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A systematic approach for prioritizing landfill pollutants based on toxicity: Applications and opportunities

Elizabeth R. Rogers [a,b,c], Ronald S. Zalesny Jr. [c], Chung-Ho Lin [a,b,*]

[a] Center for Agroforestry, University of Missouri – Columbia, 203 Anheuser-Busch Natural Resources Bldg., Columbia, MO, USA
[b] School of Natural Resources, University of Missouri –Columbia, MO, USA
[c] Institute for Applied Ecosystem Studies, USDA Forest Service, Northern Research Station, 5985, Highway K, Rhinelander, WI, USA

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ABSTRACT

Landfills in the United States are a significant source of pollution to ground and surface water. Current environmental regulations require detection and/or monitoring assessments of landfill leachate for contaminants that have been deemed particularly harmful. However, the lists of contaminants to be monitored are not comprehensive. Further, landfill leachate composition varies over space and time, and thus the contaminants, and their corresponding toxicity, are not consistent across or within landfills. One of the main objectives of this study was to prioritize contaminants found in landfill leachate using a systematic, toxicity-based prioritization scheme. A literature review was conducted, and from it, 484 landfill leachate contaminants with available CAS numbers were identified. *In vitro*, *in vivo*, and predicted human toxicity data were collected from ToxCast, ECOTOX, and CTV Predictor, respectively. These data were integrated using the Toxicological Priority Index (ToxPi) for the 322 contaminants which had available toxicity data from at least two of the databases. Four modifications to this general prioritization scheme were developed to demonstrate the flexibility of this scheme for addressing varied research and applied objectives. The general scheme served as a basis for comparison of the results from the modified schemes, and allowed for identification of contaminants uniquely prioritized in each of the schemes. The schemes outlined here can be used to identify the most harmful contaminants in environmental media in order to design the most relevant mitigation strategies and monitoring plans. Finally, future research directions involving the combination of these prioritization schemes and non-target global metabolomic profiling are discussed.

1. Introduction

Landfills in the United States are a significant source of water pollution. Though current comprehensive data do not exist, the U.S. Environmental Protection Agency (EPA) reported that the nearly 2000 active landfills in the U.S. generate leachate flows ranging from 3.8 to over 2 million L per day (U.S. EPA, 2000). Additionally, 163 landfills were identified as generating contaminated groundwater, with daily flows ranging from 22.7 to over 3.7 million L per day, and a median daily flow of about 48,000 L. The physicochemical and biological composition of landfill leachate varies widely, depending on waste characteristics, moisture content of the waste, hydrogeology of the site, and landfill age (Chu et al., 1994; Kulikowska and Klimiuk, 2008; Moody and Townsend, 2017). Landfill leachate composition is dynamic and fluctuates over time due to a combination of physical and societal factors. Recently, growing awareness of contaminants of emerging concern [CECs, xenobiotic compounds such as personal care products, pharmaceuticals, and PFAS (per- and polyfluoroalkyl substances)] within the environment, and their harmful effects, have prompted research of their existence in landfill leachate (Masoner et al., 2016). Further research regarding the fate, degradation, and transport of CECs in landfill leachate is needed (Masoner et al., 2014).

Landfill pollutants pose an immediate threat to human health and the environment if leached offsite via groundwater or surface water flow. Human health risks from contaminated water sources are dictated by leachate composition and the extent of the exposure, and can include elevated cancer risk, acute toxicity, and genotoxicity (Mukherjee et al., 2015), though health risks from exposure to newer classes of pollutants like CECs have yet to be classified comprehensively (Ramakrishnan et al., 2015). Incidental ingestion, dermal contact, and inhalation of

* Corresponding author. Center for Agroforestry, University of Missouri – Columbia, 203 Anheuser-Busch Natural Resources Bldg., Columbia, MO, USA.
E-mail address: linchu@missouri.edu (C.-H. Lin).

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volatilized leachate contaminants from water contaminated with leachate (i.e., drinking water or recreational water sources), as well as consumption of fish and other aquatic organisms living in contaminated water are the main pathways of human exposure to landfill leachate contaminants (Schiopu and Gavrilescu, 2010). Older "historic" landfills which were not properly lined and/or were constructed in low-lying floodplains pose a particular pollution risk to surrounding communities (Brand et al., 2018).

Current Monitoring Guidelines under Code of Federal Regulations (CFR) Title 40, Part 258: Criteria for Municipal Solid Waste Landfills (MSWLFs) require MSWLFs to perform Detection Monitoring at all groundwater monitoring wells for the 62 compounds listed in Appendix I of Part 258 (Detection Monitoring Program, 1991). The chief administrative official responsible for implementing the state permitting program may modify the list of pollutants a site must test for, including deletion of Appendix I compounds or development of an alternative list. If a statistically significant increase over the background concentration for the site is detected for one or more of the compounds, the site manager must move into the Assessment Monitoring phase. In this phase, groundwater is sampled and analyzed for all 218 compounds listed in Appendix II of Part 258 (Assessment Monitoring Program, 1991). In addition, the Effluent Limitations stipulated in CFR Title 40, Part 445 require any wastewater discharged from non-hazardous waste landfills to meet maximum daily concentration requirements for nine physical and chemical parameters [Effluent limitations are selected based on ability to meet them with application of the best practicable control technology currently available (BPT), 2000].

Mitigation strategies for landfill water pollution depend on location of the polluted water (surface runoff, water in the vadose zone, or groundwater) and on the physical and chemical properties of the pollutants therein. In general, landfill pollution abatement has consisted of waste containment with barriers and liners and offsite treatment of leachate, with varying degrees of success (Allen, 2001). Increased interest in sustainability along with recent technological and scientific advancements in pollution remediation have led to changes in the design and remediation of landfills (Townsend et al., 2015). Many site managers have elected to implement onsite landfill remediation, which can take many forms, such as permeable reactive barriers, electrokinetic remediation, microbial remediation, or *in situ* injection treatments (Ye et al., 2019), in addition to the longer-scale phytoremediation (Nagendran et al., 2006; Tao et al., 2018). Onsite remediation efforts have typically adopted a target approach in which systems are designed to detect, quantify, and remediate pollutants of known existence at a site. Target approaches like these have often relied on: 1) speculation of most important pollutants to target based on word of mouth or anecdotal evidence, 2) limited groundwater and leachate composition information generated through landfill monitoring procedures, and 3) regulatory lists of monitored compounds developed by traditional targeted analytical approaches. Such methods have failed to consider all the potentially harmful contaminants at a site, especially the emerging contaminants that result from the modern lifestyle. Further, these methods do not quantitatively account for the potential risks the contaminants pose to human health and the environment.

A standardized method for pollutant prioritization, based on toxicity, does not exist but could help mitigation efforts target the most potentially harmful pollutants. Current methods of pollutant prioritization include health risk assessments (Hoang et al., 2016), as well as prioritization based on regulatory standards (Von der Ohe et al., 2011), degradation half-life (Gramatica and Papa, 2007), and signal intensities and frequency in high resolution mass spectrometry (HRMS) spectra (Park et al., 2018). In addition, toxicity data are housed in multiple databases and comprise an array of endpoints (Guillén et al., 2012). This mosaic of prioritization methodologies and toxicity information has led to fragmented, site-specific pollutant mitigation efforts, which discourages cross-study comparison and cohesivity. Here, we present the utility of the toxicity prioritization scheme outlined in Danforth et al. (2020), and modifications thereof, in prioritizing landfill leachate contaminants based on available toxicity data. The original prioritization scheme presented in Danforth et al. (2020) prioritizes contaminants based on toxicity data from three databases: ECOTOX, ToxCast, and Conditional Toxicity Value (CTV) Predictor.

The objectives of the current study were to: 1) prioritize landfill leachate contaminants that have been reported in the literature using a prioritization scheme based on multiple toxicity endpoints; 2) describe possible modifications to the scheme, including the use of additional datasets and/or different weighting schemes, and; 3) provide recommendations on broader applications of the general scheme. The approach outlined here establishes the means for systematic prioritization of contaminants in landfill leachate or contaminated groundwater which can aid in subsequent monitoring, remediation and/or treatment, and research.

2. Materials and methods

2.1. A literature search for chemicals in landfill leachate

Literature regarding MSWLF leachate composition was reviewed, and a list of over 500 contaminants was compiled (Table S1). All contaminants that were detected at least once in landfill leachate, and with a reported concentration, were included. Basic descriptive information for the landfills in the identified studies is included in Table S2. This list is not intended to be all-inclusive, but rather serves as a starting point for further research involving landfill leachate contaminants. Contaminants that did not have available Chemical Abstracts Service (CAS) numbers were not included in further analysis. Therefore, toxicity data were collected for the 484 compounds with available CAS numbers (Table S1).

2.2. Collection and analysis of toxicity data for landfill leachate chemicals

The compound toxicity ranking schemes developed in the current study are based on the methods of Danforth et al. (2020), whereby compounds are prioritized according to toxicity values from three databases: ECOTOX, ToxCast, and the Conditional Toxicity Value (CTV) Predictor. These three databases provide a robust approach in covering the spectrum of toxicity data, including *in vivo* data, *in vitro* assay data, and predicted *in silico* human toxicity values, respectively. The predicted human toxicity values component is especially powerful, as it allows for the characterization of compounds that may not yet have regulatory standards.

2.2.1. ECOTOX database

ECOTOX is a U.S. EPA database that contains *in vivo* toxicity data (i.e., compound effects on a whole, live organism) for aquatic and terrestrial organisms, and is available at https://cfpub.epa.gov/ecotox/(U.S. EPA 2020a). Toxicity data for over 12,000 compounds and over 13,000 species of aquatic organisms and terrestrial plants and wildlife are reported in ECOTOX. As in Danforth et al. (2020), data for the half-maximal effective concentration (EC50, mg L^{-1}; the concentration of the toxicant that induces a response halfway between the baseline and maximum) were collected from ECOTOX, as this was the most data-rich endpoint. In the present study, the minimum EC50 value across all species in the database was collected for each compound. This approach, though conservative, accounts for sensitive species for which data are not reported, and for sensitive endpoints not represented in this scheme.

2.2.2. ToxCast screening library

The ToxCast library is another U.S. EPA database (Richard et al., 2016) and is housed under the CompTox Dashboard at https://comptox.epa.gov/dashboard/chemical_lists/toxcast (Williams et al., 2017). *In vitro* assay toxicity data from bioassays of varied types (e.g., cell type,

design, bioactivity type) are reported in ToxCast. Particularly, bioactivity (i.e., active or inactive) and half maximal activity concentration values (AC50, μM; the concentration which gives 50% activation in a bioassay) are reported for 4746 compounds (U.S. EPA 2018; U.S. EPA 2020b). In the current study, the minimum AC50 value as well as the percentage of active assays for each compound were collected from CompTox. Like the approach of selecting the minimum EC50 values from ECOTOX, we recorded minimum AC50 values as a conservative way to account for sensitive species whose AC50 data are not reported in ToxCast.

2.2.3. CTV predictor

The CTV Predictor is a web-based tool that generates human health risk data through a quantitative structure activity relationship (QSAR) model-based *in silico* approach, and is available at https://toxvalue.org/6-CTV/Cover.php (Wignall et al., 2018). Briefly, the QSAR models employed by the CTV Predictor were developed using human health toxicity values publicly available by the US EPA or the California EPA. First, researchers calculated mathematical chemical descriptors based on compound structure for each chemical using the Chemistry Development Kit (CDK) in R (Wignall et al., 2018). Random forests machine learning models were implemented to predict toxicity values of compounds based on their CDK descriptors, and the resulting models were validated and cross-validated; it is these models that the CTV Predictor is based on. The toxicity predictions generated by the CTV Predictor were shown to have smaller deviations from regulatory values than predictions based on high-throughput screening (HTS) assays and *in vitro* to *in vivo* extrapolation (IVIVE) (Wignall et al., 2018). In the current study, data for the following toxicity parameters were collected from the CTV predictor: 1) reference dose (RfD, mg kg^{-1} day^{-1}; an estimate of the daily exposure to a compound that is likely to be without negative effects), 2) reference dose benchmark dose (BMD, mg kg^{-1} day^{-1}; dose of a compound which elicits a predetermined change in the response rate of a negative effect), 3) reference dose benchmark dose lower limit (BMDL, mg kg^{-1} day^{-1}; the lower limit of a one-sided 95% confidence interval on the BMD), 4) reference dose no observed adverse effect level (NO(A)EL, mg kg^{-1} day^{-1}; the highest dose of a compound for which there are no observed negative effects), 5) oral slope factor (OSF, risk per mg kg^{-1} day^{-1}; an estimate of the increased cancer risk from oral exposure to a dose of 1 mg kg^{-1} day^{-1} for a lifetime), and 6) cancer potency value (CPV, risk per mg kg^{-1} day^{-1}; a California EPA-specific OSF) (Danforth et al., 2020; U.S. EPA 2020c; Wignall et al., 2018). These parameters were selected because they involve oral exposure, and the primary means of potential exposure to the contaminants is through ingestion of contaminated water. Existing toxicity values were collected from CTV Predictor when possible, otherwise predicted toxicity values were collected.

2.2.4. Data integration and prioritization using ToxPi

All toxicity data were uploaded into the Toxicological Prioritization Index (ToxPi), a Java-based program that integrates multiple sources of toxicity data into one dimensionless index score (Marvel et al., 2018). ToxPi is a visualization software consisting of modified iconographic displays that were developed using the R packages *graphics*, *gdata*, and *lattice* (Reif et al., 2010). Index scores are calculated in ToxPi through the weighted or unweighted combination of data from multiple sources, and are represented as unit circles made up of slices of data from different domains (Fig. 1). The width of each slice corresponds to the user-defined weight of that domain, while the slice length represents how potent the toxic effect is of the domain, for the particular chemical (Reif et al., 2010). ToxPi was used to calculate a toxicity score for each compound by integrating toxicity data from the three databases described above (i.e., ECOTOX, ToxCast, and CTV Predictor). Higher toxicity scores generated by ToxPi correspond to greater potential toxicity relative to other compounds in the dataset. Data for some of the parameters were transformed to ensure that higher values represented

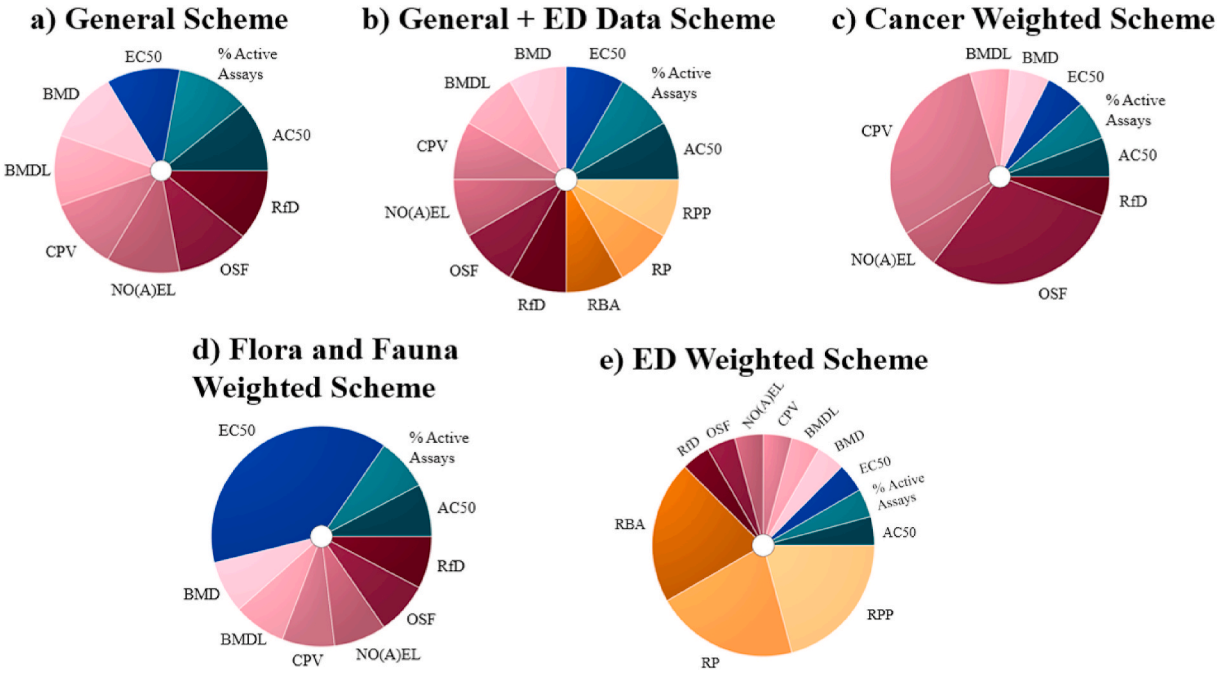

Fig. 1. ToxPi prioritization schemes. For definitions of each scheme, refer to Section 2.3. Each contaminant was analyzed using these combinations of data from multiple domains, which are represented by slices of a similar color: *in vivo* ecotoxicology endpoints (blue), *in vitro* high throughput screening assays (aqua), known or conditional human health toxicity values (red), and endocrine disruption assay data (gold). Individual slices represent data for the corresponding parameter. The distance of each slice from the center indicates the normalized value of the component. The angle of the slice represents how that component is weighted relative to the other components in the overall ToxPi calculation. BMD: reference dose benchmark dose; BMDL: reference dose benchmark dose lower limit; CPV: cancer potency value; NO(A)EL: reference dose no observed adverse effect level; OSF: oral slope factor; RfD: reference dose; RBA: relative binding activity; RP: relative potency; RPP: relative proliferation potency; AC50: half maximal activity concentration; % Active Assays: percentage of active assays; EC50: half-maximal effective concentration.

greater toxicity. The negative log was taken of EC50, AC50, RfD, BMD, BMDL, and NO(A)EL values, while remaining parameters (i.e., percentage of active assays, CPV, OSF) were linearly scaled. Toxicity profiles [i.e., visual representations of how each component (slice) influences the overall toxicity score] were generated in ToxPi for all compounds. Equal weights were given to all toxicity parameters (slices) in the analysis (Fig. 1a). Hereafter, this scheme is referred to as the "general prioritization scheme." To summarize, the general prioritization scheme prioritizes chemicals based on all the following toxicity parameters: EC50, AC50, percentage of active assays, RfD, BMD, BMDL, NO(A)EL, OSF, and CPV.

This scheme is closely based on the scheme reported in Danforth et al. (2020), except that: 1) in the current study, the negative log is taken of toxicity parameters (EC50, AC50, RfD, BMD, BMDL, NO(A)EL) and others were linearly scaled (percentage of active assays, CPV, OSF) to aid in comparisons and interpretability of the effects of the parameters on the final ToxPi profiles, and 2) the minimum EC50 value across all species and the minimum AC50 values were used in the current study, rather than the Quantile 1 values used in Danforth et al. (2020), which provides a more conservative estimate of potential toxicity. The schemes in subsequent sections demonstrate other modifications which can be made to this general scheme.

An important consideration is that the databases utilized here consider contaminants in water. Therefore, the results presented here do not take into account all of the possible synergistic or antagonistic effects that could occur within the complex landfill leachate matrix. Such a comparison was out of the scope of the present study, though could be addressed in future research.

Only contaminants for which there were available toxicity data from at least two of the three toxicity databases (i.e., ECOTOX, ToxCast, CTV Predictor) were included in ToxPi analysis. Further, compound 2,3,7,8-TCDD was found to have significantly larger toxicity parameter values than all other contaminants (Figure S1). As ToxPi assigns relative scores for each parameter based on the values of the other contaminants in the dataset, the extremely high values of 2,3,7,8-TCDD led to artificially low toxicity scores for a majority of the contaminants. Upon further review of the literature, it was found that this contaminant is associated with landfills which largely accept incinerator fly ash, or industrial wastes (Murphy, 1989; Smith et al., 1983; Baderna et al., 2011; Choi and Lee, 2006), which is not representative of MSWLFs. For both of these reasons, 2,3,7,8-TCDD was removed from the analysis. Thus, 322 contaminants (those for which there were available toxicity data from at least two of the three databases and excluding 2,3,7,8-TCDD) were prioritized in ToxPi (Table S1).

2.3. Prioritization scheme customization

The general prioritization scheme outlined above can be customized according to applied and research objectives. Two options for customization include the incorporation of toxicity data from additional datasets and the application of weighting schemes in ToxPi analysis. The following sections detail how these options were implemented in the current study.

2.3.1. Incorporating additional datasets

To illustrate the option of prioritization scheme customization, endocrine disruption (ED) data from the Endocrine Disruptor Knowledge Base (EDKB) were collected for the 322 contaminants in this study. The EDKB is an online database developed by the U.S. Food and Drug Administration (FDA) National Center for Toxicological Research (NCTR), and is available for download at https://www.fda.gov/science-research/endocrine-disruptor-knowledge-base/accessing-edkb-database (U.S. FDA, 2019). Since its inception in 1997, the EDKB has been accessed by users from government, academic, and private sectors to fulfill a variety of compound evaluation- and prioritization-related objectives (Ding et al., 2010). Rat, mouse, and human assay data for over 1800 compounds are reported in EKDB. Specifically, data for three parameters are presented in the database: relative binding activity (RBA), relative potency (RP), and relative proliferation potency (RPP). The largest value for each parameter was collected for all 322 contaminants in the current study. Contaminants were then prioritized in ToxPi according to the general scheme with the additional ED parameters. Hereafter, this scheme will be referred to as the "general + ED data" scheme (Fig. 1B). All parameters were given equal weight, as the objective of this scheme was to demonstrate the utility of incorporating other data into the general scheme. Adding toxicity data from more domains, while keeping all weights constant, is the most basic form of scheme modification. To summarize, the general + ED data scheme prioritizes chemicals based on the following parameters: EC50, AC50, percentage of active assays, RfD, BMD, BMDL, NO(A)EL, OSF, CPV, RBA, RP, and RPP.

2.3.2. Applying weighting schemes

Different weighting schemes may be implemented to further customize the prioritization scheme in order to meet research and applied objectives. In the current study, we designed three example weighting schemes to demonstrate this option: 1) cancer risk [parameters OSF and CPV were given 5x weights (Fig. 1C)], 2) risk to flora and fauna [the EC50 parameter was given 5x weights (Fig. 1D)], and 3) endocrine disruption risk [endocrine parameters (RP, RPP, RBA) were given 5x weights (Fig. 1E)]. Hereafter, these schemes will be referred to as "cancer weighted scheme," "flora and fauna weighted scheme," and "endocrine disruption weighted scheme."

2.4. Comparison to regulatory lists

There are certain regulatory standards that landfills in the United States must meet regarding monitoring of chemicals released. Title 40, Part 258 of the CFR establishes minimum criteria for all MSWLF units according to the Resource Conservation and Recovery Act (RCRA) (Purpose, Scope, and Applicability, 1991). These criteria serve to ensure protection of human health and the environment. Appendix I to Part 258, Constituents for Detection Monitoring, contains a list of 62 chemicals which must be monitored at all groundwater monitoring wells at all MSWLF units. If a statistically significant increase over the background level is detected for any of Appendix I chemicals, an assessment monitoring program must be established, in which chemicals listed in Appendix II to Part 258, List of Hazardous Inorganic and Organic Constituents, must be monitored (Assessment Monitoring Program, 1991). In the present study, both appendices were examined, and data were collected on whether each of the 322 landfill leachate contaminants was included.

3. Results and discussion

3.1. Availability of toxicity data

Toxicity data availability from each of the four databases (i.e., ECOTOX, ToxCast, CTV Predictor, and EDKB) for all compounds is summarized in Fig. 2. Toxicity data were available from all three databases (i.e., CTV Predictor, ToxCast, and ECOTOX) for a majority (>81%) of the 322 contaminants. Therefore, identifying contaminants for which toxicity data are available in at least two of the three major databases was an effective way to select data-rich contaminants. On the other hand, ED data from the EDKB were not as available. Each of the individual ED parameters (RP, RBA, RPP) had available data for less than 26% of the compounds. This low availability of ED data is likely due to the relative infancy of endocrine disruption characterization, testing, and reporting (Karthikeyan et al., 2019). In addition, not all the contaminants are EDs, and therefore do not have existing data.

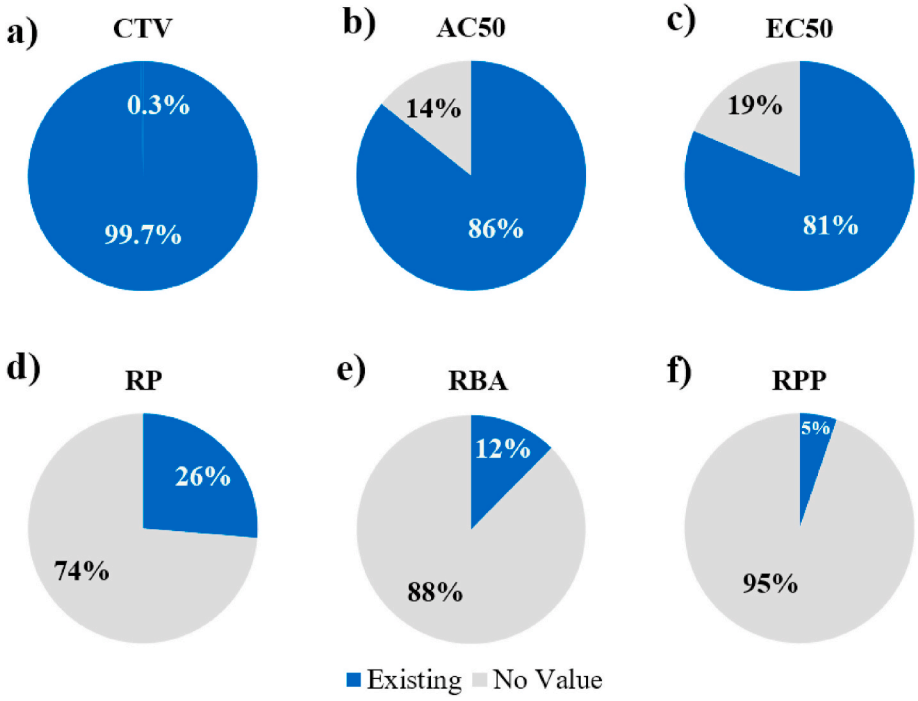

Fig. 2. Data availability for the 322 contaminants prioritized using ToxPi. (a) Availability of all parameters reported in the Conditional Toxicity Value (CTV) predictor. (b) Availability of the half-maximal activity concentrations (AC50) reported in ToxCast. (c) Availability of the half-maximal effective concentrations (EC50) reported in ECOTOX. (d), (e), and (f) were collected from the EDKB and are defined as follows: relative potency (RP), relative binding activity (RBA), and relative proliferation potency (RPP), respectively.

3.2. Data integration and prioritization using ToxPi

3.2.1. General scheme

Toxicity data from ECOTOX, ToxCast, and the CTV Predictor were integrated and prioritized using the ToxPi platform. It is important to note that ToxPi assigns relative toxicity rankings to compounds in a dataset according to the toxicity data that is input. This study focused on 322 contaminants identified in the literature; every possible landfill leachate contaminant was not investigated. The results of ToxPi analysis using the general prioritization scheme are displayed in Fig. 3. Toxicity profiles for the top 3 most toxic compounds (endrin, aldrin, and dieldrin) were very similar, exhibiting large scores for parameters BMD, BMDL, NO(A)EL, and RfD. For each of these three compounds, BMD scores were greater than 0.9373, BMDL scores were greater than 0.9493, NO(A)EL scores were greater than 0.8719, and RfD scores were greater than 0.8039 (with a value of 1 being the largest possible value). Clotrimazole, ranked 4th, demonstrated a balanced toxicity profile with relatively moderate scores for most parameters (each parameter besides BMD and BMDL had a score between 0.3827 and 0.6910), while oxytetracycline, ranked 5th, exhibited a toxicity profile dominated by the human toxicity values from CTV Predictor (BMD score = 0.8092, BMDL score = 0.8314, NO(A)EL score = 0.6180). Toxicity profiles for the top 40 contaminants according to the general scheme are listed in Table S3.

According to the general prioritization scheme, the 40 most toxic landfill leachate contaminants are listed in Table 1. The physicochemical properties of these toxic landfill leachate contaminants are listed in Table S4. The top 40 compounds are comprised of: 12 components of pesticides, fungicides, or their metabolites (endrin, dieldrin, aldrin, chlordane, heptachlor, p,p'-DDE, 4,4′-DDD, heptachlor epoxide, endosulfan I, endosulfan sulfate, lindane, tebuconazole); 8 pharmaceuticals

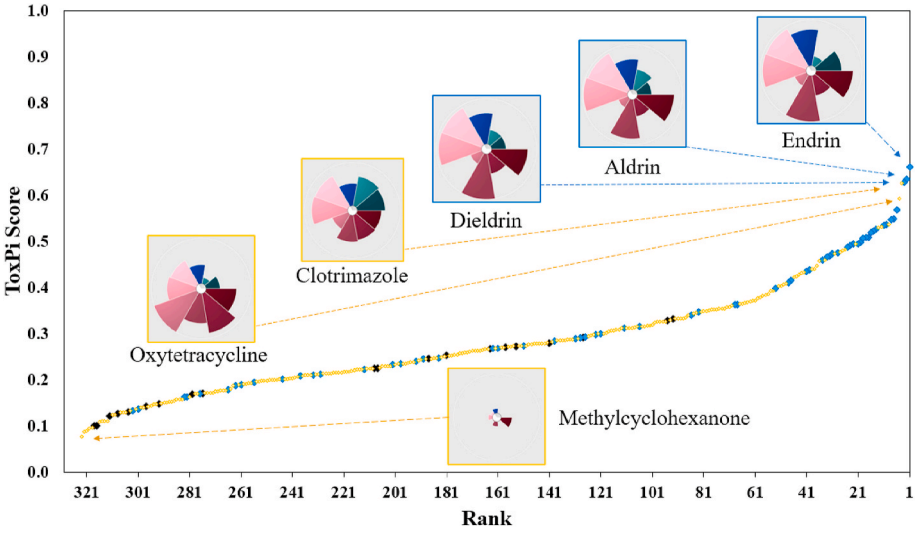

Fig. 3. Distribution dot plot of ToxPi Scores for all 322 contaminants using the general prioritization scheme. Dots represent individual contaminants. Black and blue dots represent contaminants listed in Appendices I and II of 40 C.F.R 258, respectively, while yellow dots represent contaminants that are not included in either Appendix. ToxPi toxicity profiles for the five most toxic contaminants and the least toxic contaminant are displayed in the insets.

Table 1
Uses, sources, and health impacts of compounds in landfill leachate ranked by their potential toxicity according to ToxPi analysis.

Rank	Contaminant	CASRN[a]	Uses/Sources[b]	Health Impacts[e]
1	Endrin	72-20-8	pesticide[c]	neurological, endocrine
2	Dieldrin	60-57-1	pesticide[c]	developmental, endocrine, hepatic, immunological, neurological
3	Aldrin	309-00-2	pesticide[c]	developmental, endocrine, hepatic, immunological, neurological
4	Clotrimazole	23,593-75-1	antifungal medication	potential endocrine disruptor
5	Oxytetracycline	79-57-2	antibiotic to treat bacterial infections	potential endocrine disruptor
6	Chlordane	12,789-03-6	pesticide[c]	endocrine disruption
7	Indeno (123cd)pyrene	193-39-5	industrial by-product; cigarette ingredient	animal carcinogen, possible human carcinogen
8	Heptachlor	76-44-8	insecticide[c]	developmental, reproductive, endocrine
9	Tetrabromobisphenol-A	79-94-7	flame retardant; epoxy resins of printed circuit boards	potential endocrine disruptor, neurotoxicity
10	p,p'-DDE	72-55-9	component of DDT; pesticide	developmental, endocrine, hepatic, neurological, reproductive
11	p,p'-DDT	50-29-3	component of DDT; pesticide; cigarette ingredient	developmental, endocrine, hepatic, neurological, reproductive
12	1,2,3,4,7,8-hexaCDD	39,227-28-6	industrial by-product[c]	probable carcinogen
13	Tetracycline	60-54-8	antibiotic to treat bacterial infections	endocrine disruption
14	4,4′-DDD	72-54-8	component of DDT; pesticide	developmental, endocrine, hepatic, neurological, reproductive
15	Benzo(a)pyrene	50-32-8	industrial by-product; cigarette ingredient	probable human carcinogen
16	Benzo (ghi)perylene	191-24-2	industrial by-product; cigarette ingredient	not classified
17	Benzo(b)fluoranthene	205-99-2	industrial by-product; cigarette ingredient	probable human carcinogen
18	Dibenz (ah) anthracene	53-70-3	industrial by-product; cigarette ingredient	probable human carcinogen
19	Heptachlor epoxide	1024-57-3	metabolite of heptachlor[c]	developmental, reproductive
20	PCB-187	52,663-68-0	coolants and lubricants in transformers and capacitors[c]	carcinogenic to humans, endocrine
21	Benzo(k)fluoranthene	207-08-9	industrial by-product; cigarette ingredient	possible human carcinogen
22	Doxycycline	564-25-0	antibacterial drug; antimalarial	possible endocrine disruptor
23	Benz(a)anthracene	56-55-3	industrial by-product; cigarette ingredient	probable human carcinogen
24	Endosulfan I	959-98-8	insecticide[d]	possible human carcinogen, neurological
25	Endosulfan sulfate	1031-07-8	metabolite of endosulfan	neurological, possible carcinogen
26	2,3,7,8-TCDF	51,207-31-9	industrial by-product; insecticide	possible neurological
27	BDE-47	5436-43-1	flame retardant	neurotoxicity
28	Chlortetracycline	57-62-5	veterinary antibiotic[d]	possible endocrine disruptor
29	PCB-153	35,065-27-1	coolants and lubricants in transformers and capacitors[c]	carcinogenic to humans, endocrine
30	BDE-99	60,348-60-9	flame retardant	neurotoxicity
31	PCB-128	38,380-07-3	coolants and lubricants in transformers and capacitors[c]	endocrine
32	Lindane	58-89-9	insecticide	possible carcinogen, endocrine
33	PCB-105	32,598-14-4	coolants and lubricants in transformers and capacitors[c]	carcinogenic to humans, endocrine
34	Enrofloxacin	93,106-60-6	antibiotic to treat bacterial infections[d]	not classified
35	Pentachlorophenol	87-86-5	pesticide; wood preservative	developmental, endocrine, reproductive
36	Codeine	76-57-3	pain-relief; antidiarrheal; cough suppressant	not classified
37	Tebuconazole	80,443-41-0	fungicide[d]	possible human carcinogen
38	BDE-100	189,084-64-8	flame retardant	endocrine
39	Ofloxacin	82,419-36-1	antibiotic to treat bacterial infections[d]	toxic to mammalian cells in culture
40	Pentachlorobenzene	608-93-5	fungicide; flame retardant; industrial by-product[d]	hepatic, urinary

[a] Chemical Abstracts Service Registry Number.
[b] T3DB.
[c] ATSDR.
[d] Pubchem.
[e] For details, see Table S5.

(clotrimazole, oxytetracycline, tetracycline, doxycycline, chlortetracycline, enrofloxacin, codeine, ofloxacin); 8 industrial byproducts/cigarette ingredients (indeno (123cd)pyrene, 1,2,3,4,7,8-hexaCDD, benzo (a)pyrene, benzo (ghi)perylene, benzo(b)fluoranthene, dibenz (ah) anthracene, benzo(k)fluoranthene, benz(a)anthracene); 4 coolants and lubricants (PCB-187, PCB-153, PCB-128, PCB-105); 3 flame retardants (BDE-47, BDE-99, BDE-100); and 5 multi-use compounds (tetrabromobisphenol-A, p,p'-DDT, 2,3,7,8-TCDF, pentachlorophenol, pentachlorobenzene) (Table 1).

Health impacts are compound-specific, and many of the compounds can produce multiple negative effects (Table 1). Of the top 40 compounds, 21 were reported as potential or confirmed endocrine disruptors, 14 as potential or confirmed human carcinogens, and 12 as causing neurological impacts.

A wide range of concentrations in landfill leachate have been reported for these 40 contaminants (Table 2). Pesticides and their metabolites exhibited the largest reported concentrations of over 1×10^4 ng L^{-1} (i.e., endrin, dieldrin, endosulfan I, and pentachlorophenol). However, the lowest concentrations of less than 1×10^{-1} ng L^{-1} were reported for compounds with a range of sources and uses (i.e., p,p'-DDE [pesticide], endosulfan sulfate [metabolite of pesticide ingredient], BDE-47 [flame retardant], PCB-153 [coolant and lubricant in transformers], PCB-128 [coolant and lubricant in transformers], PCB-105 [coolant and lubricant in transformers], and pentachlorobenzene [fungicide, flame retardant, industrial by-product]). Within individual compounds, the range between minimum and maximum landfill leachate concentration varied from as low as 0.5 ng L^{-1} (clotrimazole and tebuconazole) to greater than 1.3×10^5 ng L^{-1} (dieldrin). Large variation in reported concentrations for landfill leachate contaminants is likely due to the inherent variability between landfills. Landfill age and design, as well as demographic, climatic, and geographic characteristics of the area, all impact the type and concentration of contaminants within leachate (Kjeldsen et al., 2002). Because of this natural variation, the 322 landfill leachate contaminants identified in the literature and analyzed here are not likely to be detected in every leachate or groundwater sample. Therefore, site-specific data including identified contaminants and their concentrations are crucial to accurate, relevant prioritization.

This general scheme is widely applicable for diverse environmental applications as it includes *in vivo* assay data, *in vitro* assay data, and *in silico* human toxicity data. Such an integration of toxicity data allows for the identification of contaminants that pose the greatest possible threats to surrounding human and wildlife populations. Landfill site managers and researchers can take advantage of this robust method of prioritization when determining contaminants to target with remediation efforts. It should be noted, however, that the occurrence of contaminants with extremely large toxicity parameters (such as 2,3,7,8-TCDD) can influence the relative toxicity values of the rest of the dataset. Such compounds may be removed from analysis so as not to skew the final results, yet should be recognized if prioritization is being done in the interest of selecting compounds to remediate.

3.2.2. General + ED data scheme

Table 3 lists the top 40 most toxic compounds according to the general + ED data scheme. Thirty-nine compounds were found in the top 40 of both the general and the +ED schemes; bisphenol A was the only compound unique to the top 40 of the general + ED data scheme. The average change in rank between the top 40 of the general scheme and that of the general + ED data scheme was ±3.2. A majority of the compounds in the top 40 (i.e., 95%) exhibited a change in toxicity rank of less than 7 places. p,p'-DDT and bisphenol A had rank changes of 10 and 58 places, respectively. As the only difference between the two schemes is the addition of ED data in the general + ED data scheme, it can be concluded that these changes in rank are due to p,p'-DDT and bisphenol A having endocrine disruption activity. This is not unexpected; both compounds have been reported as endocrine disruptors

Table 2
Concentration range of compounds in landfill leachate ranked by their potential toxicity according to ToxPi analysis.

Rank	Contaminant	CASRN[a]	Concentration Range[b] (ng L^{-1})	References
1	Endrin	72-20-8	7–50000	Assmuth (1996); Chilton and Chilton (1992); Palma-Fleming et al. (2000)
2	Dieldrin	60-57-1	5–130,600	Argun et al. (2017); Assmuth (1996); Murray and Beck (1990)
3	Aldrin	309-00-2	3–333	Assmuth (1996); Murray and Beck (1990); Palma-Fleming et al. (2000)
4	Clotrimazole	23,593-75-1	1–1.5	Peng et al. (2014); Shi et al. (2020)
5	Oxytetracycline	79-57-2	0.7–1070	Andrews et al. (2011); Wu et al. (2015); Wu et al. (2017)
6	Chlordane	12,789-03-6	15–40	Andrews et al. (2011); Ferrell and Smith (1995); Kadlec and Zmarthie (2010)
7	Indeno (123cd)pyrene	193-39-5	2–50	Öman and Junestedt (2008); Oturan et al. (2015); Smol et al. (2016)
8	Heptachlor	76-44-8	6–350	Kadlec and Zmarthie (2010); Palma-Fleming et al. (2000); Reinhart and Grosh (1998)
9	Tetrabromobisphenol-A	79-94-7	4.5–1227	Öman and Junestedt (2008); Osako et al. (2004); Zhou et al. (2013)
10	p,p'-DDE	72-55-9	0.01–13.2	Palma-Fleming et al. (2000); Wang and Kelly (2017); Xu et al. (2008)
11	p,p'-DDT	50-29-3	22–220	Assmuth (1996); Chilton and Chilton (1992); Xu et al. (2008)
12	1,2,3,4,7,8-hexaCDD	39,227-28-6	1–47	Dudzinska et al. (2004); Dudzinska et al. (2008); Wenzel et al. (1999)
13	Tetracycline	60-54-8	50–2470	Andrews et al. (2011); Fang et al. (2020); Topal and Arslan Topal, 2015
14	4,4′-DDD	72-54-8	40–130	Assmuth (1996); Denton et al. (2005); Kadlec and Zmarthie (2010)
15	Benzo(a)pyrene	50-32-8	1–200	

(continued on next page)

Table 2 (*continued*)

Rank	Contaminant	CASRN[a]	Concentration Range[b] (ng L^{-1})	References
				Andrews et al. (2011); Xu et al. (2008); Oturan et al. (2015)
16	Benzo (ghi)perylene	191-24-2	10–120	Oturan et al. (2015); Welander and Henrysson (1998); Xu et al. (2008)
17	Benzo(b)fluoranthene	205-99-2	11–2050	Smol et al. (2016); Welander and Henrysson (1998); Xu et al. (2008)
18	Dibenz (ah) anthracene	53-70-3	1–200	Koc-Jurczyk (2014); Öman and Junestedt (2008); Smol et al. (2016)
19	Heptachlor epoxide	1024-57-3	0.2-<50	Gardiner et al. (2002); Oturan et al. (2015); Palma-Fleming et al. (2000)
20	PCB-187	52,663-68-0	0.1407	Kõrgmaa et al. (2011)
21	Benzo(k)fluoranthene	207-08-9	<3-2000	Klimiuk and Kulikowska (2004); Smol et al. (2016); Welander and Henrysson (1998)
22	Doxycycline	564-25-0	6–541.9	Andersson et al. (2006); Andrews et al. (2011); Qi et al. (2018)
23	Benz(a)anthracene	56-55-3	1–960	Kadlec and Zmarthie (2010); Oturan et al. (2015); Xu et al. (2008)
24	Endosulfan I	959-98-8	18–760,400	Argun et al. (2017); Palma-Fleming et al. (2000); Wang and Kelly (2017)
25	Endosulfan sulfate	1031-07-8	0.044–190	Kõrgmaa et al. (2011); Palma-Fleming et al. (2000); Wang and Kelly (2017)
26	2,3,7,8-TCDF	51,207-31-9	2–111.15	Dudzinska et al. (2004); Dudzinska et al. (2008); Wenzel et al. (1999)
27	BDE-47	5436-43-1	0.041–6750	Daso et al. (2017); Wang and Kelly (2017); Zhou et al. (2013)
28	Chlortetracycline	57-62-5	12.6–912	Andrews et al. (2011); Fang et al. (2020); Wu et al. (2015)
29	PCB-153	35,065-27-1	0.012–24	Kõrgmaa et al. (2011); Oturan et al. (2015); Wang and Kelly (2017)
30	BDE-99	60,348-60-9	3.41–14620	Daso et al. (2017); Kõrgmaa et al. (2011); Zhou et al. (2013)
31	PCB-128	38,380-07-3	0.1–2	Kängsepp (2008); Kõrgmaa et al. (2011)
32	Lindane	58-89-9	5–950	Andrews et al. (2011); Chilton and Chilton (1992); Oturan et al. (2015)
33	PCB-105	32,598-14-4	0.003–0.5105	Kõrgmaa et al. (2011); Wang and Kelly (2017)
34	Enrofloxacin	93,106-60-6	17.95–4026.67	Andrews et al. (2011); Wu et al. (2015); You et al. (2018)
35	Pentachlorophenol	87-86-5	200–470,000	Assmuth (1996); Chilton and Chilton (1992); Masoner et al. (2014)
36	Codeine	76-57-3	44.9–728	Andrews et al. (2011); Lu et al. (2016); Masoner et al. (2014)
37	Tebuconazole	80,443-41-0	0.3–0.8	Peng et al. (2014)
38	BDE-100	189,084-64-8	<0.15–1590	Daso et al. (2017); Kõrgmaa et al. (2011); Zhou et al. (2013)
39	Ofloxacin	82,419-36-1	9.1–79.5	Peng et al. (2014)
40	Pentachlorobenzene	608-93-5	0.042–56	Matejczyk et al. (2011); Wang and Kelly (2017)

[a] Chemical Abstracts Service Registry Number.
[b] Concentration range in landfill leachate reported in the literature.

(Rubin, 2011; Munier et al., 2016).

The incorporation of other toxicity datasets in addition to those implemented in the general prioritization scheme provides another layer of specificity in meeting specific research and community objectives. For example, specific toxicity endpoints may be included (e.g., reproductive toxicity, developmental toxicity) if certain health problems are of particular concern in a community. However, as evidenced by the minimal changes in rank between the general scheme and the general + ED data scheme, weighting may need to be applied in order to identify a greater number of compounds that exhibit the toxic effects of interest.

3.2.3. *Different weighting schemes*

Cancer Weighted Scheme

Table 4 lists the top 40 most toxic landfill leachate contaminants according to the cancer weighted sche. 1, 2,3,7,8-pentaCDD, ampicillin, fluoranthene, and amoxicillin were in the top 40 of the cancer weighted scheme, but not the general scheme. The average change in toxicity rank between the general scheme and the cancer weighted scheme was 12.7. Twenty contaminants in the top 40 of the cancer weighted scheme exhibited a change in rank of over 10 places, while 9 contaminants had a

Table 3
Top 40 most toxic chemicals found in landfill leachate according to the general + endocrine disruption data prioritization scheme. Bolded chemicals exhibited a change in rank between the general and the general + ED scheme of 10 or more.

General + ED Data Rank[a]	General Rank[b]	Contaminant	CASRN
1	**11**	**p,p'-DDT**	**50–29–3**
2	1	Endrin	72-20-8
3	10	p,p'-DDE	72-55-9
4	2	Dieldrin	60-57-1
5	3	Aldrin	309-00-2
6	4	Clotrimazole	23,593-75-1
7	**65**	**Bisphenol A**	**80–05–7**
8	5	Oxytetracycline	79-57-2
9	6	Chlordane	12,789-03-6
10	8	Heptachlor	76-44-8
11	7	indeno (123cd)pyrene	193-39-5
12	9	Tetrabromobisphenol-A	79-94-7
13	12	1,2,3,4,7,8-hexaCDD	39,227-28-6
14	14	4,4′-DDD	72-54-8
15	13	Tetracycline	60-54-8
16	15	Benzo (a) pyrene	50-32-8
17	16	Benzo (ghi)perylene	191-24-2
18	17	Benzo(b)fluoranthene	205-99-2
19	18	dibenz (ah)anthracene	53-70-3
20	19	Heptachlor epoxide	1024-57-3
21	20	PCB-187	52,663-68-0
22	21	benzo(k)fluoranthene	207-08-9
23	22	Doxycycline	564-25-0
24	23	Benz(a)anthracene	56-55-3
25	24	Endosulfan I	959-98-8
26	25	Endosulfan sulfate	1031-07-8
27	26	2,3,7,8-TCDF	51,207-31-9
28	29	PCB-153	35,065-27-1
29	27	BDE-47	5436-43-1
30	28	Chlorotetracycline	57-62-5
31	30	BDE-99	60,348-60-9
32	31	PCB-128	38,380-07-3
33	32	Lindane	58-89-9
34	33	PCB-105	32,598-14-4
35	34	Enrofloxacin	93,106-60-6
36	35	Pentachlorophenol	87-86-5
37	36	Codeine	76-57-3
38	37	Tebuconazole	80,443-41-0
39	38	BDE-100	189,084-64-8
40	39	Ofloxacin	82,419-36-1

[a] Toxicity rankings according to the general + endocrine disruption data prioritization scheme.
[b] Toxicity rankings according to the general prioritization scheme.

rank change of over 20 places. The largest rank changes were exhibited by codeine (32 places) and fluoranthene (51 places). Those contaminants that exhibit large changes in rank have an enhanced risk of cancer compared to their overall general toxicity. Site managers could use a combination approach when determining which chemicals to target with remediation efforts, by choosing to target compounds with large rank changes like codeine and fluoranthene (greater risk of cancer), as well as those that rank highly in both the general and the cancer weighted schemes, such as oxytetracycline, clotrimazole, and indeno (123cd)pyrene (they represent both large cancer risk and large toxicity risks overall).

ED Weighted Scheme

Table 5 lists the top 40 most toxic landfill leachate contaminants according to the ED weighted scheme. Three contaminants were in the top 40 of the ED weighted scheme, but not that of the general scheme: bisphenol A, octyl phenol, and butylparaben. For the top 40, the average change in toxicity rank between the general scheme and the ED weighted scheme was 10.4, and 93% of contaminants exhibited a change in rank of 10 or less places. The three largest rank changes were

Table 4
Top 40 most toxic chemicals found in landfill leachate according to the cancer weighted prioritization scheme. Bolded chemicals exhibited a change in rank between the general scheme and the cancer weighted scheme of 10 or more.

Weighted Rank[a]	General Rank[b]	Contaminant	CASRN
1	5	Oxytetracycline	79-57-2
2	22	Doxycycline	564-25-0
3	13	Tetracycline	60-54-8
4	36	Codeine	76-57-3
5	4	Clotrimazole	23,593-75-1
6	7	Indeno (123cd)pyrene	193-39-5
7	16	Benzo (ghi)perylene	191-24-2
8	28	Chlorotetracycline	57-62-5
9	18	Dibenz (ah)anthracene	53-70-3
10	1	Endrin	72-20-8
11	2	Dieldrin	60-57-1
12	3	Aldrin	309-00-2
13	17	Benzo(b)fluoranthene	205-99-2
14	15	Benzo (a) pyrene	50-32-8
15	23	Benz(a)anthracene	56-55-3
16	21	Benzo(k)fluoranthene	207-08-9
17	39	Ofloxacin	82,419-36-1
18	34	Enrofloxacin	93,106-60-6
19	12	1,2,3,4,7,8-hexaCDD	39,227-28-6
20	44	1,2,3,7,8-pentaCDD	40,321-76-4
21	31	PCB-128	38,380-07-3
22	29	PCB-153	35,065-27-1
23	26	2,3,7,8-TCDF	51,207-31-9
24	20	PCB-187	52,663-68-0
25	33	PCB-105	32,598-14-4
26	10	p,p'-DDE	72-55-9
27	8	Heptachlor	76-44-8
28	27	BDE-47	5436-43-1
29	11	p,p'-DDT	50-29-3
30	9	Tetrabromobisphenol-A	79-94-7
31	14	4,4′-DDD	72-54-8
32	19	Heptachlor epoxide	1024-57-3
33	46	Ampicillin	69-53-4
34	6	Chlordane	12,789-03-6
35	86	Fluoranthene	206-44-0
36	30	BDE-99	60,348-60-9
37	24	Endosulfan I	959-98-8
38	25	Endosulfan sulfate	1031-07-8
39	38	BDE-100	189,084-64-8
40	66	Amoxicillin	26,787-78-0

[a] Toxicity rankings according to the cancer weighted prioritization scheme.
[b] Toxicity rankings according to the general prioritization scheme.

64 (bisphenol A), 91 (octyl phenol), and 113 places (butylparaben). These three contaminants have much greater potential to negatively impact organisms' endocrine systems compared to their overall toxicity (i.e., their ranks are closer to "1" in the ED weighted scheme than the general scheme). Further, this weighted scheme has proven to be more effective in identifying endocrine-disrupting contaminants in leachate than the general + ED data scheme, based on the greater magnitude of change in rank between the ED weighted scheme and the general scheme than that of the general + ED data scheme.

Flora and Fauna Weighted Scheme

Table 6 lists the top 40 most toxic landfill leachate contaminants according to the flora and fauna weighted scheme. Nine contaminants were in the top 40 of the flora and fauna weighted scheme, but not of the general scheme (naphthalene, atrazine, propiconazole, triclocarban, hexachlorobenzene, triclosan, MCPA, hexazinone, and dichlorobenzene). The average change in toxicity rank between the general scheme and the flora and fauna weighted scheme for these 40 compounds was 14 places. 43% of compounds exhibited a change in rank of 10 or more places, while 5 compounds had a change in rank of 20 or more. Naphthalene, atrazine, hexazinone, and dichlorobenzene all exhibited a change in rank of over 50 places, suggesting that these four contaminants all have large potential to negatively impact the flora and fauna of

Table 5
Top 40 most toxic chemicals found in landfill leachate according to the endocrine disruption weighted prioritization scheme. Bolded chemicals exhibited a change in rank between the general scheme and the weighted scheme of 10 or more.

Weighted Rank[a]	General Rank[b]	Contaminant	CAS
1	65	Bisphenol A	80-05-7
2	11	p,p'-DDT	50-29-3
3	10	p,p'-DDE	72-55-9
4	95	Octyl phenol	1806-26-4
5	1	Endrin	72-20-8
6	2	Dieldrin	60-57-1
7	3	Aldrin	309-00-2
8	4	Clotrimazole	23,593-75-1
9	5	Oxytetracycline	79-57-2
10	8	Heptachlor	76-44-8
11	6	Chlordane	12,789-03-6
12	7	Indeno (123cd)pyrene	193-39-5
13	14	4,4′-DDD	72-54-8
14	9	Tetrabromobisphenol-A	79-94-7
15	12	1,2,3,4,7,8-hexaCDD	39,227-28-6
16	13	Tetracycline	60-54-8
17	15	Benzo(a)pyrene	50-32-8
18	16	Benzo (ghi)perylene	191-24-2
19	29	PCB-153	35,065-27-1
20	133	Butylparaben	94-26-8
21	17	Benzo(b)fluoranthene	205-99-2
22	18	Dibenz (ah)anthracene	53-70-3
23	19	Heptachlor epoxide	1024-57-3
24	20	PCB-187	52,663-68-0
25	24	Endosulfan I	959-98-8
26	21	Benzo(k)fluoranthene	207-08-9
27	22	Doxycycline	564-25-0
28	23	Benz(a)anthracene	56-55-3
29	25	Endosulfan sulfate	1031-07-8
30	26	2,3,7,8-TCDF	51,207-31-9
31	27	BDE-47	5436-43-1
32	28	Chlorotetracycline	57-62-5
33	32	Lindane	58-89-9
34	30	BDE-99	60,348-60-9
35	31	PCB-128	38,380-07-3
36	33	PCB-105	32,598-14-4
37	34	Enrofloxacin	93,106-60-6
38	35	Pentachlorophenol	87-86-5
39	36	Codeine	76-57-3
40	37	Tebuconazole	80,443-41-0

[a] Toxicity rankings according to the endocrine disruption weighted prioritization scheme.
[b] Toxicity rankings according to the general prioritization scheme.

a site and a relatively lower overall toxicity risk (according to the general prioritization scheme).

Weighted prioritization schemes such as those outlined above add another dimension of selectivity in meeting site objectives. These or similar weighting schemes are particularly useful to communities in which there are defined health concerns or priorities. For example, a scheme like the cancer weighted scheme would best be implemented in an area where cancer was of greater concern, such as "Cancer Alley" in the Southern United States (Singer, 2011). On the other hand, if a community was experiencing high rates of infertility or other problems related to the endocrine system, a scheme like the ED weighted scheme would be the most prudent. The flora and fauna weighted scheme lends itself well to implementation in an area where animal and plant life is of high concern or value, for example: pristine natural areas, locations with endangered species, or places where human consumption of animals (through hunting or fishing) is common.

Comparison of the most toxic compounds identified by both the general scheme and weighted schemes can aid in determining those that are most harmful according to research and community objectives. Compounds that exhibit a large change in rank between schemes, as well as those that exhibit low ranks across schemes, should then be targeted for further research on potential and known impacts to the health of humans and/or flora and fauna.

Table 6
Top 40 most toxic chemicals found in landfill leachate according to the flora and fauna weighted prioritization scheme. Bolded chemicals exhibited a change in rank between the general scheme and the weighted scheme of 10 or more.

Weighted Rank[a]	General Rank[b]	Contaminant	CAS
1	1	Endrin	72-20-8
2	2	Dieldrin	60-57-1
3	3	Aldrin	309-00-2
4	12	1,2,3,4,7,8-hexaCDD	39,227-28-6
5	15	Benzo (a) pyrene	50-32-8
6	11	p,p'-DDT	50-29-3
7	8	Heptachlor	76-44-8
8	4	Clotrimazole	23,593-75-1
9	26	2,3,7,8-TCDF	51,207-31-9
10	10	p,p'-DDE	72-55-9
11	7	Indeno (123cd)pyrene	193-39-5
12	14	4,4′-DDD	72-54-8
13	16	Benzo (ghi)perylene	191-24-2
14	6	Chlordane	12,789-03-6
15	18	Dibenz (ah)anthracene	53-70-3
16	9	Tetrabromobisphenol-A	79-94-7
17	5	Oxytetracycline	79-57-2
18	17	Benzo(b)fluoranthene	205-99-2
19	23	Benz(a)anthracene	56-55-3
20	32	Lindane	58-89-9
21	24	Endosulfan I	959-98-8
22	111	Naphthalene	91-20-3
23	77	Atrazine	1912-24-9
24	21	Benzo(k)fluoranthene	207-08-9
25	13	Tetracycline	60-54-8
26	30	BDE-99	60,348-60-9
27	33	PCB-105	32,598-14-4
28	38	BDE-100	189,084-64-8
29	42	Propiconazole	60,207-90-1
30	35	Pentachlorophenol	87-86-5
31	27	BDE-47	5436-43-1
32	51	Triclocarban	101-20-2
33	48	Hexachlorobenzene	118-74-1
34	49	Triclosan	3380-34-5
35	55	MCPA	94-74-6
36	137	Hexazinone	51,235-04-2
37	92	Dichlorobenzene	106-46-7
38	25	Endosulfan sulfate	1031-07-8
39	40	Pentachlorobenzene	608-93-5
40	22	Doxycycline	564-25-0

[a] Toxicity rankings according to the flora and fauna weighted prioritization scheme.
[b] Toxicity rankings according to the general prioritization scheme.

3.3. Comparison to regulatory lists

Interestingly, only one contaminant identified in the top 40 by one of the prioritization schemes in the current study is listed in Appendix I of 40 C.F.R 258: dichlorobenzene (flora and fauna weighted scheme, Table S6). Between 60 and 63% of the top 40 contaminants from each scheme are included in Appendix II of 40 C.F.R. 258 (see Table 7 and Tables S7-9). Generally, Appendix II compounds are not expected to be monitored unless detection of an Appendix I compound permits it. Neither appendix has been modified since 2005, and accordingly, more recently recognized CECs are not represented therein. Further, traditional regulations which target industrial compounds and related carcinogens may not address the complexity of emerging contaminants. While traditional industrial carcinogens commonly exhibit a linear relationship between level of exposure and toxicity, some CECs and EDs cause deleterious effects at much lower concentrations or exhibit nonlinear, or even nonmonotonic dose responses (Lagarde et al., 2015; US EPA, 2017; Vandenberg et al., 2013). The results of the prioritizations in this study suggest that updating landfill groundwater monitoring requirements to reflect the evolving understanding of landfill leachate composition (and toxicity of the pollutants within it) could be

Table 7
Top 40 most toxic chemicals found in landfill leachate according to the general prioritization scheme.

Rank	CAS	Contaminant	40 C.F.R. 258. App. I[a]	40 C.F.R. 258. App. II[b]
1	72-20-8	Endrin		*
2	60-57-1	Dieldrin		*
3	309-00-2	Aldrin		*
4	23,593-75-1	Clotrimazole		
5	79-57-2	Oxytetracycline		
6	12,789-03-6	Chlordane		*
7	193-39-5	Indeno (123cd)pyrene		*
8	76-44-8	Heptachlor		*
9	79-94-7	Tetrabromobisphenol-A		
10	72-55-9	p,p'-DDE		*
11	50-29-3	p,p'-DDT		*
12	39,227-28-6	1,2,3,4,7,8-hexaCDD		
13	60-54-8	Tetracycline		
14	72-54-8	4,4′-DDD		*
15	50-32-8	Benzo(a)pyrene		*
16	191-24-2	Benzo (ghi)perylene		*
17	205-99-2	Benzo(b)fluoranthene		*
18	53-70-3	Dibenz (ah)anthracene		*
19	1024-57-3	Heptachlor epoxide		*
20	52,663-68-0	PCB-187		*
21	207-08-9	Benzo(k)fluoranthene		*
22	564-25-0	Doxycycline		
23	56-55-3	Benz(a)anthracene		*
24	959-98-8	Endosulfan I		*
25	1031-07-8	Endosulfan sulfate		*
26	51,207-31-9	2,3,7,8-TCDF		*
27	5436-43-1	BDE-47		
28	57-62-5	Chlortetracycline		
29	35,065-27-1	PCB-153		
30	60,348-60-9	BDE-99		*
31	38,380-07-3	PCB-128		
32	58-89-9	Lindane		*
33	32,598-14-4	PCB-105		*
34	93,106-60-6	Enrofloxacin		*
35	87-86-5	Pentachlorophenol		
36	76-57-3	Codeine		*
37	80,443-41-0	Tebuconazole		
38	189,084-64-8	BDE-100		
39	82,419-36-1	Ofloxacin		
40	608-93-5	Pentachlorobenzene		

[a] A star indicates inclusion in Appendix I, 40 C.F.R. § 258.
[b] A star indicates inclusion in Appendix II, 40 C.F.R. § 258.

useful and effective, as this leachate may pose risks to groundwater through offsite transport.

3.4. Scheme application with modern metabolomics

Incorporating site-specific contaminant data when applying the prioritization schemes outlined in this study will provide the most accurate and applicable results. Site-specific contaminant data can be effectively generated using the combination of non-target global profiling analysis and modern metabolomics. Traditional target approaches are inferior to non-target approaches in multiple ways. Target approaches [e.g., sample analysis using low-resolution mass spectrometry (LRMS)] have relied heavily on reference analytical standards with limited commercial availability and low-resolution mass spectral libraries [e.g., those developed by the National Institute of Standards and Technology (NIST)]. Further, target approaches require lists of potential contaminants to analyze for, which are often generated by reviewing literature in scientific journals or information from regulatory agencies, and may not reflect the exact conditions at a site. Non-target approaches that implement modern high-resolution mass spectrometry (HRMS) such as time-of-flight (TOF), Orbitrap, and Fourier transform ion cyclotron resonance (FT-ICR) instrumentation, are superior to LRMS target approaches in analyzing environmental samples. Not only is mass accuracy of identified molecules greatly improved in HRMS (precision of exact mass down to four to six decimal places), but operating HRMS instruments in full scan mode with modern deconvolution algorithms allows for global metabolomic profiling (Arrebola-Liébanas et al., 2017). The use of structural fragmentation data collected through high-resolution tandem mass spectrometry (MS/MS or MS2) will further increase the confidence in compound identifications.

Following non-target analysis, metabolomics platforms such as XCMS Online can then be used to process full-scan HRMS data without the need for reference standards; XCMS Online automatically detects, integrates and annotates the signals (peaks) according to METLIN, the largest mass spectral reference database for organic molecules in the world, using novel nonlinear retention time alignment (Domingo-Almenara et al., 2018; Smith et al., 2006). Identified contaminants can be prioritized using output parameters like relative peak intensity or fold change between samples. While this approach is effective in identifying compounds with significant presence in samples, it does not integrate any health nor toxicity information. The prioritization scheme described in this paper can be integrated seamlessly into existing modern metabolomic platforms to prioritize contaminants identified in non-target analysis based on their toxicity. In this manner, both relative concentration data and potential health risks of contaminants identified at a site are taken into account. Mitigation efforts can then be designed accordingly to target contaminants which are not only the most abundant, but the most harmful as well.

4. Conclusion

Landfills contain many harmful chemicals which may leach offsite into groundwater. It is not feasible nor economically viable to monitor and remediate all possible contaminants. Prioritization schemes that incorporate numerous sources of toxicity data, such as those described here, provide the means for cost-effective identification of contaminants most relevant to community priorities and concerns. The general prioritization scheme depicted here is also highly flexible and can be easily customized. Included parameters can be modified and weighting schemes can be added or adjusted to best meet diverse media and objectives, as shown by the four modified schemes presented here. Out of the original 322 contaminants analyzed in this study, 56 were identified in the top 40 most toxic contaminants of all five schemes. The flora and fauna weighted scheme had the largest average change in rank (±14 places) when compared to the general scheme, and the general + ED data scheme had the smallest average rank change (±3.2 places). A combination of rank and change in rank can be implemented when deciding which contaminants to target with remediation efforts. Further, though the original scheme was designed particularly for pollutants in aqueous solutions, it can be modified for applications with air pollutants as well. This method holds promise for implementation in environmental pollutant mitigation, especially when used to prioritize global metabolomic data generated through HRMS non-target analysis. Landfill leachate is a continuously evolving media, both due to internal processes (e.g., waste decomposition) and external factors, such as societal change, which alter the composition of waste deposited in landfills. Future research directions, therefore, include comprehensive assessments of CECs and their impacts on human health and the environment, and implementation of the prioritization schemes defined here

to monitor landfill leachate toxicity as a function of time.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jenvman.2021.112031.

Credit author statement

Elizabeth R. Rogers, Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Visualization. Ronald S. Zalesny, Writing – review & editing, Supervision. Chung-Ho Lin, Conceptualization, Writing – review & editing, Supervision.

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