

# Flagging health risks of chemicals by combining in vitro bioactivity data with environmental and consumer product exposure modeling

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# Flagging health risks of chemicals by combining *in vitro* bioactivity data with environmental and consumer product exposure modeling

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## 1. Introduction

This work presents a framework to use *in vitro* bioactivity data in conjunction with environmental and consumer product exposure models in order to flag chemical exposures of potential risk.

To screen 229 chemicals of concern provided by the US EPA, we (1) identify exposure pathways, (2) model population-scale intake fractions and exposure, and (3) compare modeled intakes with *in vitro* bioactivity data to flag if exposure exceeds the minimum bioactive dose and potentially poses a public health risk.

## 2. Materials and methods

To model relevant exposure pathways for each chemical according to its likely use, we refined thousands of diverse chemical characterizations in the US EPA ACToR database (http://epa.gov/actor/) so that chemicals are allocated to exposure categories that indicate a model strategy. The refined exposure categories include: direct intakes (e.g. food), dermal application (e.g. cosmetics), pesticides (e.g. ingestion of residues on produce), and indoor (e.g. in-home use products) and environmental emissions. Exposure category results were also cross-checked with lists such as US government approved food additives.

Three exposure models (USEtox, CalTOX, RAIDAR) were independently evaluated and compared. Modeled outdoor and indoor intake fractions (mass taken in per mass emitted) as well as product intake fractions (chemical mass taken in per mass in product) were conservatively translated into modeled daily doses MDDs (mg/kg/day), assuming 100% production volume emitted or used in each type of consumer product.

To identify the biological dose response for each of the 229 chemicals, *in vitro* bioactivity assays performed within the ToxCast effort and were used in conjunction with estimated clearance rates [1] to back calculate the daily human oral equivalent dose OEDs (mg/kg/day). OEDs were then compared to MDDs in an effort to flag chemical exposures of concern as input to higher tier risk assessments.

## 3. Results and discussion

Most chemicals matched several exposure categories. Modeled intakes per category varied greatly (Table 1) due to chemical behavior (i.e. physicochemical properties), as well as production volume and emission estimates (data with needed improvement). Distinct exposure models tended to predict similar trends (e.g. inhalation exposure correlating with volatility) running parallel with the 1:1 line, and were within two orders of magnitude for most chemicals (Figure 1).

***Table 1: Exposure categories and number of chemical matches and corresponding modeled exposure estimates***

| Exposure category | No. of chemicals | Min intake [mg/kg/day] | Max intake [mg/kg/day] |
|---|---|---|---|
| Direct intakes | 80 | 0.057 | 2600 |
| Dermal application | 100 | $1.7 \times 10^{-4}$ | 740 |
| Indoor emission | 109 | $1.1 \times 10^{-7}$ | 82 |
| Pesticides | 125 | $2.6 \times 10^{-10}$ | 49 |
| Environmental emission | 229 | $1.7 \times 10^{-8}$ | 0.34 |

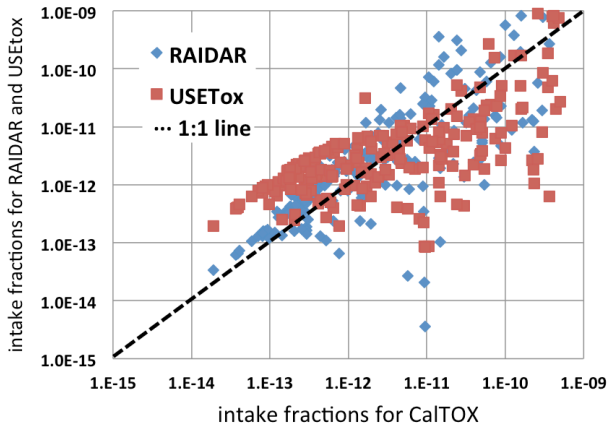


***Figure 1: intake fraction comparisons due to emission to fresh water from CalTOX, RAIDAR, and USEtox models***

As expected, direct intake and dermal application resulted in intake doses generally several orders of magnitude higher than intake resulting from environmental emissions. A priority to reduce uncertainty on exposure estimates is to collect improved data on respective chemical use in various consumer products.

Figure 2 displays the maximum MDD estimate for each chemical compared to the minimum oral equivalent dose (OED) bioactivity data. In all, we flagged 66 chemicals with a maximum MDD:OED ratio greater than or equal to one as potential public health risks. These cases were predominantly due to direct intake and dermal application of chemicals, however there were also several environmental and pesticide exposures of potential concern. We recommed that these chemical exposures be further evaluated in risk assessments.

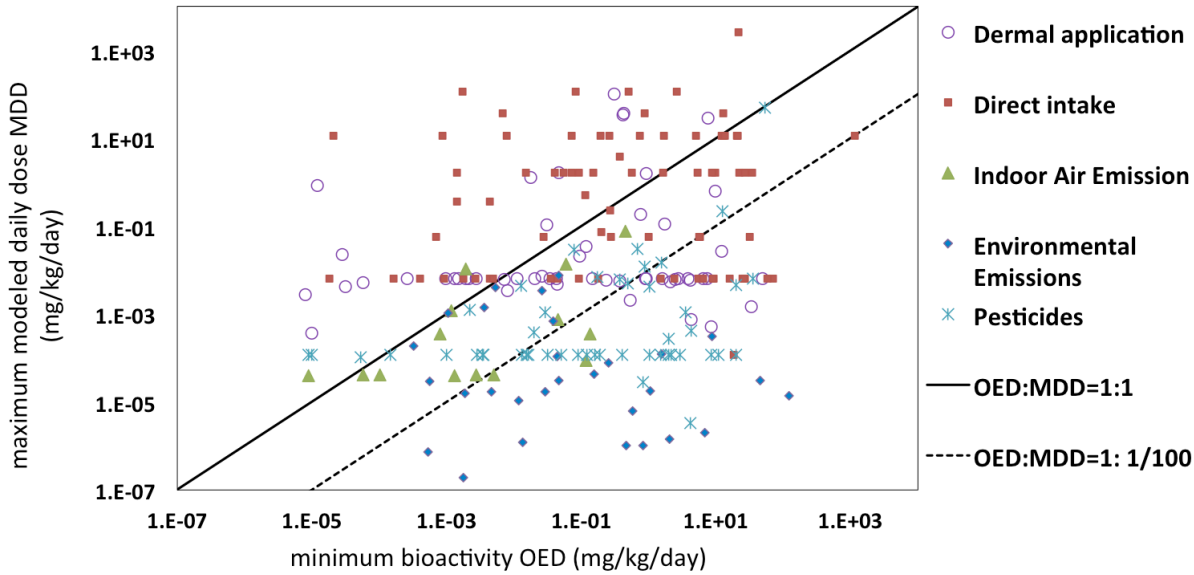


***Figure 2: minimum bioactivity oral equivalent doses versus maximum modeled daily doses***

## 4. Conclusions

Using *in vitro* bioactivity data combined with model estimates for exposure may be a useful tool for high throughput risk assessments and screening of chemicals. Using conservative approaches we found 66 out of 229 chemicals with at least one exposure category resulting in estimated intake greater than the minimum oral dose equivalent calculated from *in vitro* data. These exposures require more formal risk assessments. Improving input data and analysis of model variation could decrease uncertainty on model results.

References

[1] Wetmore, Barbara A., John F. Wambaugh, et al. 2012. Integration of Dosimetry, Exposure, and High-Throughput Screening Data in Chemical Toxicity Assessment."Toxicological Sciences 125(1):157–174.

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