Deutsche Gesellschaft für Toxikologie

GT Working Groups
Regulatory Toxicology and Mixture Toxicity

GT Advanced Course Toxicology 2026
„Mixture Toxicity“
of the GT Working Groups
Regulatory Toxicology and Mixture Toxicity

Special Thanks to the Organisers and the Program Committee:

Denise Bloch
(WG Mixture Toxicity)

Conventus

Heidrun Greim
(WG Regulatory Toxicology)

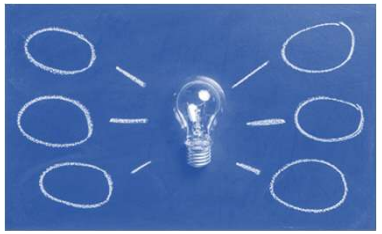
Michael Werner
(WG Regulatory Toxicology)

GT Advanced Course Toxicology 2026
„Mixture Toxicity“

10:00	Organisational and introductory remarks on „old“ EU and „new“ GHS C&L systems	Chairs of the GT Working Groups (Denise Bloch / Michael Werner)
Session 1:	**Mixtures in Hazard Assessment**	Moderation: Denise Bloch / Michael Werner
10:30	**GHS / CLP:** Additivity, synergism, antagonism; 6 pack; Longer-term toxicity	Nicolaj Heuer, BAuA, Dortmund
11:00	**CAGs / CKGs (Cumulative Assessment Groups and Common Kinetic Groups)**	Philip Marx-Stölting, BfR, Berlin
11:30	**Coffee break**	
11:50	**Practical exercise**: Calculation of classification categories on the basis of individual substance toxicities	Alkiviadis Stagkos Georgiadis BfR, Berlin
12:35	**Lunch Break + General Meeting WG RegTox**	Working Group Regulatory Toxicology
Session 2:	**Mixture risk assessment**	Moderation: Denise Bloch / Michael Werner
13:45	**EFSA Mixture Guidance**: Experimental needs considering 3Rs and challenges for implementation	Jose Tarazona, EFSA, Parma (online)
14:15	**Non-dietary risk assessment of pesticides and biocides:** Aggregate vs. cumulative risk assessments; Decision scheme for additivity or non-cumulative assessment; Regulatory issues in cumulative risk assessments	Vincent Blaschke, BfR, Berlin
14:45	**Cumulative dietary risk assessment:** Cumulative Assessment Groups; Criteria for Grouping, Prioritization and Uncertainty Assessments; Probabilistic exposure assessments;CAG-based approach and limitations	Stefanie Melching-Kolmuß, BASF, Limburgerhof
15:15	**Coffee break**	
15:35	**Mixture Toxicity under REACH:** RPF; MAF and alternatives	Hennicke Kamp, BASF, Ludwigshafen
16:05	**Plenary discussion** – Outlook on the safety of mixtures from a regulatory point of view	All Panellists Moderation: Michael Werner
16:55	**Closing remarks and end of GT Advanced Course 2026**	

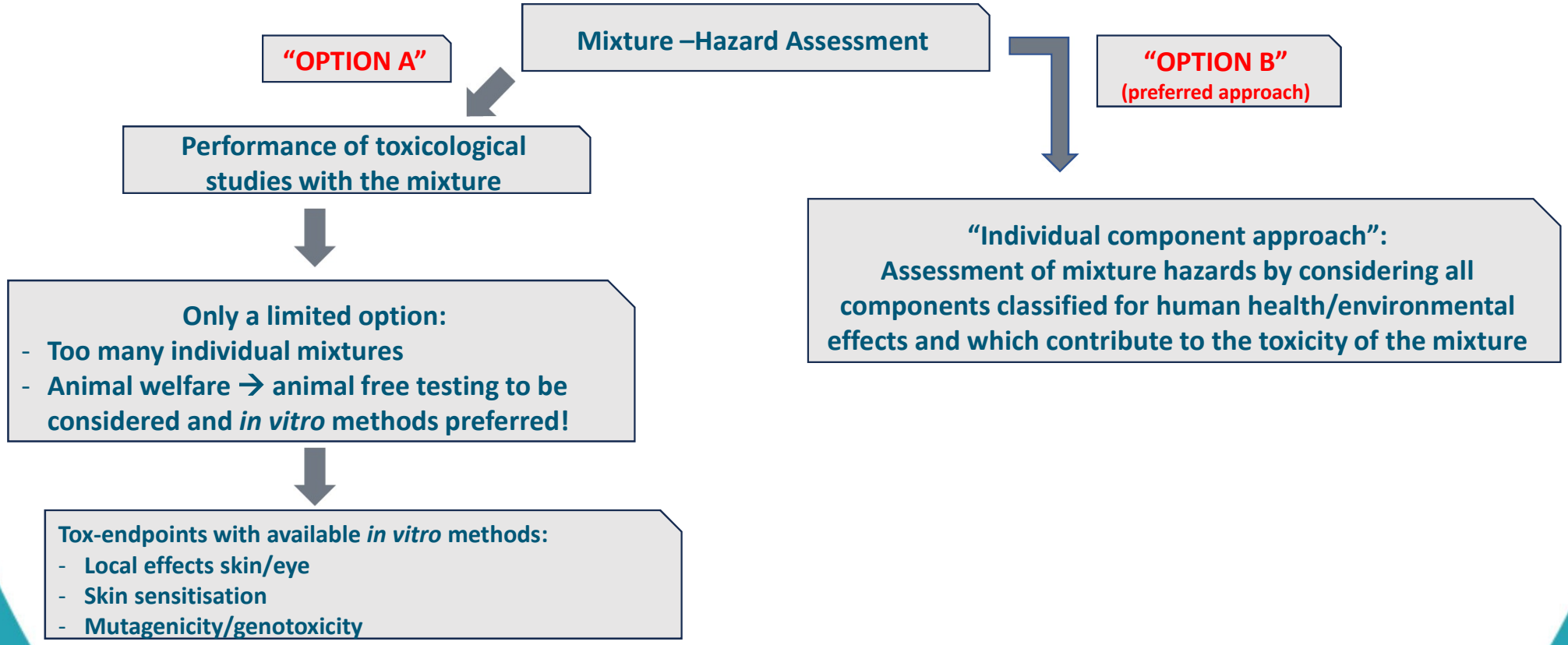
Purpose of the Advanced Course 2026

- **Gain an overview of the state of the play in the hazard and risk assessment of mixtures**
- **Understand the potential combined action (additivity, synergism) between actives and other (non-active) individual components (“substances of concern”) in mixture hazard assessment**
- **To provide a good understanding on the need of cumulative risk assessments on mixture components**
- **Realize the challenges and consequences associated with cumulative risk assessments from the technical and regulatory point of view**



Session 1: Mixtures in Hazard Assessment

- **Assessment of human health hazard of mixtures and classification/Labelling – Background:**



Session 1: Mixtures in Hazard Assessment

- **Assessment of human health hazard of mixtures and classification/Labelling – Background:**

"History" of the performance of animal studies on mixtures:

- **"6 pack" (animal studies on acute toxicity, skin/eye irritation and skin sensitisation) performed for PPPs and biocides under the respective directives (Biocides: Directive 98/8/EC; PPP: Directive 91/414/EEC)**
- **No experimental animal studies were available for "higher tier endpoints" (RDT/DART/Carcinogenicity; Endocrine disruption not relevant at that time)**

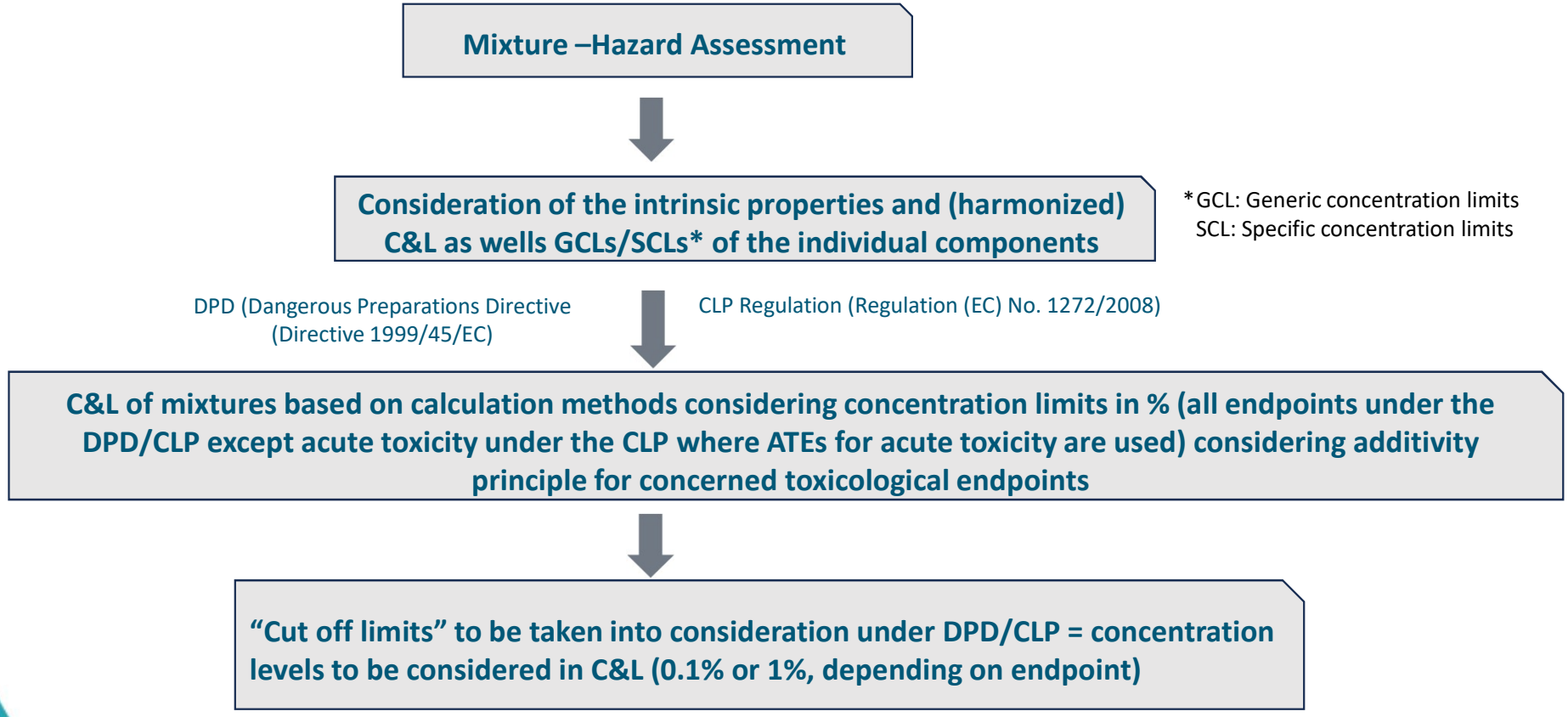
"Subjective Observations":

"6 pack studies" provided in many of the studies more favourable (or not worse) results as compared to the results obtained by the application of the convential calculation method for the C&L of mixtures!

- **Skin sensitisation**
- **Mutagenicity/genotoxicity**

Session 1: Mixtures in Hazard Assessment

- **Assessment of human health hazard of mixtures and classification/Labelling – Approaches:**



Session 2: Mixtures in Risk Assessment

❖ **Assessment of human health risks of mixtures – a bit historical background information:**

- **Advisory Committee on Plants (ACP UK): First considerations on potential synergism in mixture toxicity in the context of the evaluation of PPPs** (6th meeting, **16 November 2005**).

- Starting point - **Presence of multiple residues of PPPs** as a result of repeated **treatment of field crops with different actives and PPPs:**
  - **Trigger for considerations on combined/cumulative risk assessments: Anti-cholinesterase group of PPPs (i.e. organophosphates and carbamates) acting on the same toxic end-point by a similar mechanism.**
  - Question on potential **„cocktail effects" and interactions of the different active substances** following **(oral) exposure and ingestion of multiple residues** in foodstuff.

- **Awareness with regards to potential combinatory effects of mixtures existed!**

Session 2: Mixtures in Risk Assessment

❖ **Assessment of human health risks of mixtures – a bit historical background information:**

Conclusion/Opinion of the ACP (6th meeting, Nov. 2005):

- **Exposure levels deemed to be so low that important toxicological interactions and a health concern were not anticipated!**
- **Reference values derived for PPPs involve application of additional assessment/uncertainty factors → considered to be protective for exposure levels towards multiple residues.**
- **No necessity to carry out combined/cumulative risk assessments for substances acting by different mechanisms and with different toxic end points.**
- **But: ACP considered the possibility of toxic interactions where two or more active substances (i.e. OPs/Carbamates) are co-formulated in the same product.**

Session 2: Mixtures in Risk Assessment

❖ **Assessment of human health risks of mixtures – a bit historical background information:**

- **BfR Forum on multiple residues of PPPs in foodstuffs (09./10. November 2005) – Key Messages:**
  - **Various animal studies with mixtures demonstrated that effects were observed only above the NOAEL of the individual substances.**
  - **Doses clearly below the NOAEL of the individual substances did not show additive, synergistic or antagonistic effects in the mixture.**
- **An acceptable analysis of combination effects in mixtures would afford**
  - **Systematic mixture testing and analysis of a number of combinations of different dose ranges.**
  - **Establishment of dose-response relationships for each substance**

Virtually not possible from the practical point of view!

Session 2: Mixtures in Risk Assessment

- **Assessment of human health risks of mixtures – Initial considerations:**

Mixture –Risk Assessment

"OPTION A"

Assessment of the risks of all components by default?

→ Most likely not feasible even with the use of AI
→ Reliability of outcome still to be manually cross-checked!

"OPTION B"
(preferred approach)

More reasonable/practical approach:
→ Assessment of all "relevant" mixture components

"Relevant" components in mixture risk assessment:

→ Active substances (e.g. biocides, PPPs)
→ Substances of concern (SoCs) = non-active substances revealing a potential human health and/or environmental hazard

all of which contribute to the toxicity/C&L of the mixture

Session 2: Mixtures in Risk Assessment

- **Assessment of human health risks of mixtures - Possible way(s) forward:**

Key question: When is a Cumulative Risk Assessment of Mixtures and Mode of Action Analysis required?

Simple dissimilar (independent) action of components

→ **Mode/mechanism of action and target tissues/organs of mixture components are different**

→ **Independent ris assessment for each substance (no combined (cumulative) risk assessment)**
→ **Concept of effect addition is applied**

Simple similar action of components

→ **Substances reveal same or similar mode/mechanism of action and exert effects on the same target tissue/organ**

→ **Combined (cumulative) risk assessment is performed**
→ **Concept of dose/concentration addition is applied ("Hazard Index (HI) Approach")**
→ **Target organ-/tissue-specific reference value deduction needed?**

Session 2: Mixtures in Risk Assessment

- **Assessment of human health risks of mixtures - Possible way(s) forward:**

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Answer(s) to mixture risk assessment approaches?

GT Advanced Course 2026 „Mixture Toxicity“ !

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The Working Groups

"RegTox" and "MixTox" wish you an interesting and exciting GT Advanced Course 2026