

# Similar Mixture Approach (SMACH)

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# Whole Mixtures Risk Assessment & SMACH

- Both **components-based** (practical) and **whole mixture** (preferred) approaches are available for risk assessment of chemical mixtures.
  - **Components-based approaches** require the default assumption of additivity which limits relevance of mixtures;
  - **Whole mixture approaches** may be based on human-relevant exposures.
- Whole mixture approaches use “sufficiently similar” mixtures to represent a larger set of mixtures.

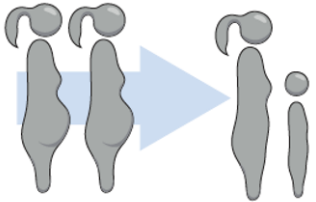


# Similar Mixture Approach (SMACH)

1. Identification of bad actors (mixtures) for health effects in epidemiological data

**Epidemiology**  
EDC levels in urine, blood and clinical data

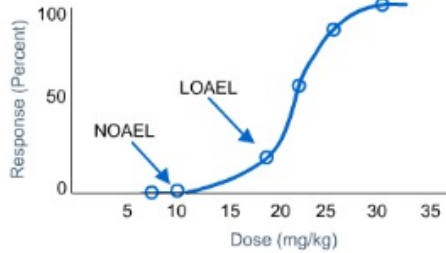
SELMA cohort



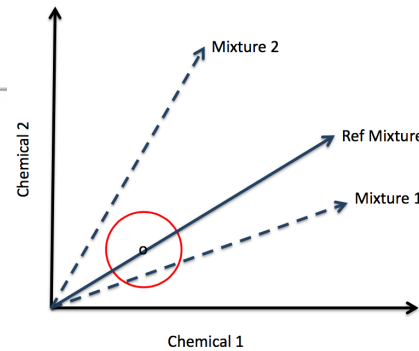
2. Composition of reference mixtures from population data for experimental evaluations



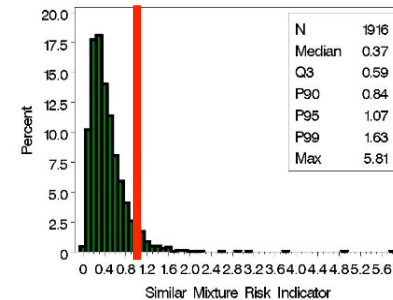
3. Experimental tests (in cells and animals) of reference mixtures for dose-response



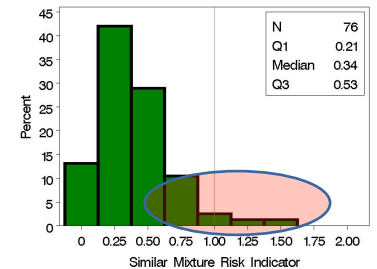
4a Test for sufficient similarity with the reference mixture (%)



4b For sufficient similar subgroups test for extreme mixture exposures, SMRI > 1 (%)



4c Demonstrate if health effects are associated with SMRI (adj risk, 95% CI)



# Human Exposures relative to Regulatory Guideline Values



**Human Exposure:**  
External estimates;  
Biomonitoring

## Experimental Evidence



*D. rerio*



*X. laevis*



**Reference  
Dose (RfD)**

$$\text{Regulatory Ratio} = \frac{\text{Human Exposure}}{\text{Reference Dose}} \text{ (Assessment Factor)}$$

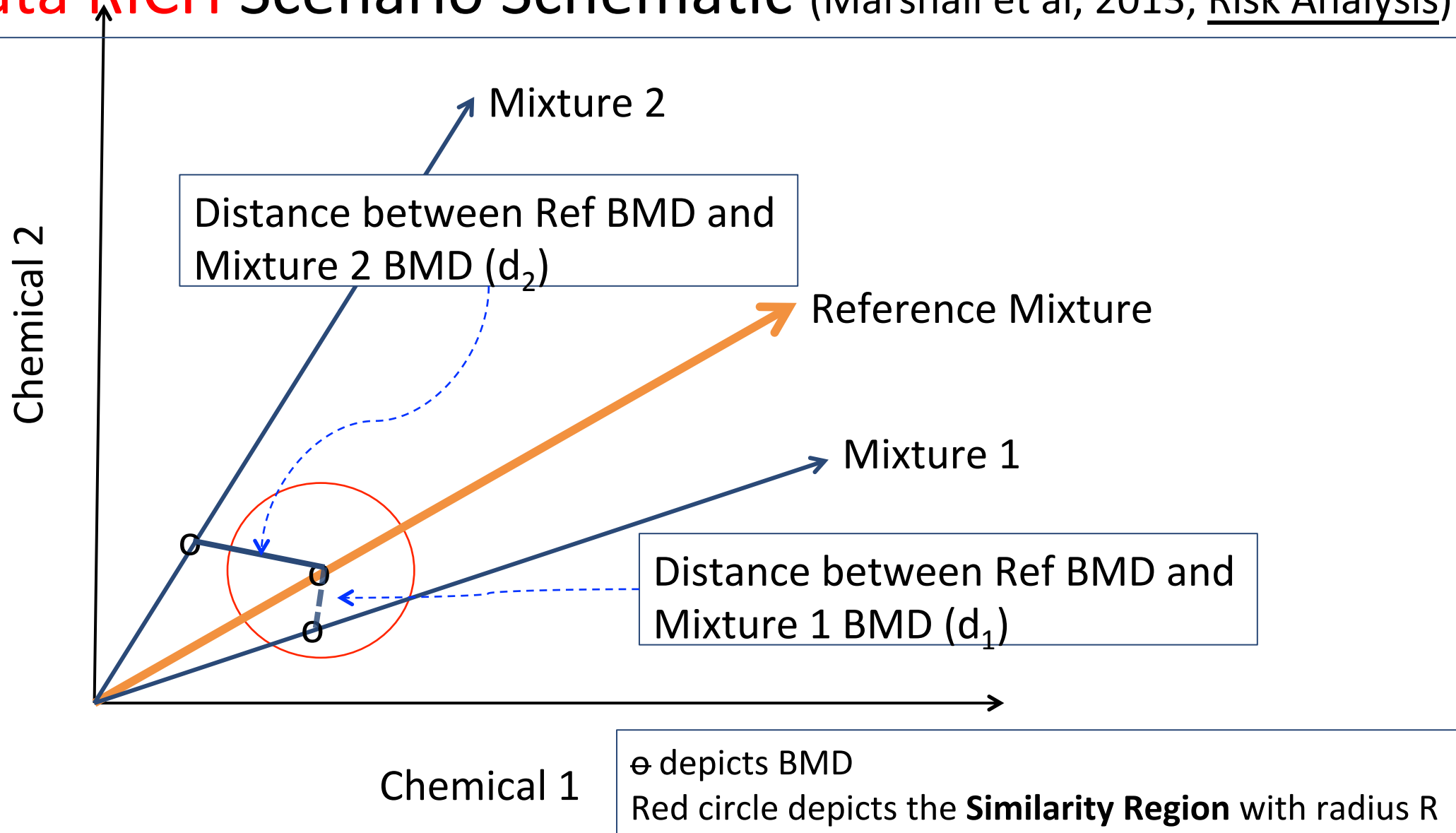
	Single Chemical	Additive Mixture	General Mixture *
Regulatory Ratio	Hazard Quotient	Hazard Index	Similar Mixture Risk Indicator

\* Calculated for mixtures **sufficiently similar** to the reference mixture



# Sufficient Similarity:

Data RICH Scenario Schematic (Marshall et al, 2013, Risk Analysis)



# Test FOR Sufficient Similarity

- Simplifying assumptions in the typical “data poor” case
- Define the radius of the similarity region to be  $R$
- Define  $d_j$  as the **distance** between the BMD for the reference mixture and the  $j^{\text{th}}$  candidate mixture (as specified from exposure data).

- **TEST FOR Sufficient Similarity:**

$$H_0: d > R \text{ vs } H_1: d < R$$

- Reject  $H_0$ , and claim sufficient similarity, when upper confidence limit on  $d < R$ .
- This is an  $\alpha$ -level test with sound statistical properties.

# Similar Mixture Risk Index (SMRI<sub>REF</sub>)

$$\text{SMRI}_{REF} = \sum_{j=1}^c \frac{\text{DI}_j \left[ \text{mols} / L \right]}{\text{mRV} \left[ \text{mols} / L \right]}$$

where

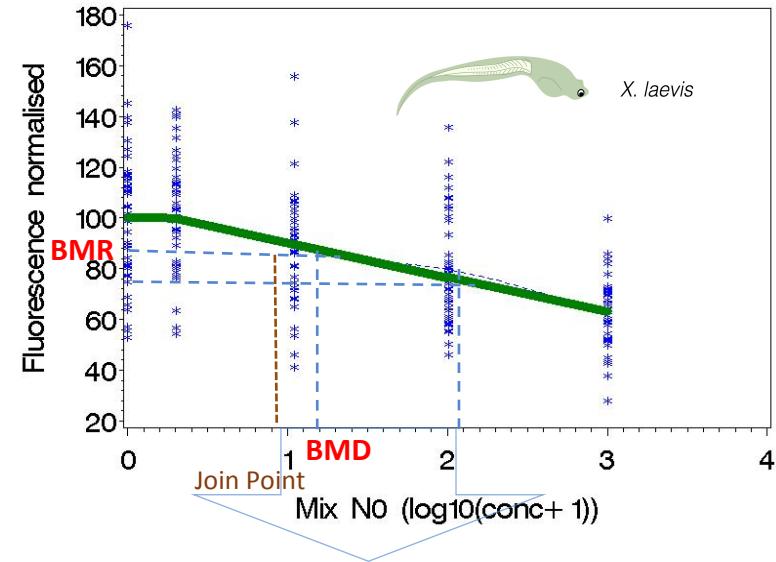
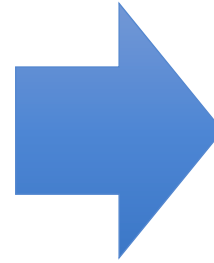
- The DI<sub>j</sub>s are estimated human exposure concentrations; and
- The mRV is the **reference value** defined from the mixture BMDL.

# Similar Mixture Approach (SMACH): Mixture N



SELMA  
Pregnant women

Chemical	Mixing Proportions
MEP	27%
MBP	23%
MBzP	11%
MINP	21%
BPA	4%
PFHxS	3%
PFNA	1%
PFOS	10%



1X = geometric mean from SELMA

DMSO, 1X, 10X, 100X, 1000X

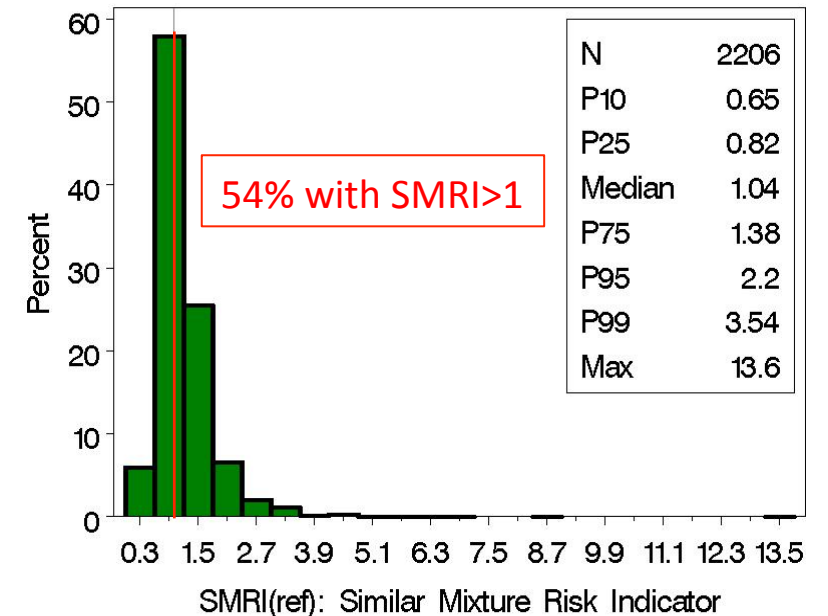
Radius of Similarity Region

## Test FOR Sufficient Similarity

**Table:** EDC-Mix Risk SMACH results for **Mixture N** where 1X approximates the geometric mean in pregnant women in the SELMA pregnancy cohort with:

- experimental evaluation in the XETA;
- OECD guidelines for XETA tests: the threshold for a response is set at 12%; and
- epidemiology evaluation of Language Delay at 2.5 yrs (N=2284)

BMD BMDL (1X units)	% Suff Similar to Ref Mixture	% SMRI>1 in Suff Similar group	SMRI: Low vs High decile: Adjusted difference
14X 8X	96%	54% (52% total)	OR=3.4 (p=0.031)



# Conclusions from SMACH

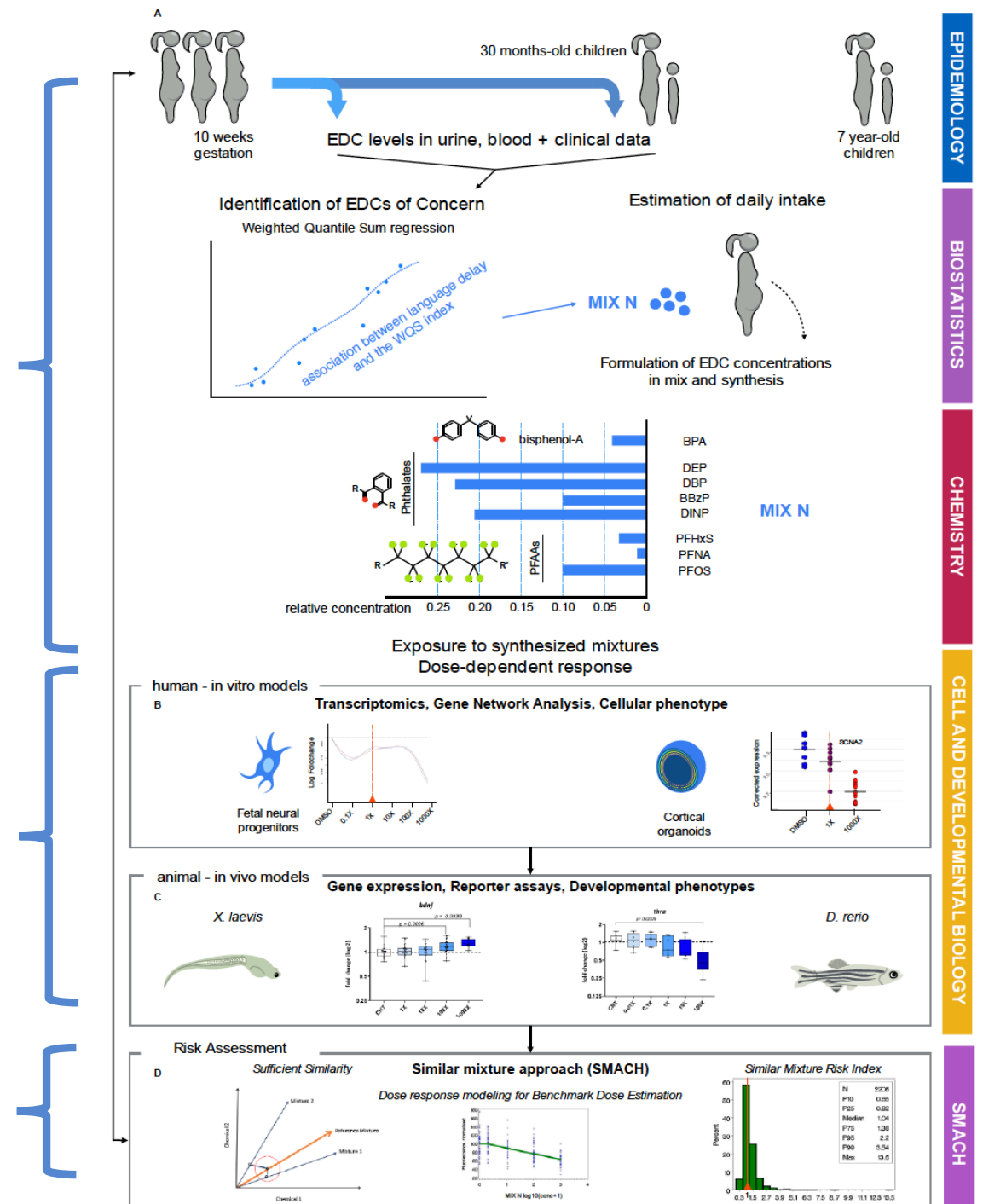
- This is an objective and transparent approach for defining sufficiently similar mixtures from exposure data without assuming additivity.
- The **test FOR sufficient similarity** has sound statistical properties.
- The SMRI index can be used to monitor changes in exposure patterns over time and locations.

# Conclusions

Exposure to a widespread chemical mixture of **endocrine disruptors during pregnancy** is associated with **language delay** in their children

At **human-relevant concentrations**, this mixture **disrupted hormone-regulated autism and intellectual disability genes** in human brain organoids and **altered behavioral responses** in *in vivo* models

54% of the pregnant women (with sufficiently similar mixtures to the reference mixture) who took part in the study were found to be exposed to experimentally defined levels of concern



# Acknowledgements

- **EDC-MixRisk consortium:**
- SELMA participants
  
- **Funding sources:**
  - EU Horizon 2020 (#234880)
  - NIH (T32 ES007334; R01ES015276)

**Thank you!**