Environmental Science & Technology

Article

pubs.acs.org/est

# Risk-Based High-Throughput Chemical Screening and Prioritization using Exposure Models and in Vitro Bioactivity Assays

Hyeong-Moo Shin,*[,†] Alexi Ernstoff,[‡,§] Jon A. Arnot,[∥,⊥,#] Barbara A. Wetmore,[▽] Susan A. Csiszar,[§] Peter Fantke,[‡] Xianming Zhang,[○] Thomas E. McKone,[◆,¶] Olivier Jolliet,[§] and Deborah H. Bennett[†]

[†]Department of Public Health Sciences, University of California, Davis, California 95616, United States

[‡]Quantitative Sustainability Assessment Division, Department of Management Engineering, Technical University of Denmark, Kgs. Lyngby 2800, Denmark

[§]Department of Environmental Health Sciences, University of Michigan, Ann Arbor, Michigan 48109, United States

[∥]ARC Arnot Research and Consulting, Toronto, Ontario M4M 1W4 , Canada

[⊥]Department of Physical and Environmental Sciences, University of Toronto, Scarborough, Toronto, Ontario M1C 1A4, Canada

[#]Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario M5S 1A8, Canada

[▽]The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina 27709, United States

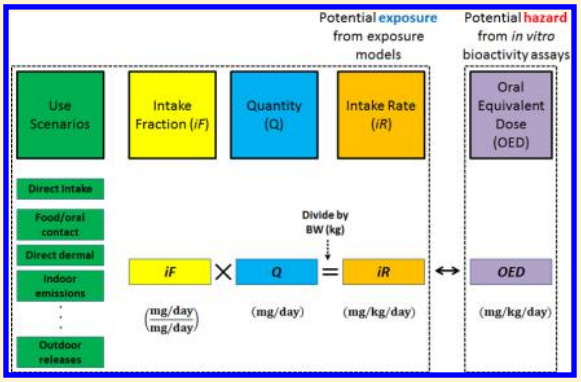
[○]Harvard School of Public Health and School of Engineering and Applied Sciences, Harvard University, Cambridge, Massachusetts 02138, United States

[◆]Environmental Energy Technologies Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720 , United States

[¶]School of Public Health, University of California, Berkeley, California 94720, United States

Supporting Information

**ABSTRACT:** We present a risk-based high-throughput screening (HTS) method to identify chemicals for potential health concerns or for which additional information is needed. The method is applied to 180 organic chemicals as a case study. We first obtain information on how the chemical is used and identify relevant use scenarios (e.g., dermal application, indoor emissions). For each chemical and use scenario, exposure models are then used to calculate a chemical intake fraction, or a product intake fraction, accounting for chemical properties and the exposed population. We then combine these intake fractions with use scenario-specific estimates of chemical quantity to calculate daily intake rates (iR; mg/kg/day). These intake rates are compared to oral equivalent doses (OED; mg/kg/day), calculated from a suite of ToxCast in vitro bioactivity assays using in vitro-to-in vivo extrapolation and reverse dosimetry. Bioactivity quotients (BQs) are calculated as iR/OED to obtain estimates of potential impact associated with each relevant use scenario. Of the 180 chemicals considered, 38 had maximum iRs exceeding minimum OEDs (i.e., BQs > 1). For most of these compounds, exposures are associated with direct intake, food/oral contact, or dermal exposure. The method provides high-throughput estimates of exposure and important input for decision makers to identify chemicals of concern for further evaluation with additional information or more refined models.




## INTRODUCTION

While a growing number of chemicals have been developed and introduced into commerce over the past several decades,[1,2] there is a dearth of exposure and toxicity information available to assess potential harmful effects of these chemicals to humans or to provide information needed to regulate and screen chemicals.[3] For this reason, high-throughput screening (HTS) assessments that incorporate both exposure and toxicity data are recommended for risk-based screening and prioritization.[4] The U.S. Environmental Protection Agency (EPA) has developed a process combining in vitro HTS assays with computational tools to facilitate rapid hazard assessments based on chemical bioactivities.[5−9] This process is incorporated in the EPA's ToxCast Program.[10] ToxCast Phase I chemicals are primarily food-use pesticides for which regulatory exposure estimates have been generated; however, exposure estimates are not available for most commercial chemicals such as those used

Received: January 28, 2015
Revised: April 27, 2015
Accepted: May 1, 2015
Published: May 1, 2015

DOI: 10.1021/acs.est.5b00498
Environ. Sci. Technol. 2015, 49, 6760−6771

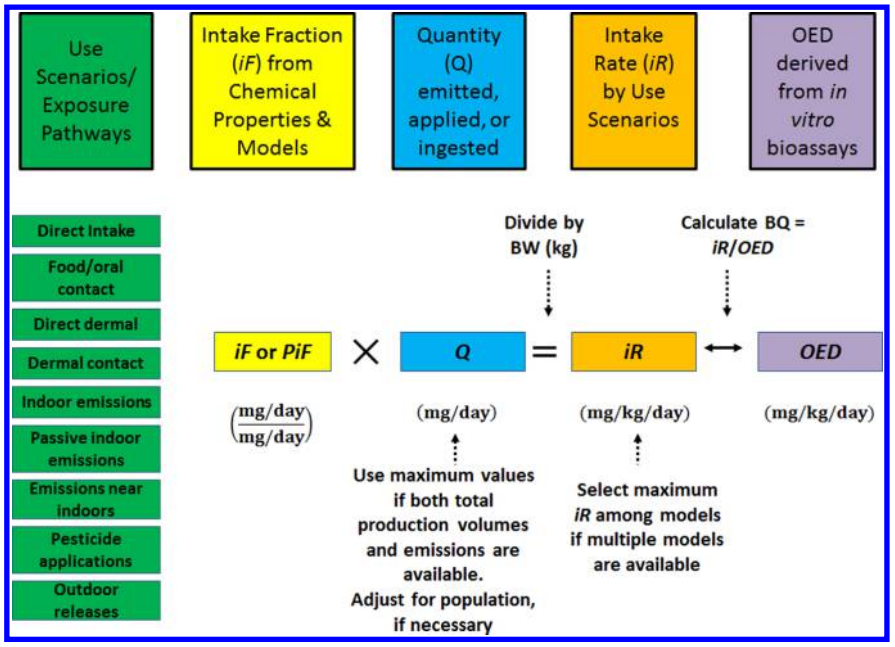



**Figure 1.** Overview of framework for risk-based high-throughput chemical screening and prioritization used this study.

in consumer products and industrial processes.[11] As a parallel effort, high-throughput (HT) methods to characterize and quantify exposures are clearly needed to facilitate risk-based HTS assessments.[12,13]

Far-field (e.g., outdoor environmental releases to ambient air, water, or soil) and near-field (e.g., indoor releases or personal care product applications) human exposure models have recently been developed and applied for screening-level exposure-based assessment and prioritization.[14−24] However, a general lack of chemical quantity and use information has hindered the parametrization of these exposure models,[25,26] and hence the application of HTS methods for exposure- and risk-based prioritization. Modeling studies have shown the actual chemical emission rate contributes the greatest variance (uncertainty) in far-field human exposure estimates[15] and information about the distribution of chemical production mass (or volume) with respect to use and release scenarios greatly influences total exposure estimates.[27,28] The intake fraction (iF), the integrated cumulative intake of a compound per unit of emission,[29] is a convenient metric for quantifying emission-to-exposure relationships, thus allowing uncertainty in chemical use and emissions to be treated separately in the exposure calculation. To begin addressing the need for identifying near-field chemical uses, the U.S. EPA has recently developed a consumer product ingredient database for chemical exposure screening and prioritization[30] and has used this database to help parametrize its exposure models.[21]

In the present study, we develop a screening-level HTS framework to provide risk-based prioritization for human health impact assessment. This framework was developed as part of ExpoDat, a program developed by the American Chemistry Council's Long-Range Research Initiative. With respect to each considered chemical we identify the applicable far-field, near-field, and personal care product exposure scenarios and apply the relevant exposure models. We then compare the estimated per capita exposures to in vitro bioactivity estimates. Simple, conservative assumptions for screening-level estimates of chemical emission, release and application rates are based on publicly available data and initial (default) assumptions on per-capita usage. Chemicals highlighted in this screening do not necessarily pose a risk, but may need additional information (e.g., how it is used) to better evaluate potential exposure. We illustrate the sensitivity of the results based on initial default assumptions, critically discuss limitations of the current framework, and provide recommendations for future research on exposure- and risk-based screening and prioritization. To our knowledge, this is the first work that incorporates a HT mechanistic exposure modeling approach with HT in vitro toxicity testing data to evaluate and prioritize chemicals for potential risk to human health.

## MATERIALS AND METHODS

**Overview.** Figure 1 provides a conceptual overview of a risk-based HT prioritization framework. We first obtain information on how the chemical is used and determine nine relevant use scenarios related to human exposures in non-occupational settings: direct intake, food/oral contact, direct dermal (e.g., direct application on skin), dermal contact, indoor emissions, passive indoor emissions, emissions near indoors, pesticide application, and environmental/outdoor emissions. For each chemical and use scenario, one or several exposure models are then used to calculate a chemical intake fraction (iF; dimensionless), or a product intake fraction (PiF; dimensionless) in the case of personal care product applications, using physical-chemical properties and assumed exposure conditions (e.g., personal care product use patterns). Chemical quantities ($Q$; mg/day) applied, used, or released to specific use scenarios are estimated based on a conservative value using the total production volumes or emission estimates, adjusting for the estimated size of the exposed population, where appropriate. Daily chemical intake rates (iR; mg/kg/day) are calculated as iF (or PiF) multiplied by $Q$ and divided by body weight (BW; kg). Because of the lack of data on the fraction of chemicals being allocated in each use scenario, this iR calculation assumes that 100% of the $Q$ is applied to each relevant use scenario. These intake rates are compared to oral equivalent doses (OED; mg/kg/day), calculated from the ToxCast in vitro bioactivity data using an in vitro-to-in vivo extrapolation (IVIVE) approach and


DOI: 10.1021/acs.est.5b00498
Environ. Sci. Technol. 2015, 49, 6760−6771

Table 1. Selected Use Scenarios Based on Database-Defined Use Categories and Assumptions for Chemical Quantity

| use scenarios | description | examples of CPCat cassettes | assumptions of population size[b] and chemical quantity use (Q)[c] |
|---|---|---|---|
| direct intake | directly ingested or inhaled | 'food_additive flavor', 'cigarettes' | 100% Q to 10% of U.S. population |
| food/oral contact | likely contact food or be placed in the mouth | 'personal_care dental', 'food_contact' | 10% Q to 10% of U.S. population |
| direct dermal | directly applied to the skin | 'personal_care cosmetics' | 100% Q to 10% of U.S. population |
| dermal contact | solid items we touch | 'apparel', 'tools', 'plastics' | 10% Q to 10% of U.S. population |
| indoor emissions | directly emitted indoors | 'air_fresheners', 'cleaning_washing' | 100% Q to 50% of U.S. household |
| passive indoor emissions | solid items placed indoors | 'furniture', 'building_material' | 10% Q to 50% of U.S. household |
| emissions near indoors | items with emissions near indoors | 'heating fire, 'lawn_ garden' | 1% Q to 50% of U.S. household |
| pesticide application | used in agriculture as a pesticide | 'pesticide' | emission distribution[d] |
| environmental emissions | applied to all chemicals[a] | | emission distribution[e] |

[a]For all compounds, intake rates were estimated assuming general environmental releases to estimate a "background" exposure related to production volume and emissions. [b]U.S. population: 300 000 000, U.S. household: 100 000 000. [c]A maximum value is selected between total production volumes and emissions estimates and applied to all relevant use scenarios of each chemical. [d]For CalTOX and RAIDAR that do not include direct application to plant, we assumed that pesticides are applied 20% air: 80% soil. For dynamiCROP that includes direct application to agricultural crops, we assumed that pesticides on average are distributed 20% air: 20% soil: 60% plant. [e]Based on the air−water partition coefficient ($K_{aw}$) value, we bin compounds as likely to be released 90% air:10% water, 75% air:25% water, 50% air:50% water, 25% air:75% water, 10% air:90% water (see SI for details).

reverse dosimetry.[8,9] The approach culminates in the calculation of the bioactivity quotient (BQ; unitless) for each chemical and each relevant use scenario. Bioactivity quotients are conceptually similar to other exposure/effect metrics such as the hazard quotient (HQ) and are estimated as

$$BQ = iR/OED \quad (1)$$

The relative rank of BQs can be used for priority setting, that is, higher BQs can be considered higher priority. Details of the data and models used for calculations are provided below.

We parametrize and apply the framework as a case study to evaluate 180 chemicals (see Table S1 in the Supporting Information (SI)), which include 50 chemicals from Phase I and 130 chemicals from Phase II of the U.S. EPA ToxCast Program for which dosimetry-adjusted *in vitro* bioactivity data were available.[8,9] For the use scenarios related to indoor emissions and outdoor releases, various exposure models are used and the maximum iR is selected. Chemicals with exposure estimates meeting or exceeding bioactivity, that is, BQs ≥ 1, do not necessarily indicate the potential for adverse health effects, but these chemicals may need additional information. In particular, the assumption that 100% of Q is being applied to each individual use scenario is a very conservative assumption for many compound/use scenario pairs. Thus, we conducted a sensitivity analysis on various default assumptions and other input parameters.

**Chemical and Assay Selection Criteria.** The chemicals selected for this analysis represent ToxCast Phase I and II chemicals for which in vitro pharmacokinetic data were available but for which exposure estimates from regulatory documents (e.g., reregistration eligibility documents) were not. Pharmaceutical and endogenous compounds were excluded. This chemical list was then checked against the ToxCast in vitro assay data set released to the public in December, 2014. This new release includes data quality flags to alert users to experimental issues that may confound data interpretation. The assay list used to select the final chemical list was filtered to exclude assays with any such data quality flags. In the end, 180 chemicals were identified that had at least one assay hit for comparison. More information on the ToxCast bioactivity data is provided in the 'In Vitro Bioactivity Data' section.

**Input Data for iR (Exposure) Calculations.** There are four types of data input required for the HT exposure calculations: (1) chemical use categorization in use scenarios, (2) chemical mass produced/emitted in the U.S., (3) the size of the exposed population, and (4) chemical properties needed to parametrize exposure models (e.g., vapor pressure, degradation half-lives).

*Use Categorization.* To investigate the potential uses of the selected chemicals, we matched chemical abstracts service (CAS) numbers to the U.S. EPA Chemical and Product Categories (CPCat) database,[31] which aggregates and harmonizes 12 different databases classifying chemical-use data into a set of 1297 cassettes (term groups) of which 824 describe chemical uses other than drugs. Of the 180 chemicals in this study, 167 matched up with over 15 000 entries in the database yielding 427 unique cassettes (see Table S2 of the SI). We iteratively classified these cassettes into a set of nine use scenarios: direct intake, food/oral contact, direct dermal, dermal contact, indoor emissions, passive indoor emissions, emissions near indoors, pesticide application, and environmental/outdoor emissions (Table 1). For 13 compounds that do not match any single cassette in CPCat, we assumed that chemicals are applied, used, or released to all nine use scenarios as a conservative approach. Moreover, all chemicals are assumed to have environmental/outdoor emissions. Many of the cassettes match to more than one use scenario. For example, in this scheme consumer-use cleaning products have both an indoor emission and a dermal contact (occurring incidentally while using the product). Table 1 includes examples of CPCat database cassettes, with a complete list of the CPCat cassettes in Table S2 of the SI.

We compiled the resulting use scenarios and conducted a preliminary review to ensure results are reasonable based on our knowledge of chemical's likely uses and identified several questionable chemical-use/exposure scenario combinations. Further investigation revealed that these questionable combinations were due to matched entries in a small number of databases which may have been created for purposes other than chemical use classification. For example, CPCat assigns the term "food additive flavors" to a list of pesticides within the "SPIN" data source, a subset of a data source within CPCat, as a


DOI: 10.1021/acs.est.5b00498
Environ. Sci. Technol. 2015, 49, 6760−6771

result of its ambiguous description of "food/feedstuff flavorings and nutrients". This description may possibly stem from an effort to establish allowable pesticide residue levels in food. However, in our framework pesticide residues are better reflected by the pesticide residue use scenario than by direct ingestion of the overall quantity of pesticide produced. For each questionable chemical-use scenario combination, we investigated the impact of removing a questionable data source to ensure it only removed false positives. This process is further outlined in the text and Table S3 of the SI. A summary of use scenarios for all 180 compounds is provided in Table S4 of the SI.

*Chemical Quantities (Q).* We used total production volume (TPV) and emission estimates as surrogates for chemical quantities ($Q$) in the U.S. For 52 compounds, we obtained TPV data from the 2006 U.S. EPA Inventory Update Reporting (IUR).[32] Note that the TPV data are recorded in "bins", spanning several orders of magnitude for a given chemical in that particular year (see Table S5 of the SI). We used the maximum value of the bounding values of the mass-use range for these compounds. We selected 10 times the minimum reported value for one compound (nitrobenzene) because only a lower bound value was reported in IUR. For 19 pesticides, aggregated application rates by state and crop from Crop Protection Research Institute (CPRI) 2002 data were used as a surrogate for TPV.[23] For the rest of compounds ($N$ = 109) whose TPV data are not available in the 2006 IUR and not covered by CPRI, we assumed a TPV of 25 000 pounds (lb), the maximum of the lowest production volume reporting bin.[23]

In addition, we extracted emission estimates for 50 compounds from at least one of the U.S. EPA databases: the National-Scale Air Toxics Assessments (NATA),[33] the Toxics Release Inventory (TRI) Program,[34] and the National Emissions Inventory (NEI).[35] For seven compounds with emissions from combustion or mobile sources where the maximum emission estimates from these U.S. EPA databases exceeded the TPV value, we chose to use maximum emissions value. The TPV data, additional emission estimates, and the selected chemical quantity ($Q$) used to calculate intake rates for all 180 compounds are provided in Table S5 of the SI.

*Size of the Exposed Population.* There is no available information source for a screening-level model to determine the fraction of the U.S. population exposed to a particular compound. Thus, we selected arbitrary numbers that imply the chemical is fairly widely distributed in commerce, but concentrates the exposure among only a fraction of the population. For example, for compounds associated with direct intake, food/oral contact, direct dermal, and dermal contact, we assumed that exposure is concentrated within 10% of the 300 million U.S. residents (i.e., those using products including the compound). For compounds associated with indoor use, we assumed that 50% of the 100 million U.S. households use the product indoors. Using a smaller exposed population increases exposure for those exposed to the compound, as the TPV is distributed across the assumed population. We also performed a sensitivity analysis to test how the selected number may affect the number of compounds with BQ > 1.

*Chemical Properties.* Chemical properties are needed to parametrize most exposure models. We obtained chemical properties and degradation half-lives using a CAS number or simplified molecular-input line-entry system (SMILES). When available, we selected measured values, otherwise we used estimated values from quantitative structure−activity (property) relationship (QSA(P)R) models in the U.S. EPA Estimation Program Interface Suite (EPI Suite), assuming the former are more reliable than the latter.[36] Details of chemical properties and assumptions are included in the SI.

**iF for Direct Intake and Food/Oral Contact.** For compounds used in food, for example as additives or preservatives, or used as cigarette ingredients, we assumed 100% intake (iF = 1), because compounds in these use scenarios are likely to be directly ingested or inhaled. We did not account for food waste in this estimate.

Compounds used in food packaging or dental products were modeled as inadvertent ingestion exposure where we assumed a maximum of 10% of the chemical mass may be taken up by the user, assumed to be a conservative estimate.

*Product iF for Direct Dermal Uptake and Dermal Contact.* For compounds categorized as personal care product ingredients, we calculated the product intake fraction (PiF). PiF is defined as the mass taken up by the user divided by the mass of chemical ingredient within the applied product[37] and was estimated assuming daily use of body lotion as a conservative archetypal product use. We also assumed that lotion is left on the body for 8 h and a volume of 4.42 $cm^3$[38] was applied once daily to an area including the feet, legs, hands, and arms[38] which cover an average surface area of 10 935 $cm^2$.[39] The PiF is estimated using a mass balance equation accounting for transfers into skin and into air, as a function of the thickness of the product applied on the skin (i.e., volume applied per area applied), the length of time the product is applied. The chemical-specific skin permeation coefficient, $K_p$ (cm/h), is derived from the ten Berge model.[40] The equations used for the dermal exposure model are provided in the SI.

For chemicals classified in the dermal contact category such as tools and sporting equipment, we assumed that a maximum of 10% of the total mass is available for dermal contact, applying the same PiF method used for direct dermal uptake.

*iF for Indoor Emissions.* For compounds classified as indoor emissions, we calculated iF using three indoor near-field exposure models. These models simulate the fate and transport of chemicals released to the indoor air, and subsequent human exposure via three exposure pathways including inhalation, dermal, and nondietary dust ingestion. The details of the indoor exposure models are described elsewhere.[17,18,22,41] For those use scenarios thought to result in a significant fraction of the compound volatilizing into the air during use (e.g., air fresheners), it was assumed that the entire compound is released to air.

Many compounds are introduced to the home as part of a solid product, such as furniture, electronics, plastic items, or other common consumer goods. Research has established that a portion of the compounds in these products will release into the air (e.g., flame retardants and plasticizers).[42] Therefore, for the "passive indoor emissions" scenario (see Table 1), we assumed 10% of the mass was introduced to the home and would release into the air. Similarly, there are products used in close proximity to the home, such as items used to care for the lawn or vehicles. For these cases, we assumed that a maximum of 1% of the mass would release to the household air.

*iF for Outdoor Releases.* For all compounds, we calculated iF using three steady-state (Level III) far-field multimedia mass-balance models, including CalTOX,[43] the United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model (USEtox),[44] and the Risk Assessment IDentification And Ranking model (RAIDAR).[45]



DOI: 10.1021/acs.est.5b00498
Environ. Sci. Technol. 2015, 49, 6760−6771

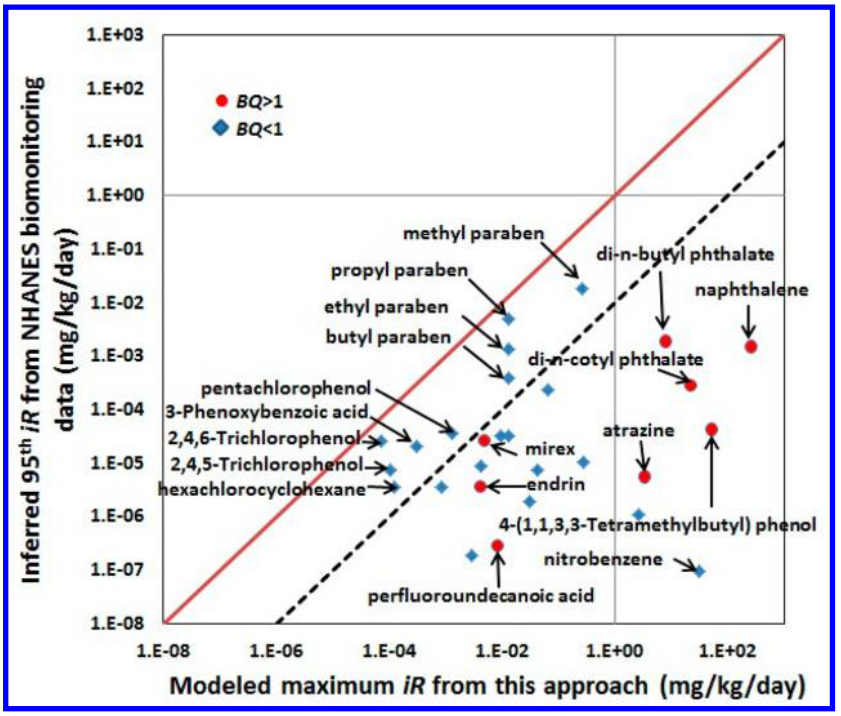



**Figure 2.** Comparison of modeled maximum iRs from this study and 95th percentile iRs inferred from NHANES biomonitoring data. Note that nitrobenzene is chemical intermediate with over 1 billion pounds produced in the U.S. and the levels in blood are below limit of detection in 2003−2004 NHANES survey.

We assumed that chemical release to soil is negligible for the generic outdoor release (see different assumptions for pesticides) and percent mode-of-entry to air and water is based on the chemical's air−water partition coefficient ($K_{aw}$) (see SI for details).

*Pesticide Residue iF.* For chemicals classified as agricultural pesticides, residues in food after crop harvest and processing were determined using results from the dynamiCROP model,[46,47] giving the maximum iF across six crop archetypes: wheat, paddy rice, tomato, apple, potato, and lettuce. In addition to the fraction of pesticide remaining in crop harvest as residue, the dynamiCROP model provides estimates of the fraction of the applied pesticide that is emitted to the environment (i.e., to soil or to air, kg emitted/kg applied) according to the crop and pesticide target class (where herbicides were assumed to not be applied directly to the crop).[19] Emitted fractions were then combined with USEtox iF for emissions to continental air and soil, respectively, and summed with the iF due to ingestion of pesticide crop residues, yielding a total iF for pesticides. We also calculated the iF values using all three far-field Level III models identified above, but only accounted for pesticide emissions to the environment, assuming 20% of the applied mass was released to air (average air emission for pesticides applied to all crop archetypes in dynamiCROP), and the remaining 80% was released to soil.

The iF values for indoor air releases, outdoor air releases, and pesticide applications as well as the PiF values for direct dermal applications are provided in Table S6 of the SI.

**ToxCast in Vitro Bioactivity Data.** *ToxCast in Vitro Bioactivity Data.* All of the in vitro bioactivity data utilized in this study were generated as a part of the U.S. EPA ToxCast Program.[5] These HT bioactivity data were collated from a set of over 650 assays spanning nine separate technologies, including receptor-binding and enzyme activity assays, cell-based protein and RNA expression assays, real-time growth measured by electronic impedance, and fluorescent cellular imaging. Each chemical was run through each assay in concentration response and, when activity was measured, an $AC_{50}$ (concentration at 50% of maximum activity) or LEC (lowest effective concentration) value was calculated. The data utilized for this study were released to the public in December, 2014 (http://epa.gov/ncct/toxcast/data.html). Several publications utilizing the in vitro screening data can be found in the peer-reviewed literature.[4,48−54]

*Estimation of $C_{ss}$ using in Vitro-to-in Vivo Extrapolation (IVIVE).* Hepatic metabolic clearance and plasma protein binding data experimentally measured in earlier studies[8,9,11] were incorporated into an IVIVE model to estimate the steady-state chemical blood concentration ($C_{ss}$) as previously described.[11] Briefly, in vitro hepatic clearance rates were experimentally measured in hepatocytes using the substrate depletion approach, adjusted for nonspecific binding, and scaled up to represent overall hepatic intrinsic clearance. These values were then incorporated with plasma protein binding data and nonmetabolic renal clearance values into a base equation to calculate $C_{ss}$ based on constant uptake of a daily oral dose. A correlated Monte Carlo approach was employed[55] using Simcyp (Simcyp V.13; Certara, Sheffield, UK) to simulate variability across a population of 10 000 individuals equally comprised of both genders, 20−50 years of age. Plasma $C_{ss}$ values for the 5th, median and 95th percentiles of the population simulated were obtained as output. The outputs for the upper 95th percentile were utilized in the calculation of the oral equivalent doses (OEDs) to provide a conservative estimate for the analyses.

*Calculation of OEDs.* Reverse dosimetry was utilized to relate $C_{ss}$ to an exposure concentration.[56] The upper 95th percentile for the $C_{ss}$ was used to generate OEDs according to the following formula:


DOI: 10.1021/acs.est.5b00498
Environ. Sci. Technol. 2015, 49, 6760−6771

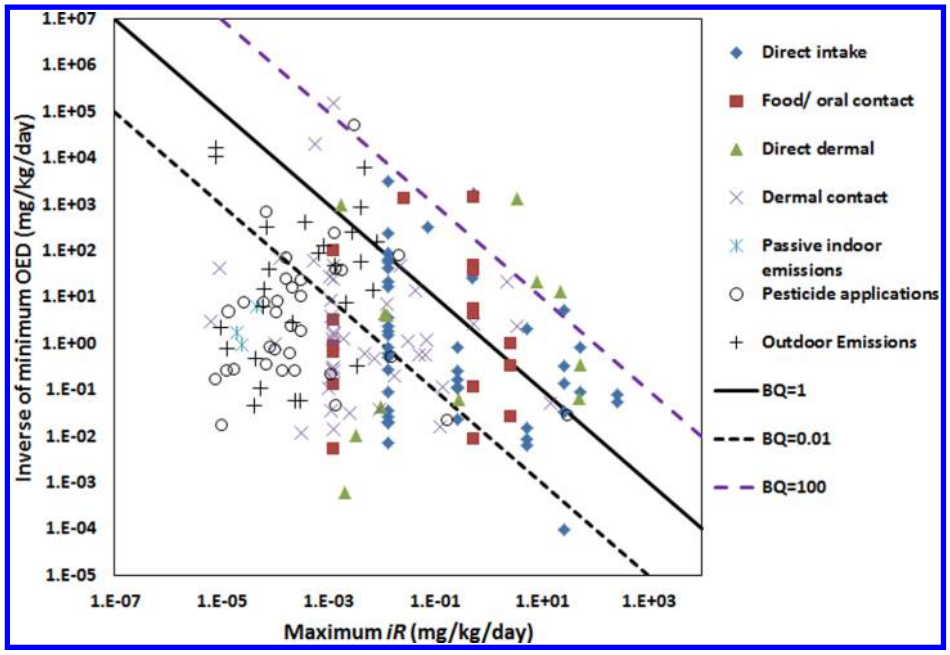



**Figure 3.** Maximum bioactivity quotients (BQs) for the case study chemicals calculated as ratios of the maximum intake rate (iR; mg/kg/day) and the minimum oral equivalent dose (OED; mg/kg/day) derived from in vitro bioassays.

$$\text{OED}[\text{mg/kg/day}] = \text{ToxCast } AC_{50} \text{or LEC}[\mu M]/\ C_{ss}[\mu M] \times 1[\text{mg/kg/day}] \quad (2)$$

In the equation above, the OED is linearly related to the in vitro $AC_{50}$ or LEC and inversely related to $C_{ss}$. This equation is valid only for first-order metabolism that is expected at ambient exposure levels. An OED was generated for each chemical and each $AC_{50}$ or LEC value across all of the in vitro assay endpoints. Only the lowest (i.e., minimum) OEDs calculated for each chemical across all assays were used in this case study and are provided in Table S7 of the SI.

## RESULTS

**Comparison of Modeled iRs and Those Inferred from Biomonitoring Data.** The iRs estimated from our conservative approach (i.e., assuming that 100% of the total production volume is being directed toward to each relevant use scenario) can be compared with those inferred from measured concentrations in biological (urine or blood) samples such as those in the National Health and Nutrition Examination Survey (NHANES).[57,58] Of the 180 chemicals considered, 95th percentile blood or urine concentrations are available in NHANES for 28 chemicals. Using the methods that are used to estimate iRs,[28] we back-calculated iRs inferred from NHANES biomonitoring data and compared with maximum iRs from our approach. As shown in Figure 2, our maximum iRs are always greater than the 95th percentile iRs inferred from biomonitoring data. We then compared results for compounds primarily used for one purpose versus those used for multiple purposes. For four parabens that are almost solely used in dermal applications and another five compounds almost solely used in pesticide applications, maximum iRs are within 2 orders of magnitude of the 95th percentile iRs inferred from biomonitoring data. In contrast, for compounds that the majority of total chemical quantity ($Q$) is expected to be released outdoors (e.g., naphthalene)[27,28] and that are determined to have also near-field use scenarios such as direct intake from cigarette smoking, the difference between maximum iRs and 95th percentile iRs inferred from biomonitoring data of these compounds is much greater (up to 7 orders of magnitude) than the former nine compounds with predominantly a single use (four parabens and five pesticides). This highlights the need for more refined information on the proportion of the mass utilized in each use scenario to improve exposure estimates.

**Comparison of Exposure and Bioactivity Potential.** In Figure 3, we plot for each chemical the maximum iR for the applicable use scenarios versus the inverse of the minimum OED. The diagonal solid line represents the threshold where the iRs are equal to the OEDs (i.e., BQ = 1). The 38 compounds to the right of the solid 1-to-1 line have maximum BQs (=iR/OED) greater than 1. A given chemical may have BQ > 1 for one or more of its modeled use scenarios. Most of the 38 compounds with BQs > 1 have direct intake, food/oral contact, direct dermal, or dermal contact as one of their applicable use scenarios. Because iFs for these use scenarios are relatively high and we allocated 100% of the chemical quantity to each relevant use scenario, this observation highlights the importance of using correct and accurate use categorization and data on the distribution of chemical mass to each use scenario in HT screening and prioritization.

Figure 4 provides a heat map to depict BQs for each relevant use scenario for each compound. For eight compounds, the estimated exposure level is 2 orders of magnitude greater than the bioactivity level (in red), primarily for use scenarios that result in closer contact between the consumer and the chemical. There are 14 compounds with BQs > 1 from at least three use scenarios, 13 other compounds with BQs > 1 from at least two use scenarios, and 11 compounds with BQs > 1 only for a single use scenario. The BQ of triphenyl phosphate, a flame retardant, is greater than 100 for four use scenarios, in part because of its large production volume (see SI Table S5) and its low minimum OED.


DOI: 10.1021/acs.est.5b00498
Environ. Sci. Technol. 2015, 49, 6760−6771

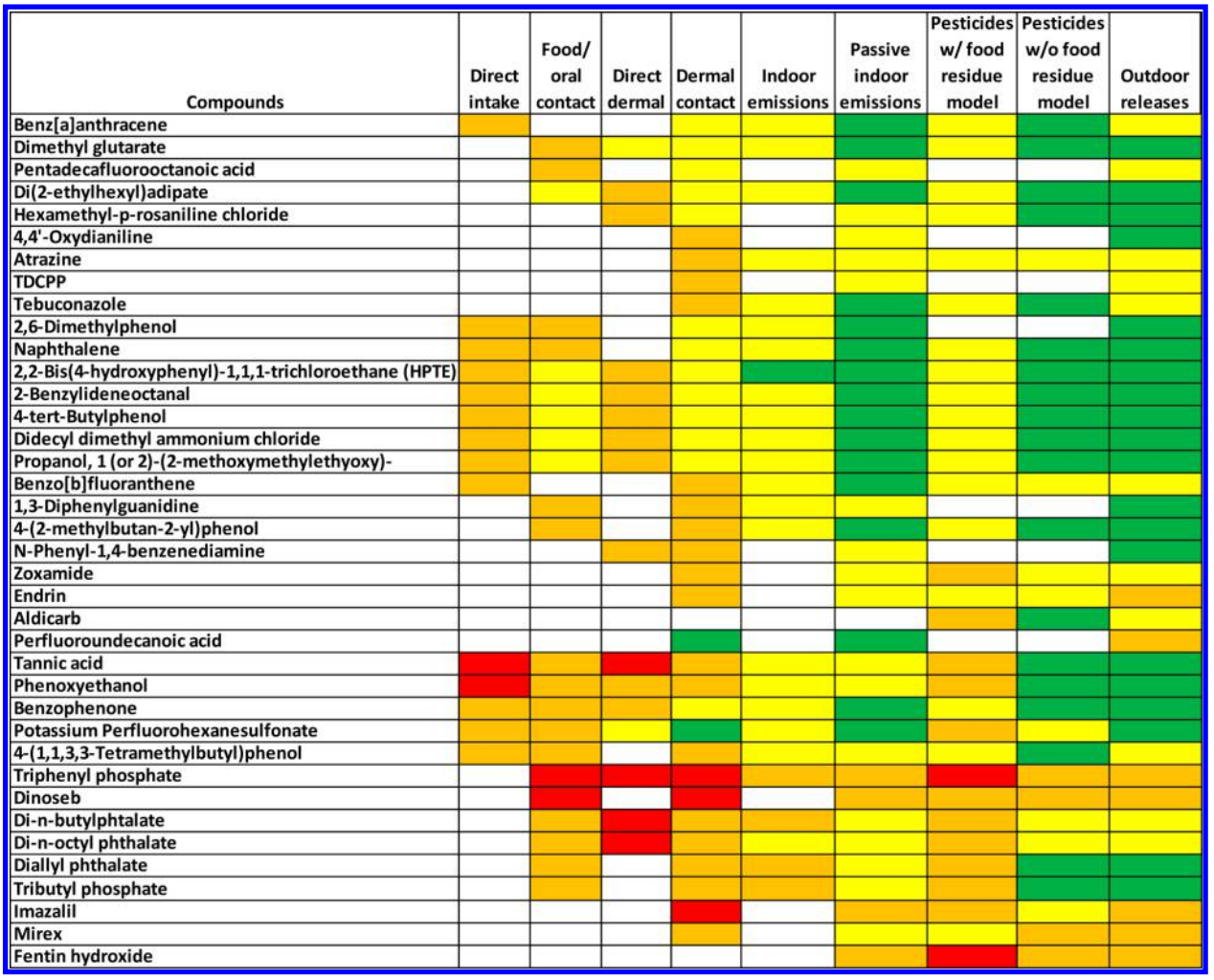



**Figure 4.** Heat map of the 38 chemicals with a bioactivity quotient (BQ) greater than 1. BQs are determined for each relevant use scenario: red: BQs $\geq$ 100; orange: 1 $\leq$ BQs < 100; yellow: 0.01 $\leq$ BQs < 1; green: BQs < 0.01; white: not a relevant exposure category or scenario.

Looking at each column of Figure 4, most of the highest BQs in red correspond to high iF values such as for direct intake (iF = 1) or direct dermal application (median of PiF = 0.49). There are 14 compounds with BQs > 1 for direct intake, 17 for food/oral contact, 14 for direct dermal, and 21 for dermal contact, highlighting the impact of iF on the iR value. For chemicals used in pesticide application, there are 13 chemicals with BQs > 1 when total exposure includes ingestion of pesticide residue, and 4 when exposure results from only overall environmental emissions (i.e., excluding residues on treated crops).

In total, there are seven compounds with BQs > 1 that are strictly due to outdoor environmental emissions. Four of these chemicals are pesticides, two of which (i.e., endrin, mirex) are persistent organic pollutants (POPs) listed under the Stockholm Convention.[18] Of the seven chemicals, the production volume estimates for four chemicals (i.e., endrin, mirex, imazalil, perfluoroundecanoic acid) are not available in the national databases and thus applying hypothetical TPV of 25 000 lb/year, the maximum of the lowest production volume reporting bin, results in a release high enough to correspond with exposures exceeding the bioactivity level (i.e., BQ > 1).

**Sensitivity Analysis.** In this study, due to the limited information on many exposure parameters (e.g., percent of the population using the product containing our study chemicals), default assumptions were made in estimating exposures and thus a variety of sensitivity analyses were conducted to evaluate the influence of these default assumptions and input data (e.g., TPV, use categorization) on overall screening results (BQs > 1). For example, we selected arbitrary numbers for the size of the exposed population (e.g., 10% of the U.S. population for direct intake, food/oral contact, direct dermal, and dermal contact) and then applied this fraction to the iR calculations (=$Q \times$ iF/0.1). We note that these are multiplicative factors. Thus, exposure estimates are directly proportional or inversely proportional to the selected value. For example, if the size of the exposed population decreases by a factor of 10, exposure estimates per person increase by a factor of 10 and subsequently, the number of chemicals with BQ > 1 increases (38 chemicals with BQ > 1 when applying 10% of the population versus 51 chemicals with BQ > 1 when applying 1% of the population).

Similarly, we assumed that 10% of the mass in solid objects was available for transfer in food/oral contact, dermal contact, and passive indoor emissions due to the lack of information. However, if the percent available in these three use scenarios decreases by a factor of 10, the number of chemicals with BQ > 1 decreases (38 chemicals with BQ > 1 when applying 10% of the TPV versus 32 chemicals with BQ > 1 when applying 1% of the TPV).


DOI: 10.1021/acs.est.5b00498
*Environ. Sci. Technol.* 2015, 49, 6760−6771

As described in the Materials and Methods section, because information about the mass of chemical used in each use scenario (e.g., direct intake, food/dermal contact, direct dermal, dermal contact, etc.) is not available, we allocated 100% of the chemical quantity to each relevant use scenario in this study. It is clear that this is a rather conservative approach, especially for some of the direct exposure pathways where only a small fraction of the total quantity may be allocated. However, if we assumed that only 1% of the total quantity was allocated to the four near-field use scenarios (i.e., direct intake, food/dermal contact, direct dermal, dermal contact), the number of compounds with BQs > 1 is reduced from 38 to 16 compounds (see SI Figure S1). This highlights the importance of obtaining information on the distribution of the TPV between these near-field use scenarios.

We also ran our model assuming that all compounds had all use scenarios and found that our results are also sensitive to the use categorization (38 chemicals with BQ > 1 when applying only relevant use scenarios versus 59 chemicals with BQ > 1 when applying all use scenarios for all compounds, see SI Figure S2). We further ran our model differentiating compounds with and without near-field exposure, but assuming the most conservative, direct intake use scenario for all compounds with near-field exposure use scenarios and found that the number of chemicals with BQ > 1 is the same as when we assumed that all compounds had all use scenarios. These results highlight the importance of using correct and accurate use categorization. Conversely, we ran the model without the more complex fate and transport models, specifically, without applying the near-field (indoor fate and transport), far-field (outdoor fate and transport), and pesticide application models and found that using only simple assumptions for the other exposure scenarios (e.g., 100% of the chemical quantity is taken up by the user for direct intake, 10% of the chemical quantity is taken up by the user for food/oral contact, etc.), would screen 35 chemicals with BQs > 1. This indicates that for these particular sets of compounds, almost all are screened as a result of near-field exposure pathways.

In addition, the selected chemical quantity estimates influence the model results. For example, we selected a maximum value of TPV within a reported range as a conservative approach. However, if half of the minimum reporting value for the smallest category and the geometric mean of the bounding values for other binned categories are selected in iR calculations, the number of chemicals with BQ > 1 is changed from 38 to 33. This highlights that applying more realistic and reliable data on the total mass (or volumes) produced in or imported to the U.S is critical to obtaining confidence in chemical screening and prioritization results.

## DISCUSSION

**Implications.** The framework described in this study provides several implications for HT chemical screening and prioritization. First, we demonstrate that chemicals can be evaluated for potential health concerns by comparing the potential exposure levels (i.e., iR) from our HTS exposure assessment framework and the potential toxicity levels (i.e., OED) from the ToxCast HTS bioactivity data. Second, for chemicals for which chemical quantity (Q) estimates are available in the U.S. national databases, our framework allows us to estimate exposures as a product of Q and iF (i.e., ratio of integrated intake to unit of emission) from exposure models. Third, we demonstrated a HT approach for assigning relevant use scenarios to chemicals based on the U.S. EPA CPCat database and this strategy refines screening results and identifies the needed information for further refinement such as the distribution of chemical quantity among multiple use scenarios. Also, the approach for assigning relevant use scenarios can be applied to a large number of chemicals. Fourth, the selection of maximum iR from multiple exposure models allows for conservative evaluation of chemical risk in the absence of studies that address the differences and variability in model results among various models.

**Limitations.** Limitations on the results of this study arise primarily from the uncertainty and variability of model input parameters. Primary sources of uncertainty in this HT assessment and prioritization results are (1) a wide range of reported TPVs or emission rates, (2) lack of data on the distribution of chemical quantity among relevant use scenarios, (3) ambiguous description of use categories defined in the databases, (4) variability in modeled iR values, (5) uncertainty and variability in measured and predicted chemical properties, and 6) uncertainty in the in vitro bioactivity data and extrapolation to OED values.

*Uncertainty in Chemical Quantity.* The chemical quantity estimates selected to represent chemical emission, application or ingestion rates are derived, for the most part, from the maximum values from a wide range for given production volume bins. In addition, a portion of the chemical may be used as a chemical intermediate which is not released into the environment or a portion may be exported or additional masses may be imported from other countries. Note that these production volume estimates are not averaged values over multiple years, but from a single year, that is, 2006 EPA IUR for industrial chemicals and 2002 CPRI for pesticides. Even such basic source information as production volumes are not available for a large fraction of the study compounds ($N$ = 82) in any national databases. We note that exposure estimates are a direct linear function of the selected mass ($Q$), such that if the selected value for $Q$ over- or underestimates actual chemical use/application quantity by $n$ orders of magnitude, then exposure estimates will have the same magnitude of error.

*Lack of Data on Allocation of Chemical Quantity to Each Use Scenario.* As discussed in the sensitivity analysis, the screening compounds in this modeling framework are very sensitive to our assumption that we allocated 100% of the chemical quantity to each relevant use scenario. For example, three polycyclic aromatic hydrocarbons, benz[a]anthracene, benzo[b]fluoranthene, and naphthalene, have BQ values over 1 for direct intake. These compounds do lead to exposure through direct intake as they are in cigarette smoke. However, exposure is likely overestimated because of the allocation of the entire emission volume to this use scenario. This overestimation was also demonstrated in Figure 2, showing iRs estimated from our exposure models are much higher than those from NHANES biomonitoring data for compounds with multiple use scenarios.

*Potential Errors in Use Classification and Oversimplified Use Information.* There may be errors in chemical use classification (e.g., CPCat database or its interpretation) and thus in the selection of relevant and appropriate exposure models for iF calculations. In this study, we only used a subset of the CPCat terms that were clearly defined and associated with a "likely" use scenario. For example, for chemicals with the CPCat term describing "food packaging", it is likely that chemicals will contact food. However, the CPCat term "plastic"


DOI: 10.1021/acs.est.5b00498
Environ. Sci. Technol. 2015, 49, 6760−6771

is more general and ambiguous than "food packaging", and indicates that a chemical is likely to be passively released indoors via consumer products, and also may "possibly" be used as a food contact material. We classified these ambiguous or general CPCat terms as "possible" use scenarios and ran our HT exposure assessment accounting for these scenarios. The number of chemicals with BQ > 1 increased from 38 to 45 (see Figure S3 of the SI), primarily resulting from "possible" food/oral contact use scenarios.

We note that we additionally identified data sources within CPCat that seemed to have incorrect classifications and suggested a method for screening these databases (see text and Table S3 of SI). We suggest future users of CPCat conduct a similar screening. Even with this preliminary screening, we still have a few chemical/category combinations that do not seem logical. For example, mirex was flagged as having a BQ value greater than 1 through dermal contact. Mirex was classified as having dermal contact because it was included in a database of consumer products. While it may have been in U.S. consumer products in the past, to our knowledge it is no longer used in this country, indicating the importance of continuing to improve available use databases.

In addition, depending on the type of personal care products (e.g., leave-on or wash-off products), dermal exposure may vary on the several orders of magnitude. However, there are issues with confirming that a chemical is used exclusively in either leave-on or wash-off products, e.g., especially when listed in CPCat as a generic "personal care" product. Therefore, future studies need to acquire more refined use information to distinguish the mass of chemical used as a leave-on versus wash-off product and to account for the subsequent differences in exposure. Further efforts to improve the accuracy of high-throughput iR estimates also require obtaining information on the market share of various cosmetics, chemical concentrations in products, the mass of product applied, the surface area of application, and the frequency of use.

*Variability in Modeled iR Values.* The variability of modeled iR values is associated with (a) results obtained from different exposure models with different model formulation and parametrization, (b) limited model applicability to a wide range of chemical properties, and (c) selection of default iF or PiF values in the absence of specific product use types or exposure models. For example, dermal uptake has large differences in model formulation and parametrization between three indoor exposure models. Intake rates between the three indoor models are compared in Figure S4 of the SI. Overall, intake rates per chemical are within 1−2 orders of magnitude between models. The differences in model assumptions, formulation, and parametrization such as differences in the assumed size of the indoor environments (e.g., volume of house), differences in the assumed flooring (e.g., percent that is carpeted), and differences in transport rate estimations between compartments (e.g., deposition rate, ventilation rate, cleaning rate), contribute to the differences between models.

For all outdoor release scenarios (i.e., air, water, soil), total intake rates are well correlated among three far-field exposure models (see Figures S5−S7 of the SI). Nevertheless, there are differences in model predictions among the three models. For example, there are recognized differences in the far-field models in terms of relative volumes of compartments, differences in the number of compartments, flow rates of water and air, treatment of food web bioaccumulation, and various other factors. Specifically, for the outdoor water release scenario, there are outliers for the intake rates, largely due to the different estimates of the bioconcentration factor (BCF) and bioaccumulation factor (BAF) used to compute food ingestion through consumption of fish as shown in Figure S8 of the SI.

For chemicals in personal care products, we used the same default "worst-case" archetype scenario of body lotion for all compounds. However, for chemicals only used in rinse-off products such as shampoo and soap, this approach will overestimate direct dermal exposure. In addition, for dibutyl phthalate, traditionally used in nail care products, there are no available models to estimate exposure (e.g., incidental dermal exposure, nail biting).

*Uncertainty and Variability in Measured and Predicted Chemical Properties.* Approximately 44% of the case-study chemicals have the potential to appreciably dissociate (>10% ionic) in pH ranges from 4 to 10. We note that for the ionized form of the molecule, the physicochemical properties are different from those of their corresponding neutral form. Due to a paucity of information for ionogenic organic chemicals and current limitations in exposure models to treat these chemicals, exposures were estimated based on only the neutral properties of these chemicals. This simplifying assumption has been adopted by other high-throughput exposure model applications[15,21,23,24] and the implications of these assumptions are a source of uncertainty that requires further measurements for these types of chemicals to improve exposure models.

*Uncertainty in $C_{ss}$ and OED Estimations and in Vitro Bioactivity Assessments.* The approach utilized to estimate the $C_{ss}$ and OEDs was designed to maintain a reasonable degree of compatibility with HT toxicity testing assessments conducted to inform testing prioritization strategies.[8,9] Two critical determinants of chemical disposition in the body−hepatic metabolic clearance and plasma protein binding−were experimentally measured, whereas a set of simplifying conservative assumptions was employed for other chemical pharmacokinetic parameters. For instance, 100% absorption was assumed, and no additional routes of chemical clearance were considered (i.e., biliary clearance, extrahepatic metabolism).[9,11,59] When they are not valid these assumptions will ultimately lead to an underestimation of clearance and subsequent overprediction of $C_{ss}$, which would ultimately be protective of human health.

Assessment of the IVIVE modeling approach used here was conducted in previous studies[11,29] by comparing the IVIVE-derived $C_{ss}$ values against the $C_{ss}$ values derived from previously published human in vivo pharmacokinetic studies for 29 environmental chemicals. The IVIVE values predicted the in vivo values to within 20-fold for 80% of the chemicals.[11,59] Overprediction of $C_{55}$ prevailed, and nearly all of the values that were under-predicted in this approach were only under-predicted by 2- to 5-fold. The exceptions to this were perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), believed to undergo the rare process of active renal resorption.[9,60] Despite the limited in vivo data to assess the IVIVE model, the findings indicate that this approach provides reasonable predictions that, when they err, do so in a conservative manner.

The OEDs, used to represent a measure of bioactivity, are derived by dividing the ToxCast assay-specific $AC_{50}$ by the chemical-specific $C_{ss}$ values. The bioactivities measured in the ToxCast assays span a range of biological targets including cytochrome P450 metabolism, nuclear receptor activation, mitochondrial effects and anti-inflammatory activities. A


DOI: 10.1021/acs.est.5b00498
Environ. Sci. Technol. 2015, 49, 6760−6771

significant debate has emerged about the utility of these assays in predicting in vivo hazard.[61−65] Alternately, one recent effort considered the utility of the bioactivity measures to serve as surrogates for points of departure rather than identifying specific adverse effects. Rat in vitro chemical pharmacokinetics were measured to derive rat OEDs for the ToxCast data. When the minimum OEDs were compared to the lowest low effect level doses (LELs) from rat in vivo studies, the rat OEDs were lower for 94% of the 57 chemicals assessed and on average 60-fold lower than the in vivo LELs.[65] Further, 60% of the minimum in vivo LELs and the minimum OEDs were within 2 orders of magnitude of each other. In the absence of causative information linking in vitro activities with in vivo effects, this dose concordance suggests that the most sensitive OEDs for each chemical can be used as a reasonably conservative surrogate for an in vivo point of departure.

**Outlook.** Momentum has grown worldwide to assess the utility of HT and in vitro screening approaches in toxicity testing since the release of the National Research Council (NRC) Report "Toxicity Testing in the 21st Century".[66] Equally, if not more important, is the requirement to obtain screening-level exposure estimates to combine with toxicity testing to inform risk-based decisions currently faced by the EPA and other international regulatory agencies.[4,12] The work presented in this paper outlines one such approach, designed to be modular and transparent to allow application of refined models and data when available. Importantly, it has identified key gaps in data availability and curation and in modeling tools that need to be addressed to allow improvement in future efforts. Addressing uncertainty across these relevant areas will be critical to inform a more robust tool for exposure prediction and, ultimately, risk-based prioritization.

As noted in the Results and Discussion sections, for more refined HT screening and prioritization, future studies need to obtain correct and accurate use categorization and data on the distribution of chemical mass to each use scenario. Also, future studies need to use more refined dermal exposure models to account for the difference in dermal exposure between leave-on and wash-off consumer products. We did not include uncertainty analysis; however, the propagation of uncertainty in chemical properties (measured or predicted) should be included in exposure calculations[15] and in future applications of the ExpoDat framework.

## ■ ASSOCIATED CONTENT

### Supporting Information

The method on how CPCat databases were checked and cleaned is described in the SI. Additional details of the dermal uptake model are provided in the SI. Further information on chemical properties estimation and percent mode-of-entry is also summarized in the SI. There are seven tables and eight figures in the SI. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.5b00498.

## ■ AUTHOR INFORMATION

### Corresponding Author

*Phone: 1.949.648.1614; fax: 1.530.752.5300; e-mail: hmshin@ucdavis.edu.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This research was funded by the Long-Range Research Initiative of the American Chemistry Council, who also provided the catalyst to develop the framework, especially Brenda Barry, Annette Guiseppi-Elie, and Larry Reiter. Peter Fantke was additionally funded by the Marie Curie project Quan-Tox (grant agreement no. 631910) funded by the European Commission under the Seventh Framework Programme. We thank Richard Judson and Kathie Dionisio, who generously provided data for chemical use categories.

## ■ REFERENCES

(1) Anastas, P.; Teichman, K.; Hubal, E. C. Ensuring the safety of chemicals. *J. Exposure Sci. Environ. Epidemiol.* **2010**, *20* (5), 395−396.

(2) Judson, R.; Richard, A.; Dix, D. J.; Houck, K.; Martin, M.; Kavlock, R.; Dellarco, V.; Henry, T.; Holderman, T.; Sayre, P.; Tan, S.; Carpenter, T.; Smith, E. The toxicity data landscape for environmental chemicals. *Environ. Health Perspect.* **2009**, *117* (5), 685−695.

(3) Muir, D. C. G.; Howard, P. H. Are there other persistent organic pollutants? A challenge for environmental chemists. *Environ. Sci. Technol.* **2006**, *40* (23), 7157−7166.

(4) Committee on Toxicity Testing and Assessment of Environmental Agents, National Research Council. *Exposure Science in the 21st Century; A Vision and a Strategy*; The Nationial Academies Press: Washington, D.C., 2007.

(5) Judson, R. S.; Houck, K. A.; Kavlock, R. J.; Knudsen, T. B.; Martin, M. T.; Mortensen, H. M.; Reif, D. M.; Rotroff, D. M.; Shah, I.; Richard, A. M.; Dix, D. J. In vitro screening of environmental chemicals for targeted testing prioritization: The ToxCast Project. *Environm. Health Perspect.* **2010**, *118* (4), 485−492.

(6) Judson, R. S.; Kavlock, R. J.; Setzer, R. W.; Hubal, E. A. C.; Martin, M. T.; Knudsen, T. B.; Houck, K. A.; Thomas, R. S.; Wetmore, B. A.; Dix, D. J. Estimating toxicity-related biological pathway altering doses for high-throughput chemical risk assessment. *Chem. Res. Toxicol.* **2011**, *24* (4), 451−462.

(7) Knight, A. W.; Little, S.; Houck, K.; Dix, D.; Judson, R.; Richard, A.; McCarroll, N.; Akerman, G.; Yang, C.; Birrell, L.; Walmsley, R. M. Evaluation of high-throughput genotoxicity assays used in profiling the US EPA ToxCast (TM) chemicals. *Regul. Toxicol. Pharmacol.* **2009**, *55* (2), 188−199.

(8) Rotroff, D. M.; Wetmore, B. A.; Dix, D. J.; Ferguson, S. S.; Clewell, H. J.; Houck, K. A.; LeCluyse, E. L.; Andersen, M. E.; Judson, R. S.; Smith, C. M.; Sochaski, M. A.; Kavlock, R. J.; Boellmann, F.; Martin, M. T.; Reif, D. M.; Wambaugh, J. F.; Thomas, R. S. Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening. *Toxicol. Sci.* **2010**, *117* (2), 348−358.

(9) Wetmore, B. A.; Wambaugh, J. F.; Ferguson, S. S.; Sochaski, M. A.; Rotroff, D. M.; Freeman, K.; Clewell, H. J., III; Dix, D. J.; Andersen, M. E.; Houck, K. A.; Allen, B.; Judson, R. S.; Singh, R.; Kavlock, R. J.; Richard, A. M.; Thomas, R. S. Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment. *Toxicol. Sci.* **2012**, *125* (1), 157−174.

(10) Dix, D. J.; Houck, K. A.; Martin, M. T.; Richard, A. M.; Setzer, R. W.; Kavlock, R. J. The ToxCast program for prioritizing toxicity testing of environmental chemicals. *Toxicol. Sci.* **2007**, *95* (1), 5−12.

(11) Wetmore, B. A.; Wambaugh, J. F.; Sochaski, M. A.; Houck, K. A.; Ferguson, S. S.; Setzer, R. W.; Allen, B.; Cantwell, K.; Judson, R. S.; Clewell, H. J.; LeCluyse, E.; Thomas, R. S.; Andersen, M. E. Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing, submitted for publication.

(12) Cohen Hubal, E. A.; Richard, A.; Aylward, L.; Edwards, S.; Gallagher, J.; Goldsmith, M.-R.; Isukapalli, S.; Tornero-Velez, R.; Weber, E.; Kavlock, R. Advancing exposure characterization for chemical evaluation and risk assessment. *J. Toxicol. Environ. Health, Part B* **2010**, *13* (2−4), 299−313.



DOI: 10.1021/acs.est.5b00498
*Environ. Sci. Technol.* 2015, 49, 6760−6771

(13) Egeghy, P. P.; Vallero, D. A.; Hubal, E. A. C. Exposure-based prioritization of chemicals for risk assessment. *Environ. Sci. Policy* **2011**, *14* (8), 950−964.
(14) Jayjock, M. A.; Chaisson, C. F.; Franklin, C. A.; Arnold, S.; Price, P. S. Using publicly available information to create exposure and risk-based ranking of chemicals used in the workplace and consumer products. *J. Exposure Sci. Environ. Epidemiol.* **2009**, *19* (5), 515−524.
(15) Arnot, J. A.; Brown, T. N.; Wania, F.; Breivik, K.; McLachlan, M. S. Prioritizing chemicals and data requirements for screening-level exposure and risk assessment. *Environ. Health Perspect.* **2012**, *120* (11), 1565−1570.
(16) Little, J. C.; Weschler, C. J.; Nazaroff, W. W.; Liu, Z.; Hubal, E. A. C. Rapid methods to estimate potential exposure to semivolatile organic compounds in the indoor environment. *Environ. Sci. Technol.* **2012**, *46* (20), 11171−11178.
(17) Shin, H.-M.; McKone, T. E.; Bennett, D. H. Intake fraction for the indoor environment: A tool for prioritizing indoor chemical sources. *Environ. Sci. Technol.* **2012**, *46* (18), 10063−10072.
(18) Wenger, Y.; Li, D.; Jolliet, O. Indoor intake fraction considering surface sorption of air organic compounds for life cycle assessment. *Int. J. Life Cycle Ass.* **2012**, *17* (7), 919−931.
(19) Fantke, P.; Juraske, R.; Anton, A.; Friedrich, R.; Jolliet, O. Dynamic multicrop model to characterize impacts of pesticides in food. *Environ. Sci. Technol.* **2011**, *45* (20), 8842−8849.
(20) Mitchell, J.; Arnot, J. A.; Jolliet, O.; Georgopoulos, P. G.; Isukapalli, S.; Dasgupta, S.; Pandian, M.; Wambaugh, J.; Egeghy, P.; Hubal, E. A. C.; Vallero, D. A. Comparison of modeling approaches to prioritize chemicals based on estimates of exposure and exposure potential. *Sci. Total Environ.* **2013**, *458*, 555−567.
(21) Isaacs, K. K.; Glen, W. G.; Egeghy, P.; Goldsmith, M.-R.; Smith, L.; Vallero, D.; Brooks, R.; Grulke, C. M.; Özkaynak, H. SHEDS-HT: An integrated probabilistic exposure model for prioritizing exposures to chemicals with near-field and dietary sources. *Environ. Sci. Technol.* **2014**, *48*, 12750−12759.
(22) Zhang, X.; Arnot, J. A.; Wania, F. Model for screening-level assessment of near-field human exposure to neutral organic chemicals released indoors. *Environ. Sci. Technol.* **2014**, *48* (20), 12312−12319.
(23) Wambaugh, J. F.; Setzer, R. W.; Reif, D. M.; Gangwal, S.; Mitchell-Blackwood, J.; Arnot, J. A.; Joliet, O.; Frame, A.; Rabinowitz, J.; Knudsen, T. B.; Judson, R. S.; Egeghy, P.; Vallero, D.; Hubal, E. A. C. High-throughput models for exposure-based chemical prioritization in the Expo Cast project. *Environ. Sci. Technol.* **2013**, *47* (15), 8479−8488.
(24) Wambaugh, J. F.; Wang, A.; Dionisio, K. L.; Frame, A.; Egeghy, P.; Judson, R.; Setzer, R. W. High throughput heuristics for prioritizing human exposure to environmental chemicals. *Environ. Sci. Technol.* **2014**, *48* (21), 12760−12767.
(25) Breivik, K.; Arnot, J. A.; Brown, T. N.; McLachlan, M. S.; Wania, F. Screening organic chemicals in commerce for emissions in the context of environmental and human exposure. *J. Environ. Monit.* **2012**, *14* (8), 2028−2037.
(26) Breivik, K.; Alcock, R. Emission impossible? - The challenge of quantifying sources and releases of POPs into the environment. *Environ. Int.* **2002**, *28* (3), 137−138.
(27) Shin, H.-M.; McKone, T. E.; Bennett, D. H. Evaluating environmental modeling and sampling data with biomarker data to identify sources and routes of exposure. *Atmos. Environ.* **2013**, *69*, 148−155.
(28) Shin, H.-M.; McKone, T. E.; Bennett, D. H. Attributing population-scale human exposure to various source categories: Merging exposure models and biomonitoring data. *Environ. Int.* **2014**, *70*, 183−191.
(29) Bennett, D. H.; McKone, T. E.; Evans, J. S.; Nazaroff, W. W.; Margni, M. D.; Jolliet, O.; Smith, K. R. Defining intake fraction. *Environ. Sci. Technol.* **2002**, *36* (9), 206A−211A.
(30) Goldsmith, M. R.; Grulke, C. M.; Brooks, R. D.; Transue, T. R.; Tan, Y. M.; Frame, A.; Egeghy, P. P.; Edwards, R.; Chang, D. T.; Tornero-Velez, R.; Isaacs, K.; Wang, A.; Johnson, J.; Holm, K.; Reich, M.; Mitchell, J.; Vallero, D. A.; Phillips, L.; Phillips, M.; Wambaugh, J. F.; Judson, R. S.; Buckley, T. J.; Dary, C. C. Development of a consumer product ingredient database for chemical exposure screening and prioritization. *Food Chem. Toxicol.* **2014**, *65*, 269−279.
(31) U.S. EPA. Chemical and Product Categories (CPCat) database, 2008. 2014. http://actor.epa.gov/cpcat/faces/home.xhtml (accessed December 2014).
(32) U.S. EPA. 2006 Inventory Update Reporting: Data Summary, Washington, DC, 2008. http://www.epa.gov/cdr/pubs/2006_data_summary.pdf accessed December 2014).
(33) U.S. EPA. 2002 National-Scale Air Toxics Assessment, Washington, DC, 2009.A http://www.epa.gov/nata2002/ (accessed December 2014).
(34) U.S. EPA. Toxics Release Inventory (TRI) Program, Washington, DC, 2014. http://www2.epa.gov/toxics-release-inventory-tri-program (accessed December 2014).
(35) U.S. EPA. National Emissions Inventory, Washington, DC, 2014. http://www.epa.gov/ttnchie1/trends/ (accessed December 2014).
(36) U.S. EPA. Estimation Programs Interface Suite for Microsoft® Windows, v 4.10, Washington, DC, 2014. http://www.epa.gov/oppt/exposure/pubs/episuite.htm (accessed December 2014).
(37) Jolliet, O.; Ernstoff, A.; Csiszar, S. A.; Fantke, P. Defining the product intake fraction to quantify exposure to consumer products. *Environ. Sci. Technol.*, in press.
(38) Loretz, L. J.; Api, A. M.; Barraj, L. M.; Burdick, J.; Dressler, W. E.; Gettings, S. D.; Han Hsu, H.; Pan, Y. H. L.; Re, T. A.; Renskers, K. J.; et al. Exposure data for cosmetic products: Lipstick, body lotion, and face cream. *Food Chem. Toxicol.* **2005**, *43* (2), 279−291.
(39) U.S. EPA. Exposure Factors Handbook, Washington, DC, 2011. http://www.epa.gov/ncea/efh/pdfs/efh-complete.pdf (accessed December 2014).
(40) ten Berge, W. A simple dermal absorption model: Derivation and application. *Chemosphere* **2009**, *75* (11), 1440−1445.
(41) Bennett, D. H.; Furtaw, E. J. Fugacity-based indoor residential pesticide fate model. *Environ. Sci. Technol.* **2004**, *38* (7), 2142−2152.
(42) Shin, H.-M.; McKone, T. E.; Nishioka, M. G.; Fallin, M. D.; Croen, L. A.; Hertz-Picciotto, I.; Newschaffer, C. J.; Bennett, D. H. Determining source strength of semivolatile organic compounds using measured concentrations in indoor dust. *Indoor Air* **2014**, *24* (3), 260−271.
(43) McKone T. E. *CalTOX, A Multimedia Total-Exposure Model for Hazardous Waste Sites*; Livermore, CA, 1993.
(44) Rosenbaum, R. K.; Bachmann, T. M.; Gold, L. S.; Huijbregts, M. A. J.; Jolliet, O.; Juraske, R.; Koehler, A.; Larsen, H. F.; MacLeod, M.; Margni, M.; McKone, T. E.; Payet, J.; Schuhmacher, M.; van de Meent, D.; Hauschild, M. Z. USEtox-the UNEP-SETAC toxicity model: Recommended characterisation factors for human toxicity and freshwater ecotoxicity in life cycle impact assessment. *Int. J. Life Cycle Assess.* **2008**, *13* (7), 532−546.
(45) Arnot, J. A.; Mackay, D. Policies for chemical hazard and risk priority setting: Can persistence, bioaccumulation, toxicity, and quantity information be combined? *Environ. Sci. Technol.* **2008**, *42* (13), 4648−4654.
(46) Fantke, P.; Jolliet, O. Life cycle human health impacts of 875 pesticides. *Int. J. Life Cycle Assess.* **2015**, in press.
(47) Fantke, P.; Wieland, P.; Juraske, R.; Shaddick, G.; Sevigné, E.; Friedrich, R.; Jolliet, O. Parameterization models for pesticide exposure via crop consumption. *Environ. Sci. Technol.* **2012**, *46* (23), 12864−12872.
(48) Huang, R.; Xia, M.; Cho, M. H.; Sakamuru, S.; Shinn, P.; Houck, K. A.; Dix, D. J.; Judson, R. S.; Witt, K. L.; Kavlock, R. J.; Tice, R. R.; Austin, C. P. Chemical genomics profiling of environmental chemical modulation of human nuclear receptors. *Environ. Health Perspect.* **2011**, *119* (8), 1142−8.
(49) Knudsen, T. B.; Houck, K. A.; Sipes, N. S.; Singh, A. V.; Judson, R. S.; Martin, M. T.; Weissman, A.; Kleinstreuer, N. C.; Mortensen, H. M.; Reif, D. M.; Rabinowitz, J. R.; Setzer, R. W.; Richard, A. M.; Dix, D. J.; Kavlock, R. J. Activity profiles of 309 ToxCast chemicals


DOI: 10.1021/acs.est.5b00498
*Environ. Sci. Technol.* 2015, 49, 6760−6771

evaluated across 292 biochemical targets. *Toxicology* **2011**, *282* (1−2), 1−15.
(50) Martin, M. T.; Dix, D. J.; Judson, R. S.; Kavlock, R. J.; Reif, D. M.; Richard, A. M.; Rotroff, D. M.; Romanov, S.; Medvedev, A.; Poltoratskaya, N.; Gambarian, M.; Moeser, M.; Makarov, S. S.; Houck, K. A. Impact of environmental chemicals on key transcription regulators and correlation to toxicity end points within EPA's ToxCast program. *Chem. Res. Toxicol.* **2010**, *23* (3), 578−90.
(51) Houck, K. A.; Dix, D. J.; Judson, R. S.; Kavlock, R. J.; Yang, J.; Berg, E. L. Profiling bioactivity of the ToxCast chemical library using BioMAP primary human cell systems. *J. Biomol. Screen.* **2009**, *14* (9), 1054−66.
(52) Rotroff, D. M.; Beam, A. L.; Dix, D. J.; Farmer, A.; Freeman, K. M.; Houck, K. A.; Judson, R. S.; LeCluyse, E. L.; Martin, M. T.; Reif, D. M.; Ferguson, S. S. Xenobiotic-metabolizing enzyme and transporter gene expression in primary cultures of human hepatocytes modulated by ToxCast chemicals. *J. Toxicol. Environ. Health, Part B* **2010**, *13* (2−4), 329−46.
(53) Kleinstreuer, N. C.; Yang, J.; Berg, E. L.; Knudsen, T. B.; Richard, A. M.; Martin, M. T.; Reif, D. M.; Judson, R. S.; Polokoff, M.; Dix, D. J.; Kavlock, R. J.; Houck, K. A. Phenotypic screening of the ToxCast chemical library to classify toxic and therapeutic mechanisms. *Nat. Biotechnol.* **2014**, *32* (6), 583−591.
(54) Rotroff, D. M.; Dix, D. J.; Houck, K. A.; Kavlock, R. J.; Knudsen, T. B.; Martin, M. T.; Reif, D. M.; Richard, A. M.; Sipes, N. S.; Abassi, Y. A.; Jin, C.; Stampfl, M.; Judson, R. S. Real-time growth kinetics measuring hormone mimicry for ToxCast chemicals in T-47D human ductal carcinoma cells. *Chem. Res. Toxicol.* **2013**, *26* (7), 1097−1107.
(55) Jamei, M.; Marciniak, S.; Feng, K.; Barnett, A.; Tucker, G.; Rostami-Hodjegan, A. The Simcyp((R)) population-based ADME simulator. *Expert Opin. Drug Metab. Toxicol.* **2009**, *5* (2), 211−223.
(56) Tan, Y. M.; Liao, K. H.; Clewell, H. J., 3rd Reverse dosimetry: Interpreting trihalomethanes biomonitoring data using physiologically based pharmacokinetic modeling. *J. Expo. Sci. Environ. Epidemiol.* **2007**, *17* (7), 591−603.
(57) Centers for Disease Control and Prevention (CDC). Third National Report on Human Exposure to Environmental Chemicals, Atlanta, GA, 2005. http://www.clu-in.org/download/contaminantfocus/pcb/third-report.pdf (accessed January 2015).
(58) Centers for Disease Control and Prevention (CDC). Fourth National Report on Human Exposure to Environmental Chemicals, Atlanta, GA, 2009. http://www.cdc.gov/exposurereport/pdf/fourthreport.pdf (accessed January 2015).
(59) Wetmore, B. A. Quantitative in vitro to in vivo extrapolation in a high-throughput environment. *Toxicology* **2014**, DOI: 10.1016/j.tox.2014.05.012.
(60) Loccisano, A. E.; Campbell, J. L., Jr.; Andersen, M. E.; Clewell, H. J., III. Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model. *Regul. Toxicol. Pharmacol.* **2011**, *59* (1), 157−175.
(61) Kleinstreuer, N. C.; Judson, R. S.; Reif, D. M.; Sipes, N. S.; Singh, A. V.; Chandler, K. J.; DeWoskin, R.; Dix, D. J.; Kavlock, R. J.; Knudsen, T. B. Environmental impact on vascular development predicted by high-throughput screening. *Environ. Health Perspect.* **2011**, *119* (11), 1596−1603.
(62) Martin, M. T.; Knudsen, T. B.; Reif, D. M.; Houck, K. A.; Judson, R. S.; Kavlock, R. J.; Dix, D. J. Predictive model of rat reproductive toxicity from ToxCast high throughput screening. *Biol. Reprod.* **2011**, *85* (2), 327−339.
(63) Sipes, N. S.; Martin, M. T.; Reif, D. M.; Kleinstreuer, N. C.; Judson, R. S.; Singh, A. V.; Chandler, K. J.; Dix, D. J.; Kavlock, R. J.; Knudsen, T. B. Predictive models of prenatal developmental toxicity from ToxCast high-throughput screening data. *Toxicol. Sci.* **2011**, *124* (1), 109−127.
(64) Thomas, R. S.; Black, M. B.; Li, L.; Healy, E.; Chu, T.-M.; Bao, W.; Andersen, M. E.; Wolfinger, R. D. A comprehensive statistical analysis of predicting in vivo hazard using high-throughput in vitro screening. *Toxicol. Sci.* **2012**, *128* (2), 398−417.
(65) Wetmore, B. A.; Wambaugh, J. F.; Ferguson, S. S.; Li, L.; Clewell, H. J., III; Judson, R. S.; Freeman, K.; Bao, W.; Sochaski, M. A.; Chu, T.-M.; Black, M. B.; Healy, E.; Allen, B.; Andersen, M. E.; Wolfinger, R. D.; Thomas, R. S. Relative impact of incorporating pharmacokinetics on predicting in vivo hazard and mode of action from high-throughput in vitro toxicity assays. *Toxicol. Sci.* **2013**, *132* (2), 327−346.
(66) Committee on Toxicity Testing and Assessment of Environmental Agents, National Research Council. *Toxicity Testing in the 21st Century; A Vision and a Strategy*; The National Academies Press: Washington, D.C., 2007.


DOI: 10.1021/acs.est.5b00498
*Environ. Sci. Technol.* 2015, 49, 6760−6771