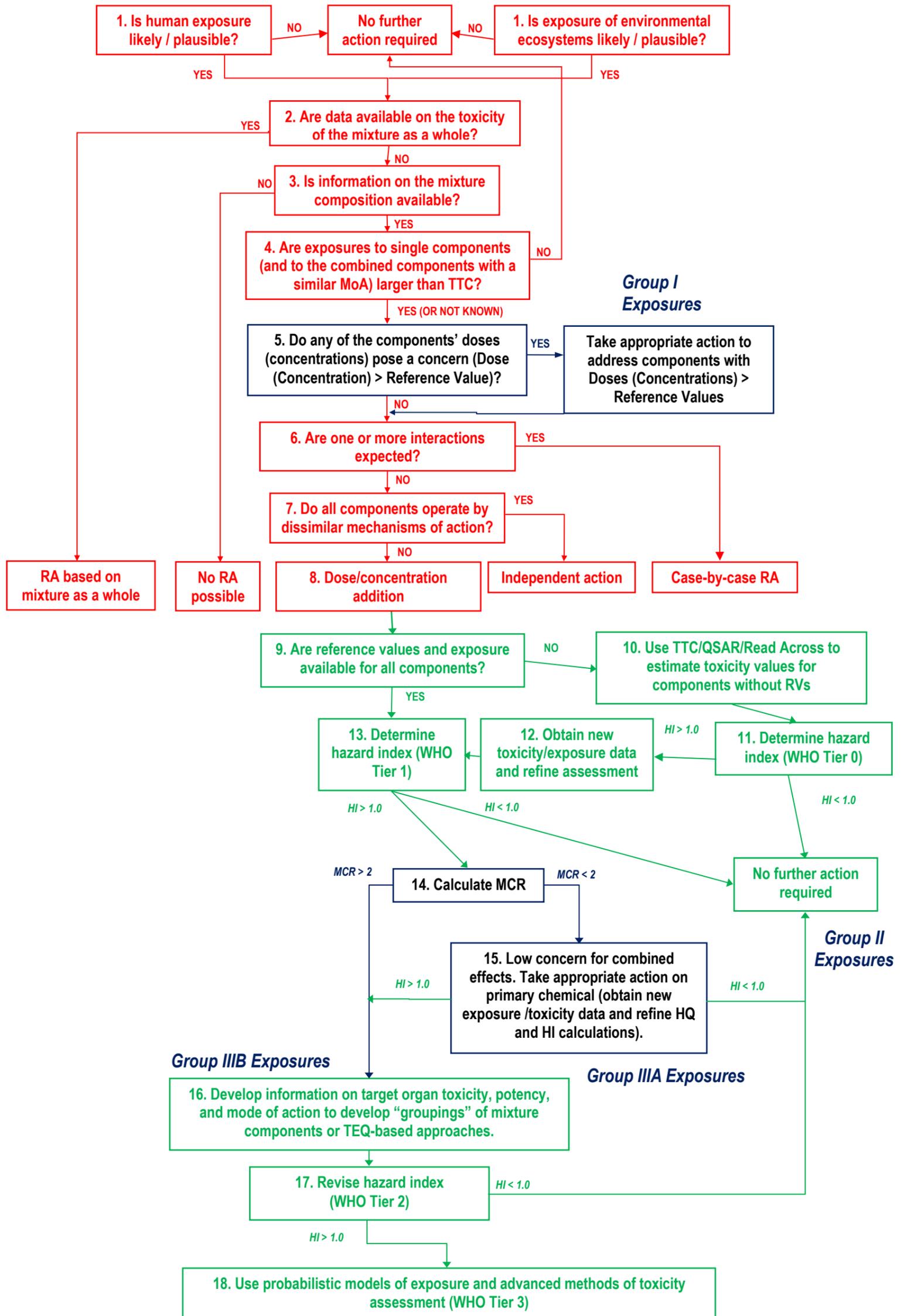


COMBINATION EFFECTS OF CHEMICALS DECISION TREE*



* supporting information on the back

Cefic Decision Tree Tool

Purpose of a Decision Tree for assessing effects from exposures to multiple substances¹

- Identify the right tools for use in an assessment of combined risks;
- Use a tiered approach to evaluate combined exposures;
- Determine if concern with combined exposures are driven by one chemical or are driven by multiple chemicals; and
- Determine which chemical(s) are drivers of combined risks and focus efforts to refine the assessment on those compounds.

Development of the Decision Tree

The Cefic decision tree for combination effects of chemicals builds on existing EU and WHO guidance and new findings in mixture assessments. The sources used are color coded:

- European Scientific Committees' decision tree (Text and boxes in **RED**)
- WHO framework for mixtures (Text and boxes in **GREEN**)
- Research on patterns of combined exposures using the Maximum Cumulative Ratio – MCR² (Text and boxes in **BLACK**)

Value of the Decision Tree

The Decision Tree provides a useful tool for identifying 4 different groups of combined exposures, which facilitates risk assessment and risk management decisions:

- **Group I** - combined exposures that are a concern because one or more individual chemicals are a concern;
- **Group II** - combined exposures where there is a low concern for both individual chemicals and for their combined effects; and
- **Group III** - combined exposures where there is a low concern for individual chemicals but there is a concern for the combined effects. This is the critical group for further assessments since the concern for these exposures cannot be identified using a chemical-by-chemical risk management approach. This group is further divided into:
 - **Group IIIA** where one chemical provides the majority of toxicity of the combined exposures; and
 - **Group IIIB** where no chemical dominates the toxicity of the exposures.

Each of the four groups requires different strategies for managing combined effects:

- **Group I exposures** need to address the chemical specific concerns for the exposures. Efforts to refine the assessment need to focus on the chemicals that are a concern before addressing risks from the combined exposures.
- **Group II exposures** can be set aside as a low concern when evaluating combined exposures.
- **Group IIIA exposures** have one chemical that is responsible for the majority of the toxicity received by a receptor. As a result, that chemical should be the focus of either refining the risk assessment or reducing exposure.
- **Group IIIB exposures** need to be the focus for refining the assessment by developing data on the modes of action (MoAs) for the chemicals that drive the toxicity of exposures.

Summary

The application of this tool to existing data on combined exposures can provide valuable guidance on which populations receive exposures that could pose a concern, the magnitude of the concern, and the chemicals that drive the exposures.

Acronyms

HI	Hazard Index	HQ	Hazard Quotient	MCR	Maximum Cumulative Ratio
MoA	Mechanism of action	QSAR	Quantitative Structure Activity Relationship	TTC	Threshold for Toxicological Concern
RA	Risk Assessment	TEQ	Toxicity Equivalents		
WHO	World Health Organisation				

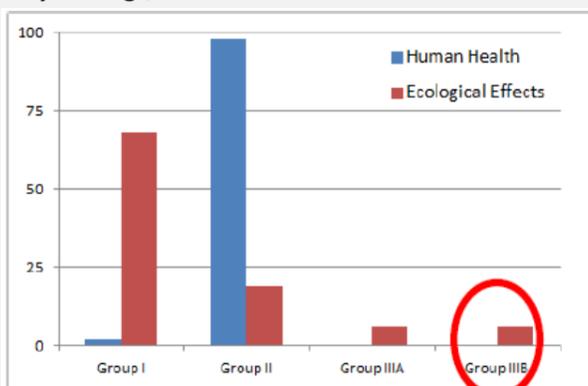
CASE STUDY: MIXTURES OBSERVED IN SAMPLES OF E.U. SURFACE WATERS AND MUNICIPAL WASTE WATER EFFLUENTS³

Purpose/Objective: The objective of this study is to apply the decision tree to real world mixtures with moderate to large numbers of chemicals observed in the E.U.

Data sets:

- United Kingdom Water Industry Research and the Environment Agency of England and Wales.
- Juliane Hollender and Heinz Singer (Eawag, Switzerland).
- JRC study of polar compounds.

Key findings/Results:



Data on 559 mixtures were identified

Human Health:

- Under 2% (9 mixtures) fell into Group I (combined exp. concern due to toxicity of one or more individual chemicals).
- 98% (550 of the 559) fall into in Group II (low concern from combined exposures and individual substances).
- No mixtures fell into Groups IIIA (concern from combined effects where toxicity is due to one chemical) or Group IIIB (concern from combined effects where no chemical dominates toxicity).

Environment

- 68% of the 559 mixtures were a concern because one or more chemicals were above their reference values.
- 6% (34 mixtures) fell in to Group IIIA and 6% (34 mixtures) fell into Group IIIB.

Conclusion:

- The decision tree indicated that the fractions of mixture exposures falling into Group IIIB are relatively small (0% for human and 6% for ecological effects).
- Data on MoA are only required for these Group IIIB compounds.
- This work suggests that mixture risks are often (but not always) driven by individual chemicals.

Brussels, June 2012

¹ Price P et al., Environmental Sciences Europe 2012, 24:26

² Price P and Han X. 2011. Int. J. Environ. Res. Public Health 8, 2212-2225 and Han X and Price P. 2011. Int. J. Environ. Res. Public Health 2011, 8(12), 4729-4745

³ Price P et al., Environmental Sciences Europe 2012, 24:34