaterials). Publishing activity and U.S. regulatory actions were correlated for several CECs investigated.

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## 1. Introduction

Harmful biological, chemical and physical agents represent a threat to humans, animals, plants, and microorganisms as well as to the totality of all ecosystems and eco-services humanity relies on. Environmental stress is a constant companion of all life. However, with the industrialization of the world, the number and sources of environmental stress have rapidly increased for both humans and wildlife. Over half of all diseases afflicting humanity are thought to be influenced directly or indirectly by environmental factors. And among the large spectrum of known pollutants, contaminants of emerging concern are considered one important group contributing to environmental diseases of uncertain etiology [1].

The term *contaminants of emerging concern* or CECs, has been in wider use since the early 2000s [2], and has gained popularity over the terminology “*emerging contaminants*.” The latter word suggests the need for the discovery of a new agent of concern, when indeed all that is required is a change in the view of the risks posed by a given substance, irrespective of whether it is newly discovered or has already been known to exist for some time. The term CEC has been defined appropriately as: “A chemical for which there are increasing concerns regarding its potential risks to humans and ecological systems, including endocrine disruption and neurotoxicity,” while adding the qualifying statement that “Within the broad category of CECs monitored, however, agencies have widely different definitions as to what a CEC actually is” [3].

As knowledge of environmental hazards increases, so does the count of specific, harmful CECs, which currently are estimated at a total of more than 40,000 substances, with an estimated six new compounds of CEC potential being added to the chemical inventory of the world every day [3].

Intuitively, one may postulate a course of knowledge generation for CECs progressing through multiple, distinct stages (Fig. 1), i.e., (a) absence of concern due to ignorance of a potential hazard or risk; (b) increase in concern upon realization of a potential threat or knowledge gap; (c) initial height or peak of concern; (d) decrease in concern as a result of accumulating knowledge and risk management strategies, including behavioral changes, exposure control, voluntary phase-out of substances and regulatory actions taken; (e) establishment of a new baseline of residual concern; (f) potential renewed increase in concern possibly due to novel adverse effects observed; (g) second peak of concern; (h) decrease to a new baseline level of concern and so on.

The term *concern* in the CEC moniker is subject to interpretation and may mean different things such as *interest*, *importance* or *cause of anxiety*; all of these interpretations have in common that they are difficult to measure objectively. However, regardless of the nature of *concern*, the latter almost certainly will trigger an elevated activity in scientific research. Thus, research activity may serve as a proxy to track and quantify *concern* regarding specific

contaminants. This approach was adopted in the present study, as it promises both convenient access to relevant data and a low risk of study bias, due to reliance on rigorously maintained scientific databases.

The present meta-analysis of the scientific literature was designed to elucidate the process of CEC emergence and to determine over what timeframe CECs emerge as a threat, and what factors are responsible for triggering their emergence. This work was carried out to better understand past emergences of chemicals and to predict future ones from available data. Twelve case studies were chosen and examined for commonalities and differences in CEC emergence. The selection process was guided by: (i) the need to include substances whose combined emergence histories covered a sufficiently broad time interval of at least four decades; (ii) evidence of public health importance of the substances; (iii) representation of a spectrum of chemical compositions and properties. The agents selected and discussed in the following represent a convenience sample, reflecting these qualities. They include chemical compounds and biological materials that have received extensive attention in scientific journals and the news media alike.

## 2. Time course of CEC emergence

Although common trends of CEC emergence have been speculated to exist [4], yet unanswered questions regarding the epistemology of CECs include:

- How long does the process of CEC emergence take?
- Upon CEC emergence, how long does it take for concern to subside to a lower baseline?
- Can one and the same CEC emerge repeatedly, as suggested in the hypothetical scenario shown in Fig. 1?
- Does the emergence of CECs follow a distinct temporal pattern?

Identifying and characterizing an inherent pattern of CEC emergence would be quite valuable for conceptualizing the ongoing emergence of CECs. If CEC emergence and subsidence indeed are occurring along a common timeline, this may enable one to forecast future developments, e.g., predict future years of peak concern for currently emerging CECs. Such insights into the periodicity of scientific progress have proven beneficial in other scientific disciplines, where for example, Moore's realization in 1965 [5] of the constant rate of miniaturization of microprocessors (known as *Moore's Law*), has enabled fairly accurate forecasting of technical developments for 50 years and counting.

To begin to answer the above questions and probe for an underlying “law of emergence”, a meta-analysis of the peer-reviewed literature was performed in January/February 2014 for the twelve prominent CECs listed in Table 1. Annual publishing activity was chosen as a study metric and proxy for the amorphous term *concern*. Published papers compiled in the Chemical Abstract Service (CAS) database were extracted using SciFinder Web software (v2014). The SciFinder registry was queried using the substance identifier to establish a CAS registry number for each contaminant. References for each registry entry were retrieved for the substances selected. Additional queries were limited to the following categories, or combinations of categories: (1) *adverse effect, including toxicity*; (2) *biological study*; and (3) *occurrence*. Contaminant classes for which no CAS registry numbers were available (i.e., nanomaterials, prions, and microplastics) were queried by research topic and categorized by Chemical Abstract Section Title.

Data on publishing activity per calendar year were extracted from the literature and analyzed systematically. The time point of peak publishing activity was defined as the year for which the most publications for the compound were on record, not the 3-year

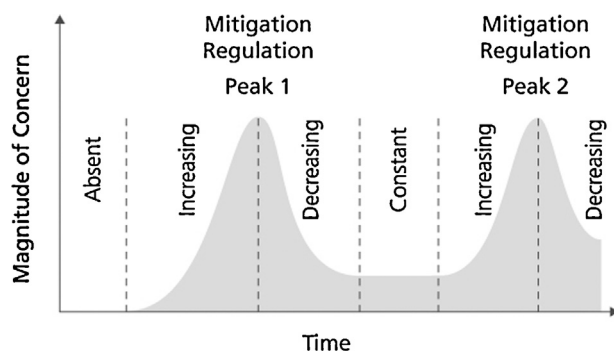


Fig. 1. Hypothesized time course and stages of the emergence of contaminants of concern.

**Table 1**  
Characteristics and metadata of specific contaminants of emerging concern examined in this study.

CECs <sup>a</sup>	DDT	1,4-D	NM <sup>b</sup>	NDMA	MTBE	MP <sup>b</sup>	PC	Prions <sup>b</sup>	TCAA	TCC	TCE	TCS
CAS number	50-29-3	123-91-1	N/A	62-75-9	1634-04-4	N/A	14797-73-0	N/A	76-03-9	101-20-2	79-01-6	3380-34-5
Molecular formula	C <sub>14</sub> H <sub>9</sub> Cl <sub>5</sub>	C <sub>4</sub> H <sub>8</sub> O <sub>2</sub>		C <sub>2</sub> H <sub>6</sub> N <sub>2</sub> O	C <sub>5</sub> H <sub>12</sub> O		ClO <sub>4</sub>		C <sub>2</sub> HCl <sub>3</sub> O <sub>2</sub>	C <sub>13</sub> H <sub>6</sub> Cl <sub>3</sub> N <sub>2</sub> O	C <sub>2</sub> H <sub>2</sub> Cl <sub>3</sub>	C <sub>12</sub> H <sub>7</sub> Cl <sub>3</sub> O <sub>2</sub>
<b>Year of first publication by database category</b>												
Any category	1947	1947	1991	1891	1927	1976	1882	1956	1885	1957	1946	1964
Biological studies	1947	1947	N/A	1966	1972	N/A	1967	N/A	1945	1967	1946	1967
Occurrence	1948	1970	[68]	1970	1977	[69]	1966	[70]	1952	1978	1952	1975
Adverse effect/toxicity	1947	1968		1967	1983		1986		1952	1974	1946	1974
<b>Total number of publications by database category</b>												
Any category	37,136	26,031	30,015	8434	13,188	107	6839	27,468	14,084	1027	30,241	6974
Biological studies	20,339	2304	N/A	5778	2464	N/A	1022	N/A	5473	691	8688	5416
Occurrence	11,955	746	[68]	1926	2571	[69]	589	[70]	2469	200	9732	1259
Adverse effect/toxicity	4361	386		2041	615		148		752	83	3277	558
<b>Peak annual publications activity by database category</b>												
	1134	220	5356	415	414	41	152	1928	364	80	979	473

<sup>a</sup> DDT, dichlorodiphenyltrichloroethane; 1,4-D, 1,4-dioxane; NM, nanomaterials; NDMA, nitrosodimethylamine; MTBE, methyl *tert*-butyl ether; MP, microplastics; PC, perchlorate; TCAA, trichloroacetic acid; TCC, trichloroethane; TCE, trichloroethylene; TCS, trichloroethane. N/A, not applicable.

<sup>b</sup> Nanomaterials, microplastics and prions do not feature unique CAS numbers, which precluded them from entering the search algorithm that produced most of the data in this table. For the convenience of the reader, key references are provided for unpopulated data fields.

moving average. Points of acceleration and subsidence of publishing activity were called out as departures from the baseline publication frequency; specific criteria that all needed to be met simultaneously by a compound's dataset in order to define a baseline departure included: (i) availability of a minimum of seven years of data preceding initial emergence to establish a publication frequency baseline and associated data fluctuations; (ii) occurrence of at least four positive or four negative year-to-year changes in publishing activity within a 5-year period; (iii) year-to-year increases of at least 17% on average for the above 5-year period. Average durations of emergence and subsidence were computed from information on the investigated compounds and are reported with their respective standard deviations.

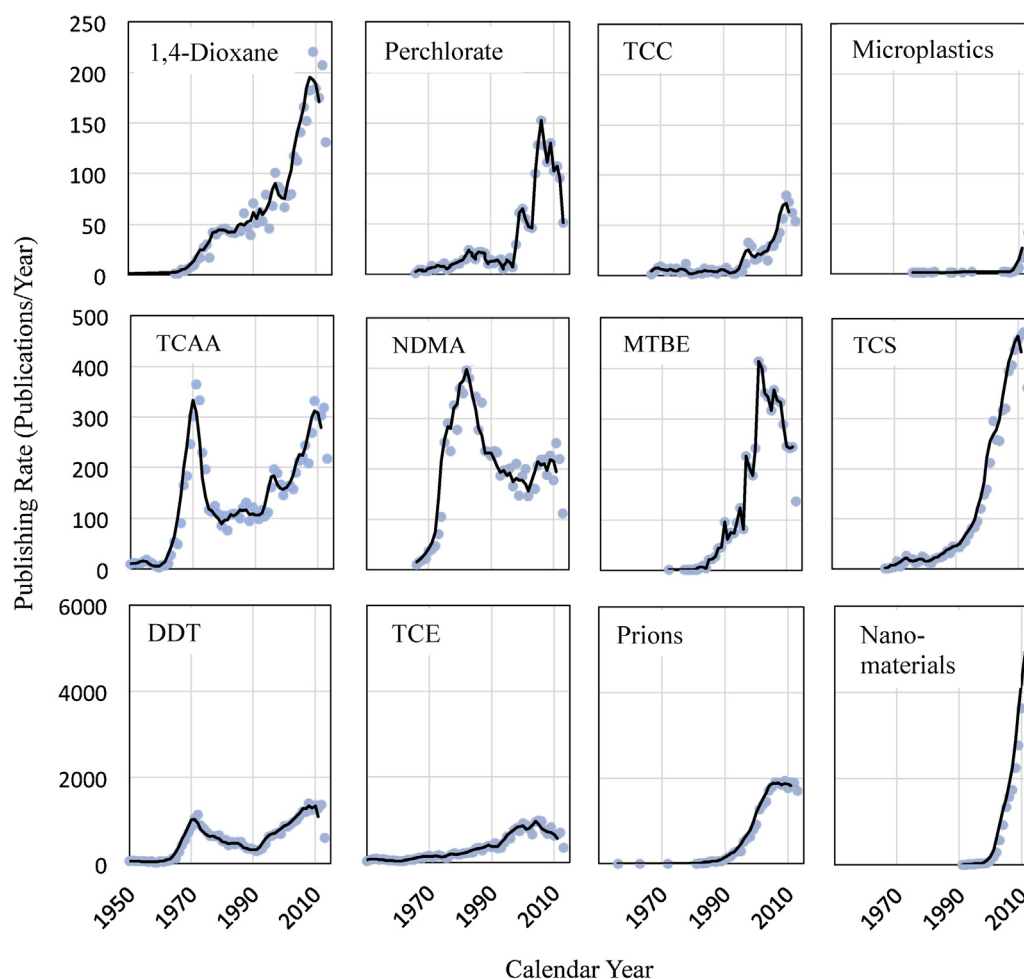
Analysis of the CEC literature enabled the compilation of time-course plots illustrating the emergence of 12 different CECs over the course of the past 63 years from 1950 to 2013 (Fig. 2). Contaminants investigated included: dichlorodiphenyltrichloroethane or DDT; 1,4-dioxane; nanomaterials; *N*-nitrosodimethylamine or NDMA; methyl *tert*-butyl ether or MTBE; microplastics; perchlorate; prions; trichloroacetic acid; triclocarban; trichloroethylene or TCE and triclosan. Obtained plots of publishing activity by compound are presented in an arbitrary order, grouped simply by common magnitudes of scientific inquiry.

A cursory examination of the panels in Fig. 2 readily reveals that there is indeed a rise and ebb in publication activity as hypothesized in Fig. 1. The solid trend lines in the plots represent 3-year moving averages. Chemicals are separated into three groups (rows) by the magnitude of annual publishing activity; within each row, chemicals are shown in the order of their chemical emergence in time. Peak shapes approximating the idealized shape shown in Fig. 1 were obtained for trichloroacetic acid, *N*-nitrosodimethylamine, triclosan, dichlorodiphenyltrichloroethane, and nanomaterials. Data for 1,4-dioxane, perchlorate, triclocarban and methyl *tert*-butyl ether showed more scatter from year to year, deviating somewhat from the hypothesized time course of CEC emergence. For 2 of the 12 CECs investigated (microplastics and nanomaterials), publishing activity apparently is still increasing.

Available data confirm that one and the same CEC indeed may emerge more than once, as illustrated by the example of DDT which peaked in 1972 but saw a reemergence in years since (1991–2008). Similarly, trichloroacetic acid peaked in 1971 and, beginning in 1993, experienced a reemergence resulting in a second peak in 2009.

Table 1 provides additional information on the chemicals investigated in this study and on related publishing activity. At the end of 2013, the most researched and published on substances were in declining order: DDT (37,136), trichloroethylene (30,241), nanomaterials (30,015), prions (27,468), 1,4-dioxane (26,031), trichloroacetic acid (14,084), methyl *tert*-butyl ether (13,188), *N*-nitrosodimethylamine (8434), triclosan (6974), perchlorate (6839), triclocarban (1027) and microplastics (107).

Information obtained from the literature meta-analysis (Fig. 2 and Table 1) was extracted and complemented with information on regulatory action on CECs to arrive at the plot shown in Fig. 3. Here, chemicals are arranged in the order of onset of chemical emergence starting with dichlorodiphenyltrichloroethane (year 1961) and ending with microplastics (year 2008). A statistical analysis of the publication trends for those contaminants that have peaked at least once ( $n = 10$ ) suggests an average duration of CEC emergence from obscurity to maximum level of concern to take about  $14.1 \pm 3.6$  years standard deviation. Similarly, the descent down from the height of research activity to a lower baseline level also shows some commonality, averaging 14.5 years in duration  $\pm 4.5$  years standard deviation; however, this second estimate is based on a much more limited dataset ( $n = 3$ ; DDT, NDMA, trichloroacetic acid).



**Fig. 2.** Publishing activity (1950–2013) for selected contaminants of concern (CECs). Shown is the sum of publications per year (circles) by CEC and publication trend lines (black line) computed from 3-year moving averages of annual publication activity.

The discovery of a common pattern intrinsic to the emergence and subsidence of CECs theoretically may be exploited to forecast the likely year of peak concern for still emerging CECs, and the likely trajectory of future declines in research activity thereafter. Accordingly, nanomaterials are predicted to peak soon and likely no later than the year 2016. Microplastics triggered initial concern only very recently, starting in 2008; if current trends continue, which at this point is uncertain, scientific attention is projected to peak in 2022 ( $\pm 4$  years).

### 3. U.S. regulatory actions and their relationship to levels of concern over CECs

Intuitively, one may expect that regulatory actions may play a key and determining role in limiting the rise and forcing the decline of concerns over chemicals. The thinking being here that a chemical is regulated only if a notable magnitude of concern exists, and that the latter will be diminished by the implementation of regulatory statutes to curb unwanted exposures and ill effects. Speaking for regulations in the United States solely, such a correlation indeed was detected for some but not all of the CECs investigated here. A global analysis of regulatory actions on the CECs discussed here may have provided further insights but unfortunately was beyond the scope of the present study.

In the U.S., use of the pesticide DDT was first prohibited in 1957 for specified protective strips of land around aquatic areas under jurisdiction of the Forest Service of the United States Department of

Agriculture (USDA) [6]. This action preceded the onset of emerging concern over the compound in 1961 (Fig. 3) and was followed in 1964 by a directive from the U.S. Secretary of the Interior, calling for an avoidance of use of chlorinated hydrocarbons on interior lands unless no suitable substitutes were available [6]. Further restrictions were implemented in 1970 for DDT and 15 other types of pesticides on land managed by the USDA [6]. Finally, in 1971, the U.S. Environmental Protection Agency issued notices of intent to void all existing federal registrations of DDT-containing products, an action that was triggered by a court order forced by the Environmental Defense Fund. Effective December 31, 1972, DDT was banned from use in the U.S. except for public health and quarantine purposes [6]. Indeed, the year of peak publishing activity and the ban of DDT in 1972 coincide; yet, a resurgence in scientific interest in DDT was observed, with a second peak occurring in 2008 absent of any further regulatory actions. This finding may be explained in part by ongoing biomonitoring for the compound around the world, new findings on the mechanisms and effects of DDT toxicity, and its controversial continued and resurging use as an indoor pesticide for disease vector control in the developing world.

Trichloroacetic acid is a haloacetic acid and byproduct of the purification of drinking water by chlorine disinfection. TCAA is regulated by the U.S. EPA. Rather than instituting individual limits for haloacetic acids, the Agency regulates TCAA in the haloacetic acid group (HAA5) along with monochloroacetic acid, dichloroacetic acid, bromoacetic acid and dibromoacetic acid. The maximum allowable concentration in U.S. drinking water for all five haloacetic



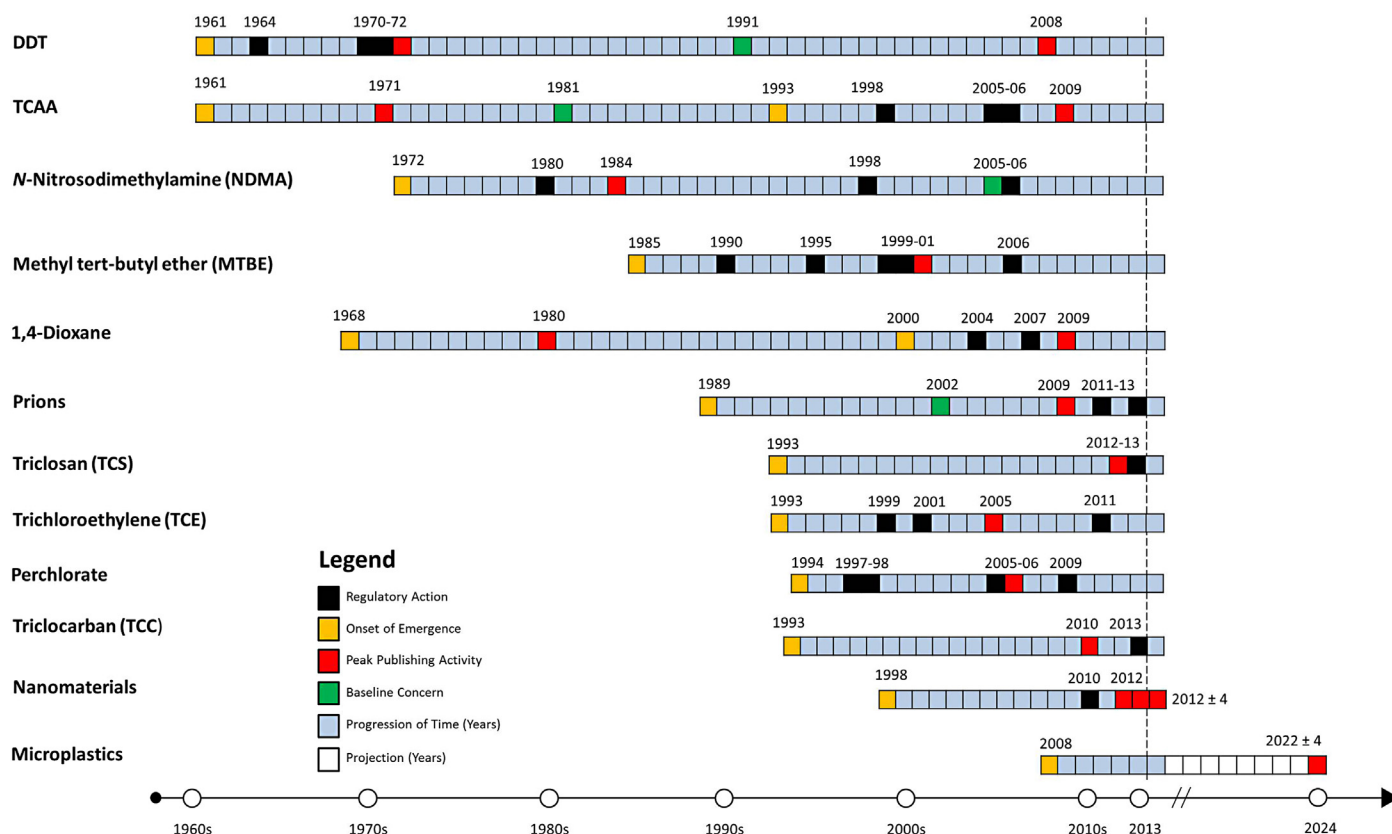


Fig. 3. Chronology of emergence of 12 contaminants of concern (CECs) investigated in this study, and relevant regulatory events in the United States.

acids combined in 60 µg/L. The corresponding regulations were issued in 1998 [7] and 2005/2006 [8]. Despite these regulatory actions, publishing activity for TCAA continued and peaked four years later, in 2009. The reasons are uncertain for what looks like a delayed peak in scientific attention for TCAA; however, it is interesting to note that TCAA is one of only a small number of substances that are regulated as a mixture, which may artificially amplify its prevalence, as the compound will be mentioned in any publication dealing with the HAA5 group as a whole.

N-nitrosodimethylamine is a carcinogen associated with the production of rocket fuel and the disinfection of drinking water [9]. Originally recognized as a contaminant of U.S. food and urban air in the early 1970s, NDMA more recently gained notoriety as an unwanted byproduct of drinking water disinfection [9]. Included as a compound of concern in the Unregulated Contaminant Monitoring Rule 2 of the U.S. EPA, NDMA was detected in 26% of all public water systems evaluated in the U.S. [10]. After the International Agency for Research on Cancer (IARC) classified NDMA as a “possible carcinogen to humans” (Group 2B) in 1978, the first regulatory actions were taken in the U.S. in 1980 by the EPA via publication of an ambient water quality criteria document for nitrosamines [11]. After reclassification of NDMA in 1987 by IARC as a “probable carcinogen to humans” (Group 2A), the California Department of Health Services established a notification level for NDMA in 1998 [12]. Following publication of U.S. EPA Method 521 for detection of nitrosamines in 2004, the State of California established a Public Health Goal for NDMA in drinking water in 2006 [13]. Although the U.S. EPA has been considering NDMA as a priority pollutant since 2001 [14], a Maximum Contaminant Level (MCL) under the Safe Drinking Water Act (SDWA) has not been issued yet. Annual publication activity for NDMA peaked in 1984 and has stabilized somewhat since the early 1990s at an elevated level of about 200 publications per year. There is no apparent association between the

above noted regulatory actions taken and the publishing activity trends for NDMA shown in Figs. 2 and 3.

Methyl *tert*-butyl ether or MTBE, a hydrocarbon ether of moderate toxicity, has been in use in the U.S. as an anti-knocking agent and fuel oxygenate since 1979 to replace tetraethyl lead, protect automotive engines and improve urban air quality. Amendments to the Clean Air Act adopted in 1990 required the use of reformulated or alternative fuels in the most polluted U.S. urban centers [15]. Regulations went in effect in 1995 for ozone non-attainment centers, requiring sale of gasoline containing 2% oxygenates, typically represented by MTBE [15]. In 1999, the State of California banned MTBE over concerns of rampant groundwater contamination and the federal government followed up in 2000 with a bill to phase out MTBE by 2006 [16,17]. Use of MTBE in Europe continued past this date, in contrast. Annual publishing activity for MTBE peaked in 2001 at 414 articles/year (Figs. 2 and 3) and aligns well with the regulatory actions taken to address human health and ecological concerns.

1,4-Dioxane is an organic solvent and toxicant, classified by the U.S. EPA as a Group B2, probable human carcinogen [18]. The compound is a common groundwater and drinking water contaminant due to widespread uses in the past. In the U.S., statewide regulations first concentrated on establishing a preliminary removal goal for 1,4-dioxane in drinking water in 2004, and in 2007, as well as guidelines for medium-specific screening levels and for risk-based maximum concentrations of 6.1 µg/L in drinking water in multiple regulatory regions [19]. A federal MCL has not yet been set for 1,4-dioxane. Annual publishing activity for 1,4-dioxane peaked in 2009 at 220 articles/year, shortly after preliminary actions were taken to protect the U.S. population from exposure through drinking water consumption.

Prions, proteinaceous infectious particles named in 1982 by scientist and Nobel Laureate Stanley Prusiner, are biological agents

responsible for animal and human illnesses including Scrapie, Kuru, and Creutzfeldt-Jakob disease. In 2011, the U.S. EPA published a proposed rule in the Federal Register, recognizing prions as a “pest,” covered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The rule was finalized in 2013 [20]. Aside from the above classification, no direct regulatory actions have been taken yet in the U.S. in response to prion threats, although changes in the production and processing of livestock have been implemented to stem potential prion releases and associated exposures. Annual publishing activity on prions accelerated beginning in 1989 and peaked in 2009 at 1928 publications per year. The timing of peak concerns over prions is aligned with classification of prions under FIFRA.

Trichloroethylene is an organic solvent and potent toxicant, designated as a Hazardous Air Pollutant and commonly found in groundwater at thousands of hazardous waste sites across the U.S., including over 760 national priority cleanup (Superfund) sites. Industrial uses of TCE focused primarily on degreasing and metal cleaning activities using the solvent as a dense non-aqueous phase liquid (DNAPL). Exposure risks to the public result from consumption of contaminated drinking water, and inhalation of contaminated air, particularly of indoor air impacted by soil vapor intrusion. Since the 1970s, TCE has been considered a priority pollutant under the Water Pollution Control Act and has been tightly regulated as a contaminant in drinking water, as an air pollution hazard in occupational settings, and as a residue in processed food, including decaffeinated coffee beans [21]. In 1987, the EPA had classified TCE as a “probable human carcinogen.” A reassessment began in 1989 and was published in 2001 as a draft, designating TCE as “highly likely” to cause cancer and increasing its estimates of toxic potency by 5- to 65-fold [22]. Whereas the California EPA already had reclassified the agent as a known human carcinogen in 1999, scrutiny of TCE by the federal government continued much longer and the more stringent finalized health assessment was published years later, in 2011, identifying TCE as carcinogenic to humans and as a human noncancer health hazard [23]. Peak annual publishing activity for TCE occurred at 979 articles per year in 2005, with important regulatory actions clustered around this point in time.

Perchlorate is a naturally occurring and industrially produced oxyanion featuring four oxygen atoms bonded to a single central chlorine atom. Since the 1940s, perchlorate has been used extensively as an oxygen source in solid rocket propellants, munitions, and fireworks, and more recently in vehicular airbags and signal flares [24]. It also can be present in mined Chilean nitrate fertilizers, disinfectants and herbicides, and is known to form in the atmosphere during lightning storms [24,25]. Contamination of groundwater with perchlorate is a common problem at federal sites historically engaged in the manufacture, testing, and disposal of ammunitions and rocket fuels [24]. Perchlorate is an endocrine disrupting compound impacting the thyroid hormone homeostasis in vertebrates including mammals and humans [26]. Since over 16 million Americans are thought to be at risk of drinking perchlorate impacted groundwater, the U.S. EPA included perchlorate on the federal Contaminant Candidate List (CCL) in 1998, 2005 and 2009, and is expected to publish in 2014 a proposed final rule establishing an MCL under SDWA [26]. California, being among the first state to establish action, notification, and enforceable drinking water levels for perchlorate, initially set a value of 18  $\mu\text{g/L}$  in 1997, and later adjusted downward to 4  $\mu\text{g/L}$  in 2002, and upward to 6  $\mu\text{g/L}$  in 2004 [27]. Annual publishing activity of perchlorate peaked in 2006 at 152 papers per year among a cluster of regulatory steps taken in the United States.

Triclosan and triclocarban are two structurally similar trichlorinated binuclear aromatic antimicrobials that are in widespread use in the U.S. and around the world. Both compounds have been identified as common pollutants of drinking water resources [28],

and have attracted regulatory scrutiny due to their toxic effects on wildlife and humans, including endocrine disrupting activity [29–32]. In the U.S., they are regulated jointly under the topical antimicrobial drug products Over-the-Counter (OTC) Drug Monograph of the Food and Drug Administration (FDA). This piece of regulation was originally drafted in 1974, published as a tentative final draft in 1978, and updated in 1994. In late 2013, the FDA announced pending regulatory actions following entry into a consent decree after a law suit brought on by the Natural Resources Defense Council (NRDC) in 2010 complaining about the multiple decade long delay in finalizing the monograph [33]. In addition, triclosan has been registered as a pesticide by the U.S. EPA under FIFRA since 1969 [34]. Annual publishing activity for triclosan and triclocarban peaked in 2012 and 2010 at 473 and 80 papers per year, respectively, and scrutiny for the need of tighter regulations continues to date, as summarized in a recent review of the regulatory history of both compounds [33].

Nanomaterials are an umbrella term for substances measuring approximately 1–100 nm in length. Engineered nanomaterials (ENMs) have been introduced purposefully into commerce since the late 1980s, initially as Buckminster Fullerenes ( $\text{C}_{60}$ ) and later as carbon nanotubes (CNT) and other materials primarily made from carbon and metals [35]. Nanomaterials feature size-dependent unique properties and also pose unique toxicological risks stemming from their chemical composition and, equally or more important, their physical size and shape [36,37]. The regulatory framework for ENMs is still evolving and subject to scientific discourse. In 2013, the U.S. EPA proposed new legislation within the Toxic Substances Control Act (TSCA) of gathering additional information under the Significant New Use Rule (SNUR); the latter process requires ENMs manufacturers to notify the federal government of nanoscale materials, and to subject to testing certain nanomaterials whether newly introduced or already in use in commerce [38,39]. A parallel effort under FIFRA seeks to collect information on ENM-containing pesticides through a provision for general data collection and data call-in notices for existing registrants [40]. In 2010, the U.S. National Organic Program endorsed the recommendation of the U.S. National Organic Standards Board (NOSB) to prohibit ENMs in certified organic products, including ENM uses in production, processing, and packaging of the same [41]. Annual publishing activity for nanomaterials has risen continuously since 1999 and, in 2013, amounted to 5356 papers per year. This increase in publishing activity has been flanked by the above U.S. efforts to develop a protective, yet practical regulatory framework for these novel materials. Publishing activity on nanomaterials is projected to peak no later than by the year 2016.

Microplastics are small objects of plastic polymers, broadly defined as measuring less than 5 mm in length and extending well into the microscopic range [42]. *Primary microplastics* are produced intentionally as ingredients of abrasive cosmetic products, such as toothpastes and exfoliating skin cleansers; *secondary microplastics* are the unwanted product of breakdown of larger consumer products made out of plastic that once discarded, frequently are found together with primary microplastics in freshwater and marine environments as well as on inland and coastal beaches [42]. Microplastics pose unique risks to ecosystems because they can physically obstruct the respiratory and digestive tract of wildlife including those of birds and fish, and also are known to accumulate toxic environmental pollutants that lead to harmful chemical exposures upon ingestion of manufactured microplastics and microplastic debris [42–44]. First believed to be mostly a marine ecosystem threat, microplastics more recently have been detected at high numbers in freshwater environments, including in rivers and lakes in the U.S. and abroad [44,45]. Whereas plastic debris has been recognized as a source of environmental pollution for decades, regulations specific to microplastics do not exist yet in the U.S.

but are sought by state legislatures, for example, of California and New York [45]. Annual publishing activity on microplastics has increased rapidly since 2008 but overall was still comparatively low in 2014 at 41 publications per year. Scientific attention to microplastics is projected to peak around the year 2022 ( $\pm 4$ ).

#### 4. Non-regulatory drivers modulating the level of concern over contaminants

Aside from regulatory actions taken, there are a number of other important factors influencing the publishing activity on CECs. A non-exhaustive list may include new methods for CEC detection, paradigm shifts in scientific understanding, breakthroughs in the design and manufacture of materials, and changes in marketing and consumer behavior leading to increased chemical consumption.

Novel detection techniques can propel long ignored environmental contaminants into the public eye as illustrated by perchlorate, triclocarban, nanomaterials and MTBE. Realization and tracking of environmental contamination with perchlorate were brought about by breakthrough developments in analytical instrumentation and methods introduced in 1999 and 2000 that lowered the detection limit for perchlorate analysis by ion chromatography from hundreds of parts-per-billion down to 4 ppb [46] and below 1 ppb using mass spectrometry [47] and tandem mass spectrometry [48]. Triclocarban was overlooked as an environmental contaminant for almost half a century [28] and emerged only after the introduction in the U.S. of a simple liquid chromatography/mass spectrometry in 2004 and tandem mass spectrometry methods in 2007 [49–51]. Development of novel tools in nanometrology between 2009 and 2013 enabled not only the detection of ENMs but also helped to inform on the ubiquity of pre-existing and natural nanomaterials [52–57]. The fuel oxygenate MTBE may serve as an example where, due to the lack of reliable detection techniques, the extent of environmental contamination initially was overestimated in nationally maintained databases; this occurred in years prior to 2001 because of a lack of robust methods capable of differentiating between this analyte and co-occurring petroleum hydrocarbons that interfered with reliable detection and caused high levels of false-positive detections for MTBE and related fuel oxygenates [16].

Paradigm shifts in science also can have a profound impact on public concern and publishing activity as illustrated by the discovery of prions as the infectious agents responsible for various neurodegenerative diseases [58–62].

Nanomaterials and microplastics may stand as examples for how the introduction of new materials of utility can drive public concern and spark both a boost in publishing activity and the development of new regulations [42,45,56,57,63–67].

Finally, vigorous marketing efforts and changes in consumer behavior can trigger and accelerate the emergence of CECs. Triclosan and triclocarban both can serve as a case in point. Both compounds saw substantial increases in consumption after forceful marketing campaigns and an increase in the number of antimicrobial products from a few dozens to more than 2000 over the course of 20 years; this development was enabled in part by the 1994 update of the Tentative Final Monograph of the FDA governing their uses in the U.S. [33].

#### 5. Summary and conclusions

The present meta-analysis of over 143,000 publications identified a common pattern of emergence and subsidence of concern over the investigated 12 CECs. On average, about 14 years go by from the onset of concern over a given CEC to the first peak of concern. It then takes another 15 years for scientific research activity,

and thus concern, to level off to a new baseline level. The cases of trichloroacetic acid and DDT illustrate that CECs may emerge more than once. Emergence of CECs was identified as a multifactorial process in which regulatory actions appear to play an important role in arresting the growth of concern and causing a reversal toward a lower baseline level of concern. However, the here performed analysis of regulatory actions was limited to U.S. law only, making more global statements impossible.

At twelve compounds, the sample size of the present survey was manageable, informative, yet limited. Consideration of additional CECs and their inclusion in the present analysis was beyond the scope of this work but may be helpful in the future for refining the time estimates for CEC emergence reported here for the first time. However, it is also important to understand that such retrospective analyses have their limitations and that the ultimate goal is to influence future developments and protect human health and the environment: knowledge gained from the epistemology of CECs should be applied to impact the discovery and regulatory process by shortening the duration of CEC emergence and the time period to reemergence, and by reducing the frequency of reemergence of CECs through the design of intrinsically safer chemicals informed by green chemistry and engineering [33].

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