The SFA Risk Thermometer and integration of effect data to advance chemical risk charaterization

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Background

Developments motivated by a need for more comparative risk assessment at the agency

- Questions from SFA management on which hazard to focus on
- EU requirements regarding a risk-based food control
  - Distribute resources/samples over foods-chemical combinations based on risk
- Support risk communication

General reflection

- Health-based guidance values for chemicals often exceeded - approaches that can grade risk/health concern may be helpful

Overview of presentation

- The Risk Thermometer - *A Tool for Risk Comparison*, SFA Report 8, 2015

  (Salomon Sand, Roland Lindqvist, Hanna Eneroth, Leif Busk, Rickard Bjerselius, Jorun Färnstrand)

- Dose-Related Severity Sequence, and Risk-Based Integration, of Chemically Induced Health Effects. Toxicol. Sci. 165, 74-89, 2018

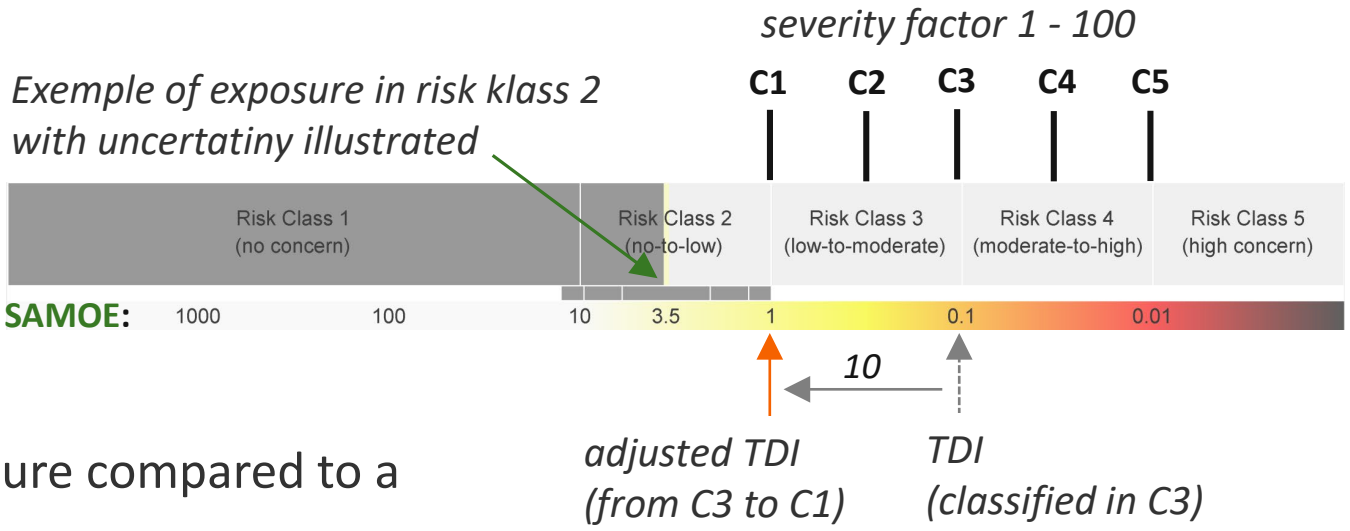
  (Salomon Sand, Roland Lindqvist, Dietrich von Rosen, Nils-Gunnar Ilbäck)

- A Novel Method for Combining Outcomes with Different Severities or Gene-Level Classifications, ALTEX, accepted, 2021

  (Salomon Sand)

SFA Risk Thermometer

Swedish Food Agency report 8, 2015



Starting point

- Traditional approach where estimated exposure compared to a Tolerable Daily Intake (TDI) or similar
  - MOE = TDI / exposure

- Severity-adjustment of TDI to reflect a “mild” effect
- Guided by 5-graded effect classification scheme (C1 to C5)
  - **SAMOE**: adjusted TDI / exposure

- Represents a broader take on “the dose makes the poison”, but..
- Size of adjustment factor (1 to 100) based on risk management

SFA Risk Thermometer

Swedish Food Agency report 8, 2015

- Results have mainly be used to support the SFA food control
- Results based on data from Swedish Market Basket survey 2015
  - Dioxins and certain metaller ranked the highest (risk class 3)
- Currently, the Risk Thermometer is part of a new scoring approach used for determination of control program for contaminants
  - 152 regulated food products covering about 26 chemicals
- Consumer oriented Risk Thermometer on SFA webpage:

- Ongoing project regarding chemicals in drinking water lead by SLU

Chemical	SAMOE	Risk Class
dioxin	0.14	3
Al	0.17	3
Hg	0.17	3
Pb	0.22	3
Ni	0.45	3
Cd	0.63	3
iAs	1.3	2
3-MCPD	1.6	2
Deoxynivalenol	2.6	2
zearalenone	2.6	2
T2 and H2	3.1	2
glycidol	5.2	2
BDE-99	5.5	2
I-PFOS	7.0	2
fumonisins	8.3	2
I-PFOA	8.9	2
ochratoxin a	15	1
BDE-153	19	1
ndl-PCB	24	1
BDE-47	29	1
PAH4	33	1
BaP	34	1
HCB	74	1
Cu	88	1
Cr III	530	1
DDT	930	1
HBCD	982	1
CP (sum)	2436	1
TCDPP	4743	1
Ag	6182	1
TCEP	13126	1
TPHP	26042	1
BDE-209	26443	1
TCPP	33731	1

Development for traditional data

Sand et al 2018, Tox Sci

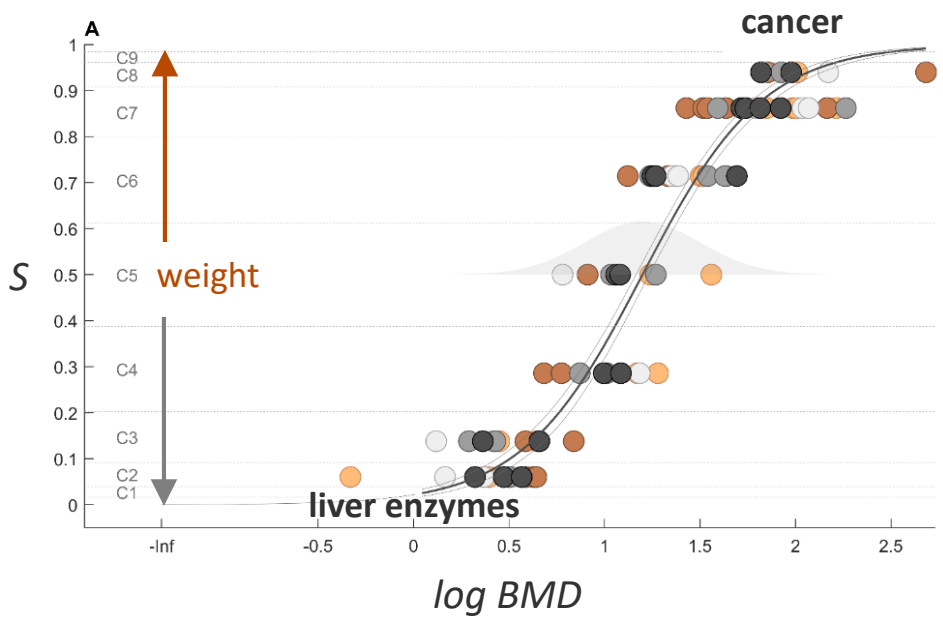
- Joint consideration of data on multiple effects
  - Advancing the “hazard side” of the Risk Thermometer

- Case study on dioxin-like chemicals and their mixtures
  - Benchmark doses (*BMD*s) estimated for liver effects
  - *BMD*: dose that corresponds to small (10%) response change

- *BMD*s are ranked on a 9-graded severity scale (C1 to C9)
- C1 to C9 mapped to quantitative scale, S = 0 to S = 1

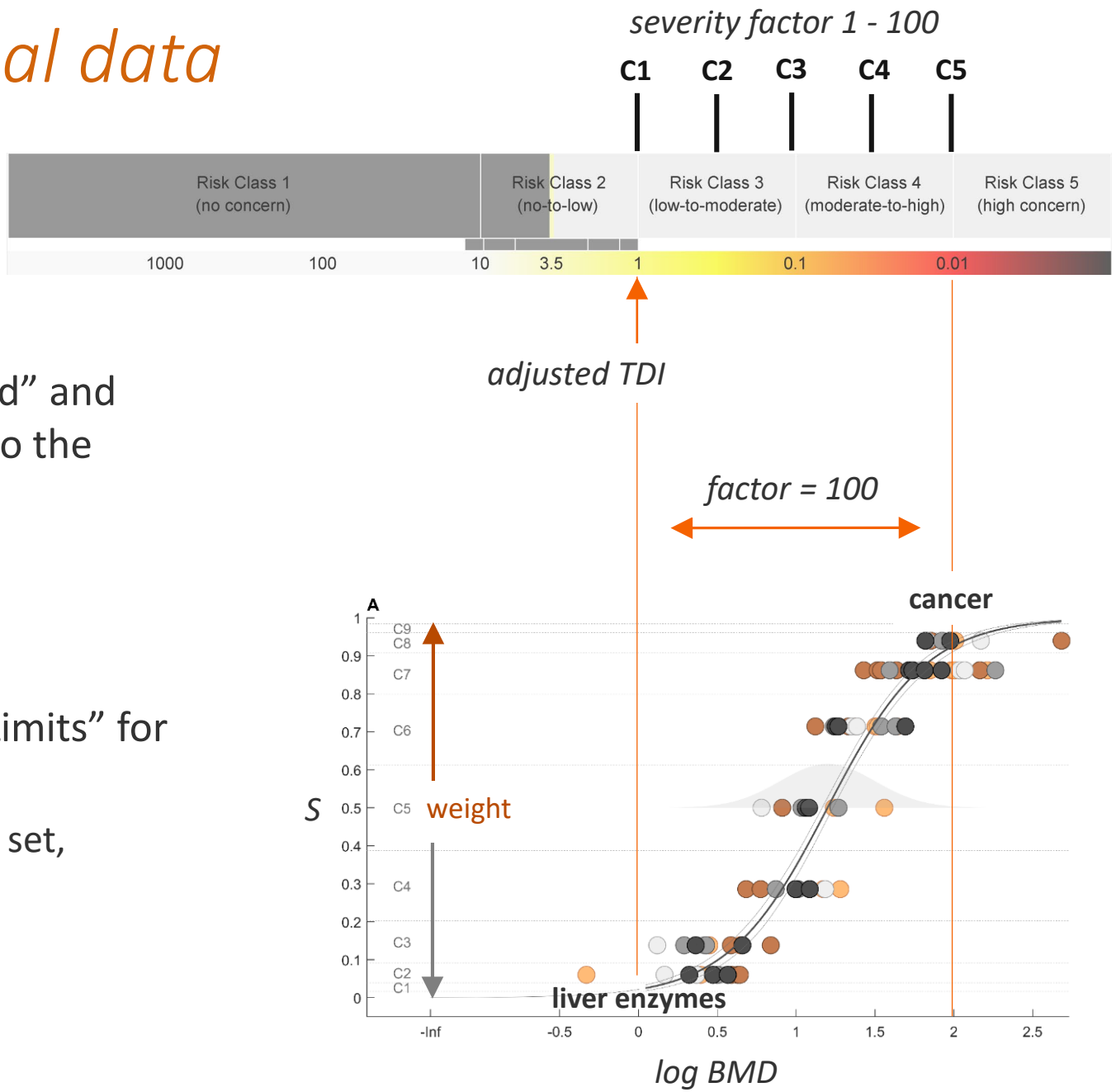
- Mapping can be modified by attached weight function

Model based on data on rodents from the US NTP: TCDD, PecDF, PCB126, 2- and 3-component mixtures



Development for traditional data

Sand et al 2018, Tox Sci



Sand et al 2018 vs. Risk Thermometer

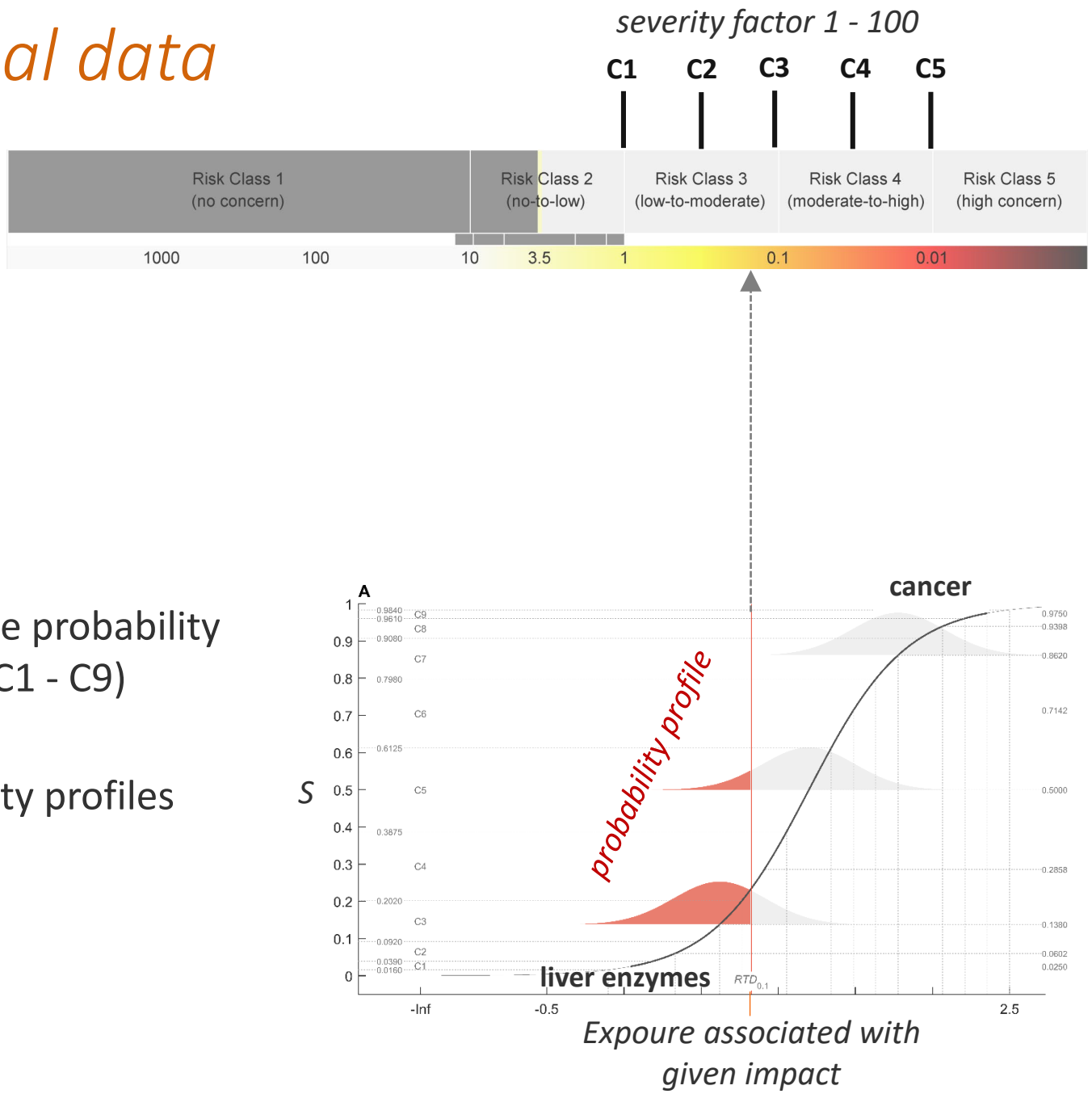
- The dose separation between *BMD*s for ”mild” and ”severe” effects approximates (*in this case*) to the maximum value of the severity-factor (100)

Relation to other methods

- Sand et al (2018) relates to the approach for etablishment of ”Acute Exposure Guideline Limits” for airborne chemicals by the U.S EPA.
  - For each chemical three Referense Doses are set, representing three severity levels

Development for traditional data

Sand et al 2018, Tox Sci

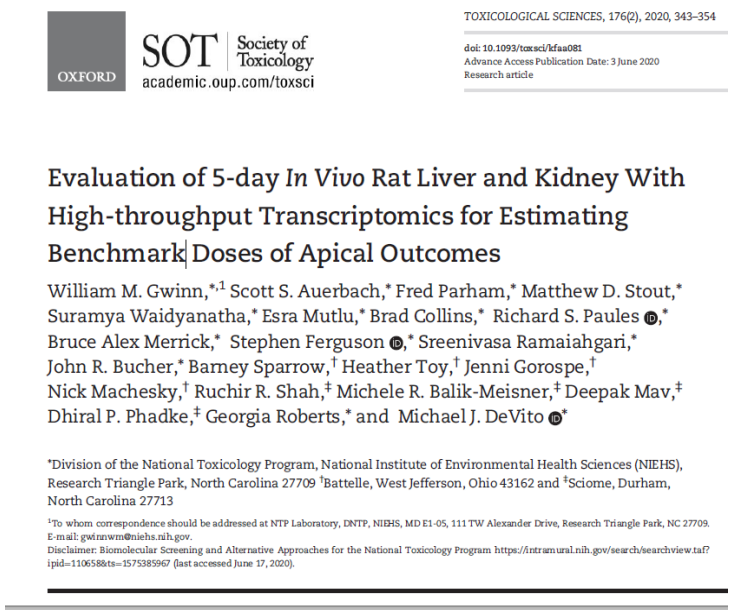


- Method in Sand et al. (2018) can evaluate the probability to exceed the *BMD* for all effect categories (C1 - C9)
- As set of reference values for given probability profiles may define ”new” Risk Classes

Development for alternative data

Introduction

- US NTP performs short-term (5-day) toxicogenomic studies
  - A bridge between in vitro approaches and traditional studies
- The NTP approach identifies a *BMD* (a potency estimate) for each gene exhibiting a dose-related response to treatment
- Genes grouped by gene ontology (GO)
- Gene-set *BMD*: median/mean *BMD* for each *GO-term*
- Lowest gene-set *BMD* correlates quite well to the lowest *BMD* from traditional studies (e.g., Gwinn et al 2020)
  - A rapid approach for prioritizing chemicals for furter testing?



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Research article

Evaluation of 5-day *In Vivo* Rat Liver and Kidney With High-throughput Transcriptomics for Estimating Benchmark Doses of Apical Outcomes

William M. Gwinn,*,[1] Scott S. Auerbach,* Fred Parham,* Matthew D. Stout,* Suramya Waidyanatha,* Esra Mutlu,* Brad Collins,* Richard S. Paules,* Bruce Alex Merrick,* Stephen Ferguson,* Sreenivasa Ramaiahgari,* John R. Bucher,* Barney Sparrow,† Heather Toy,† Jenni Gorospe,† Nick Machesky,† Ruchir R. Shah,‡ Michele R. Balik-Meisner,‡ Deepak Mav,‡ Dhiral P. Phadke,‡ Georgia Roberts,* and Michael J. DeVito*

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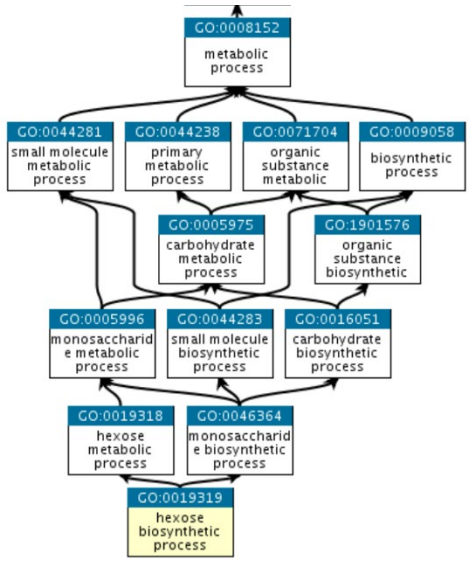
Disclaimer: Biomolecular Screening and Alternative Approaches for the National Toxicology Program https://intramural.nih.gov/search/searchview.taf?ipid=110658&ts=1575385967 (last accessed June 17, 2020).



http://geneontology.org/docs/ontology-documentation/

Development for alternative data

Sand 2021, ALTEX

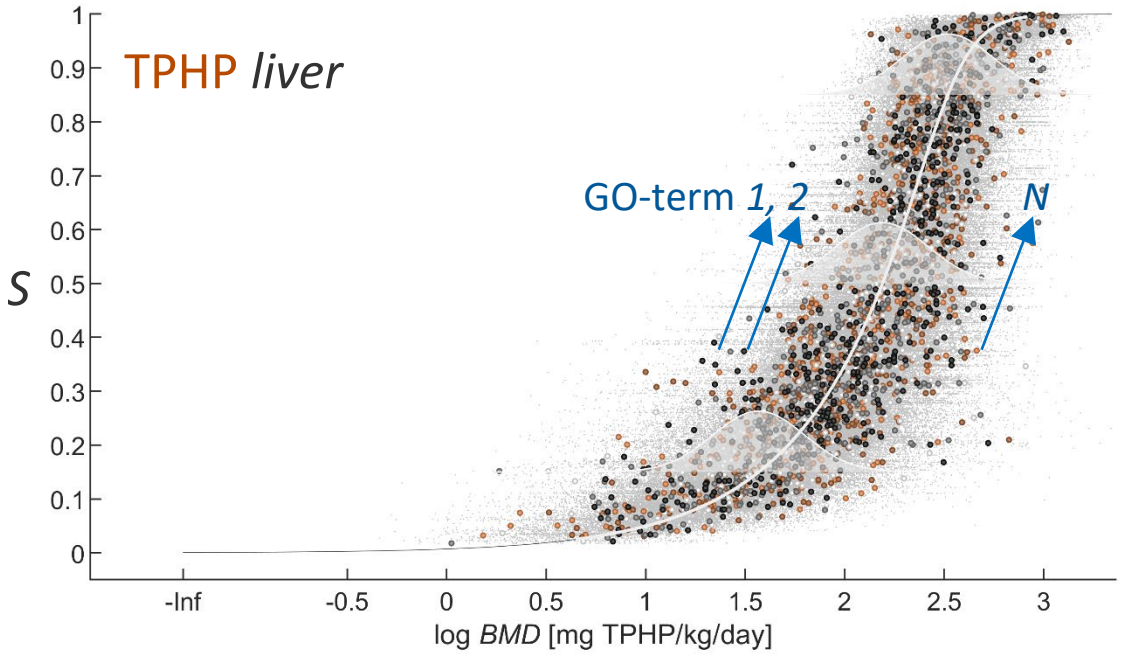
- Adaption of method in Sand et al (2018)

Data on 5 chemicals from NTP (9 data sets)	No. of unique *BMD*s/no of GO-terms
Triphenyl phosphate (TPHP liver)	559/1248
4-methylcyclohexanemethanol (MCHM liver)	68/321
4-methylcyclohexanemethanol (MCHM kidney)	108/371
Propylene glycol phenyl ether (PPH liver)	81/282
Propylene glycol phenyl ether (PPH kidney)	97/479
2,2,4,4-tetrabromodiphenyl ether (PBDE-47 pnd 22)	151/129
2,2,4,4-tetrabromodiphenyl ether (PBDE-47 pnd 4)	83/302
Technical pentabromodiphenyl (DE-71 pnd 22)	257/205
Pentabromodiphenyl (DE-71 pnd 4)	171/573

Development for alternative data

Sand 2021, ALTEX

- Difficult to rank bioactivity by severity, *instead*..
- Model describes how *BMD*s within GO-terms are distributed
  - Solid white curve correspond to the cumulative distribution function for the central GO-term
- The variation across GO-terms also decribed
  - Normal distribution associated with solid curve
- Model estimated by interative approach that also accounts for *BMD* uncertainty



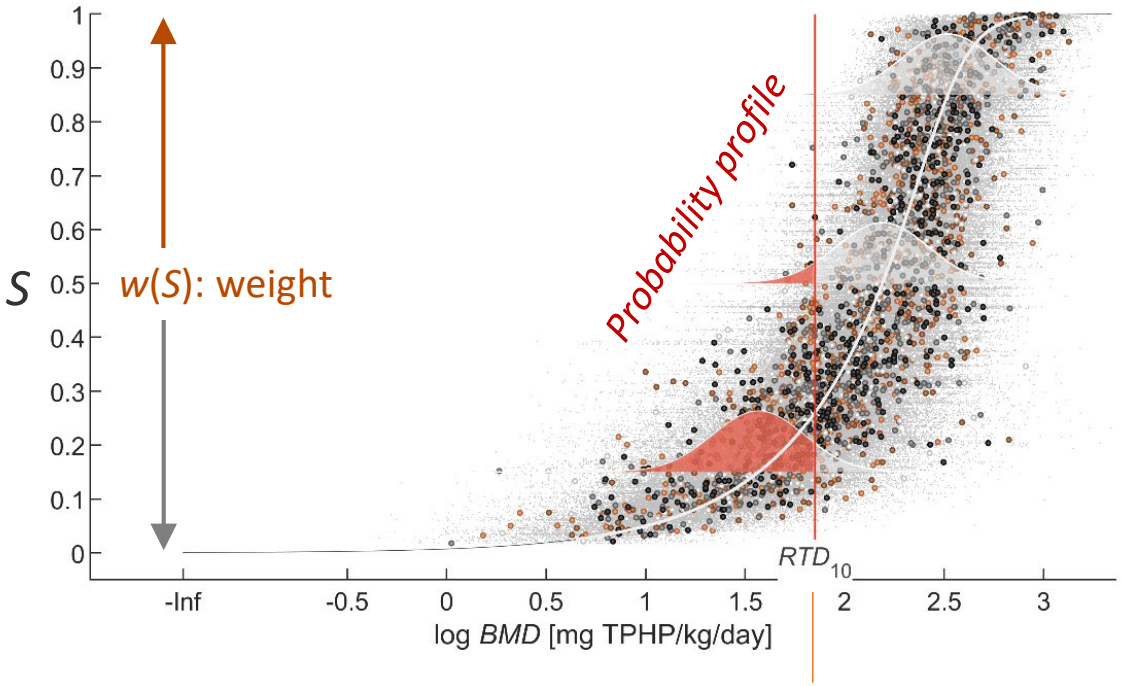
Gray dots in background: *BMD*s across all GO-terms and *S*-values

Larger colored dots: 1% of iterations

Development for alternative data

Sand 2021, ALTEX

- The probability to exceed *BMD*s across all GO-terms can be estimated
  - Describes the degree of gene-level impact
- May help to provide a mechanism for probabilistic realization of the definition/s of future exposure guidelines (or similar)
  - e.g., doses that do not lead to significant perturbation of toxicity pathways (e.g., Whelan and Andersen 2013)



Degree of gene-level impact at given exposure

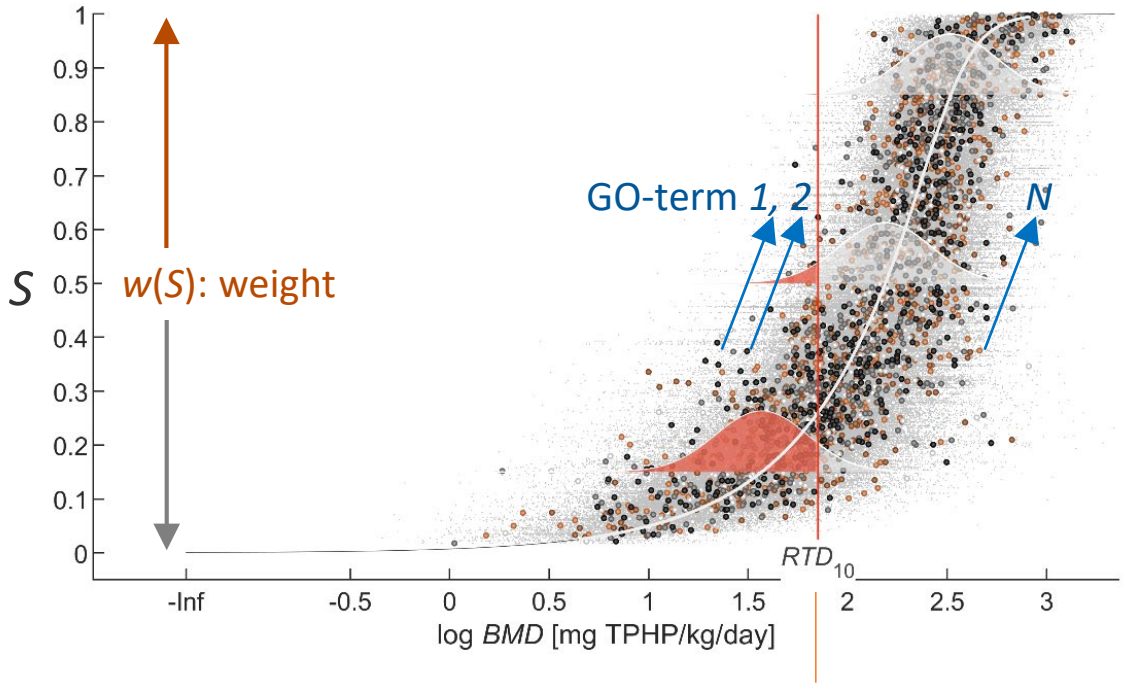
Significance of impact may be modulated by weight function, w(S)

Development for alternative data

Sand 2021, ALTEX

- The gene ontology knowledgebase enables quantitative comparison of gene sets, e.g., using semantic similarity metrics
  - *In contrast to value-based comparsion (severity categorization) of traditional effects..*

- Further analysis may evaluate if such comparions can inform the attached weight function
  - *Comparison of sematic similarity suggested that GO-terms distant in dose location (term 1 vs. N) may be less similar than closely located terms (term 1 vs. 2).*



Degree of gene-level impact at given exposure

Significance of impact may be modulated by weight function, w(S)

Development for alternative data

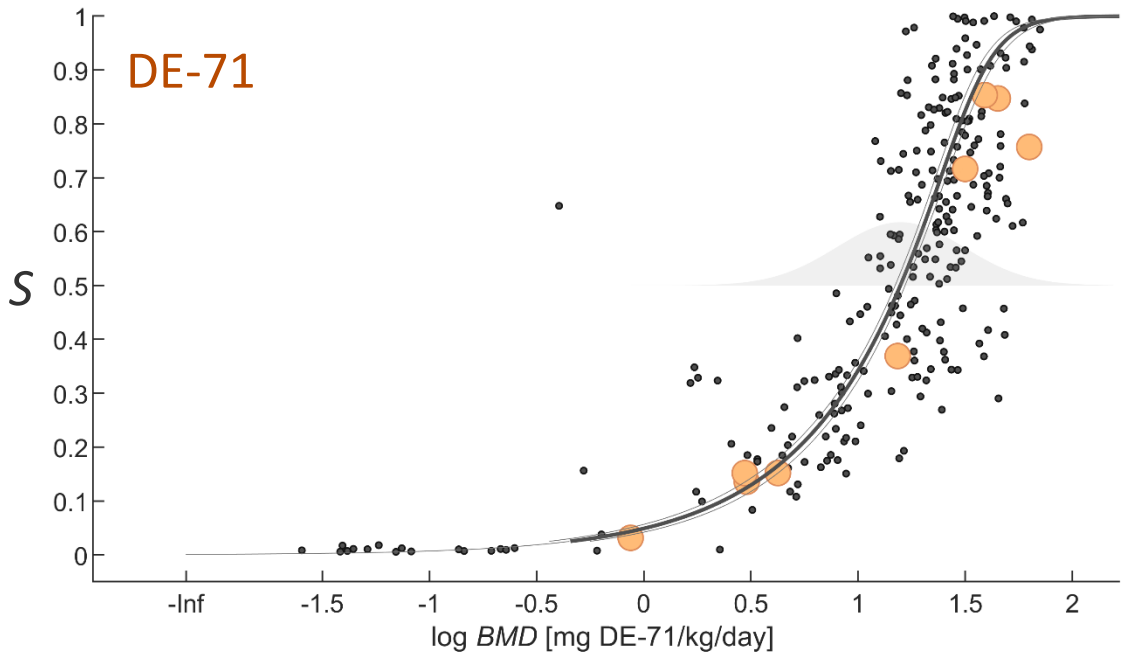
Sand 2021, ALTEX

Transcriptomic vs. traditional data (liver effects)

- Model for pentabromodiphenyl ether mixture (DE-71) based on data from both a short-term transcriptomic study and a 2-year NTP study in the same rat strain

- Small circles: *BMD*s from the short-term study
- Large circles: *BMD*s from the 2-year NTP study

- One iteration of the approach is illustrated



S-values for traditonal BMDs (large circles) generally describe a rank order similar to that based on "severity" for the same type of liver effects considered in Sand et al. (2018)

Summary

The method/s are generalizations of the traditionell approach using *a single* (critical) effekt

- Standardization - *Systematic organization of effects/BMDs*
- Refinement - *May better clarify level of concern*
- Enrichment - *Quantitative risk metric that accounts for mutliple effects*

Possibility to update the Risk Thermometer based on Sand et al. (2018, 2021)

- *Update borders between risk classes*
- *Develop/improve interpretation of risk classes*

International Risk Ranking Workshop, October 19-20 in Uppsala

Livsmedelsverket
Swedish Food Agency

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