Assessing the safety of polymers: Examples of grouping approach

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ecetoc
WE ARE THE CENTRE FOR CHEMICAL SAFETY ASSESSMENT

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- European Registered Toxicologist and Diplomate of the American Board of Toxicology
- > 15 years of experience with risk assessment of diverse polymers
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- Involved with working groups in Cefic, ECETOC, ILSI Europe, CosmeticsEurope
- Heli Hollnagel | LinkedIn / Heli Miriam Hollnagel (researchgate.net)

Agenda

Programme		
15:00-15:05	Welcome	Heli M. Hollnagel, Dow Europe
15:05-15:15	The ECETOC Conceptual Framework for Polymers (CF4Polymers) grouping approach	Jens C. Otte, BASF
15:15-15:30	*Example 1:* Grouping across a continuum of polymers: **Alcohol ethoxylates**	Jens C. Otte, BASF
15:30-15:45	*Example 2:* Grouping considering proportion of monomers in the polymer: **BADGE polymers**	Philippe G. Gottis, Hunstman
15:45-16:00	*Example 3:* Grouping of polymers and read-across to corresponding oligomers: **PEOLs**	Isabel D. Krug, BASF
16:00-16:05	*Break*	
16:05-16.30	Q&A	
16:25-16.30	Wrap-up	

Why is the Grouping Concept important?

Testing based on single substance triggers with subsequent read-across

Reducing uncertainty in risk assessment by strategic selection of test materials and study types in group registration

Opportunity for reduced uncertainty + less animals sacrificed

The ECETOC Conceptual Framework for Polymers (CF4Polymers) grouping approach

ECETOC TR 133-3

Presented by Dr. Jens C. Otte

Dr. Jens C. Otte

- Diploma in Biology (Heidelberg University)
- Master's degree with major in (Eco)Toxicology (Uppsala University)
- Research Stay (University of Saskatchewan, Canada)
- PhD (Eco)Toxicology / Developmental Biology (Karlsruhe Institute of Technology / Heidelberg University)

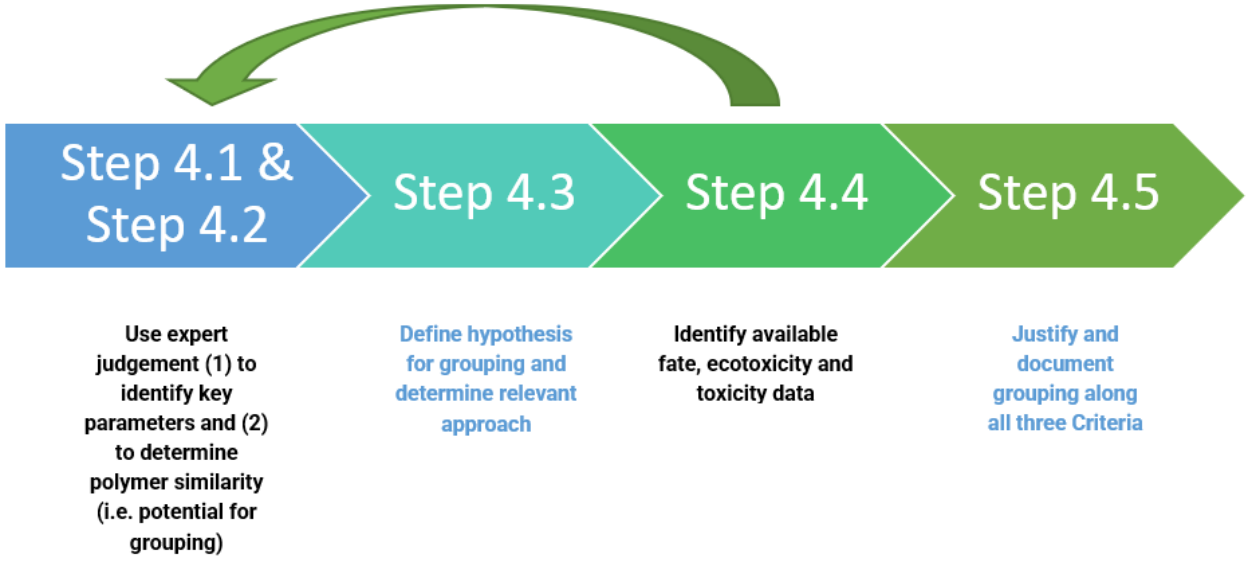
- > 10 years of experience with risk assessment of chemicals
- Senior Specialist Product Safety at BASF SE

- Involved and leading in working groups at ECETOC, ICCA, Cefic, ACC

Why such dedicated grouping approach to polymers?

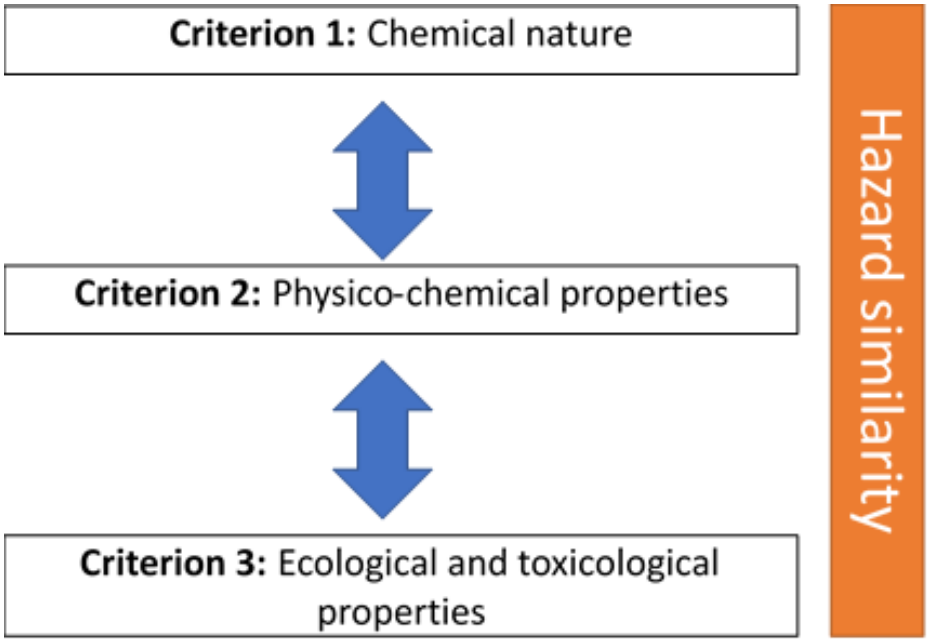
- The reason is the **building block nature of polymer chemistry**. Related polymers are often homologues manufactured from the same starting materials and similar processes, leading to a large number of similar structures. But even if few of the building blocks are different, such chemical variation in a small part of a macromolecule does usually not lead to differences in physico-chemical or biological properties.
- In the present TR No. 133-3, the **internationally agreed grouping concepts has been further advanced** to better scope the complexity and versatility of polymers.
- A central role has been assigned to the term **'hazard similarity'** which is the overarching aim of the polymer grouping approach to define 'similarity' of different polymers and, consequently, the final group.
- The polymer grouping approach proposed here allows to **significantly simplify and structure the data requirements for polymer hazard and risk assessment** and gives rise to a **pragmatic and reasonable description of the substance identity** for polymers.

Illustration of the stepwise grouping approach of the CF4Polymers



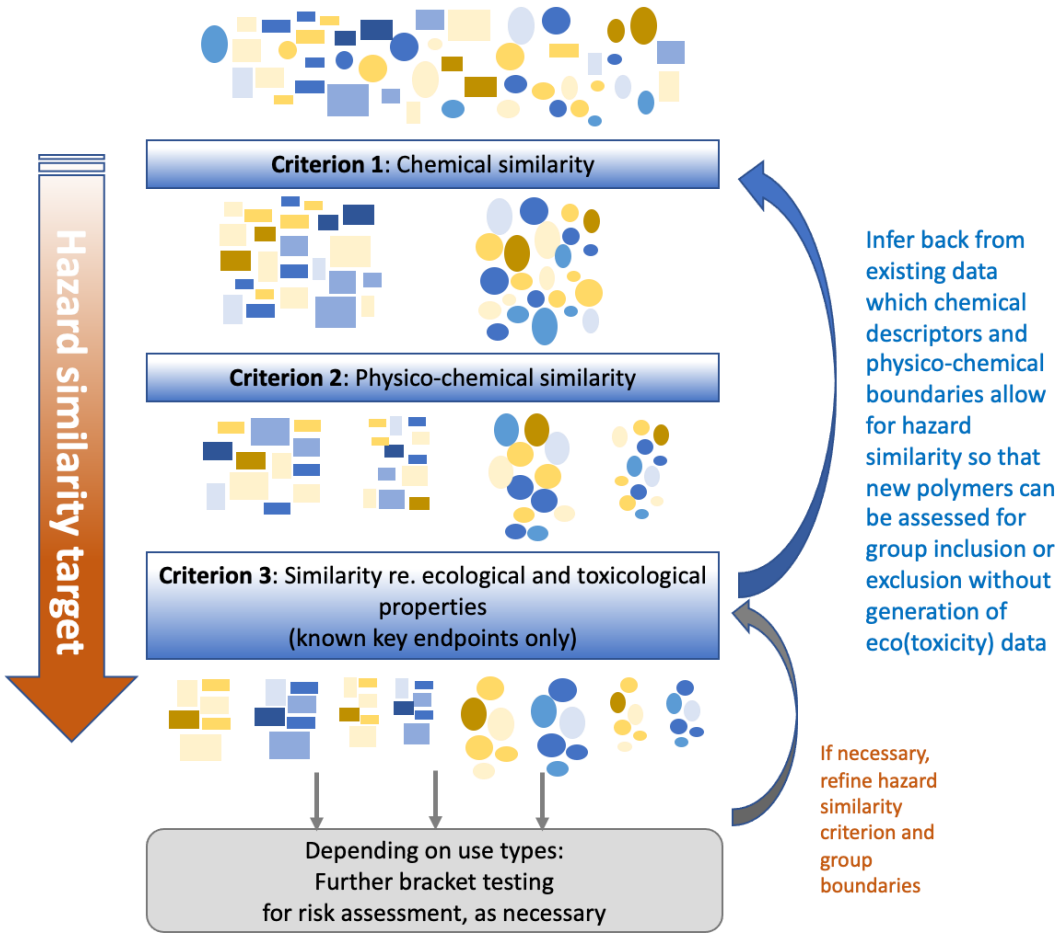
- The CF4P grouping approach evaluation consists of five steps
- This sequence of steps is not necessarily passed through in a consecutive order
- The grouping approach for polymers presented here enhances the outline of Steps 4.1 to 4.5 by introducing a three-Criteria approach to defining and justifying polymer similarity throughout the five steps

Three Criteria to enhance the grouping approach evaluation



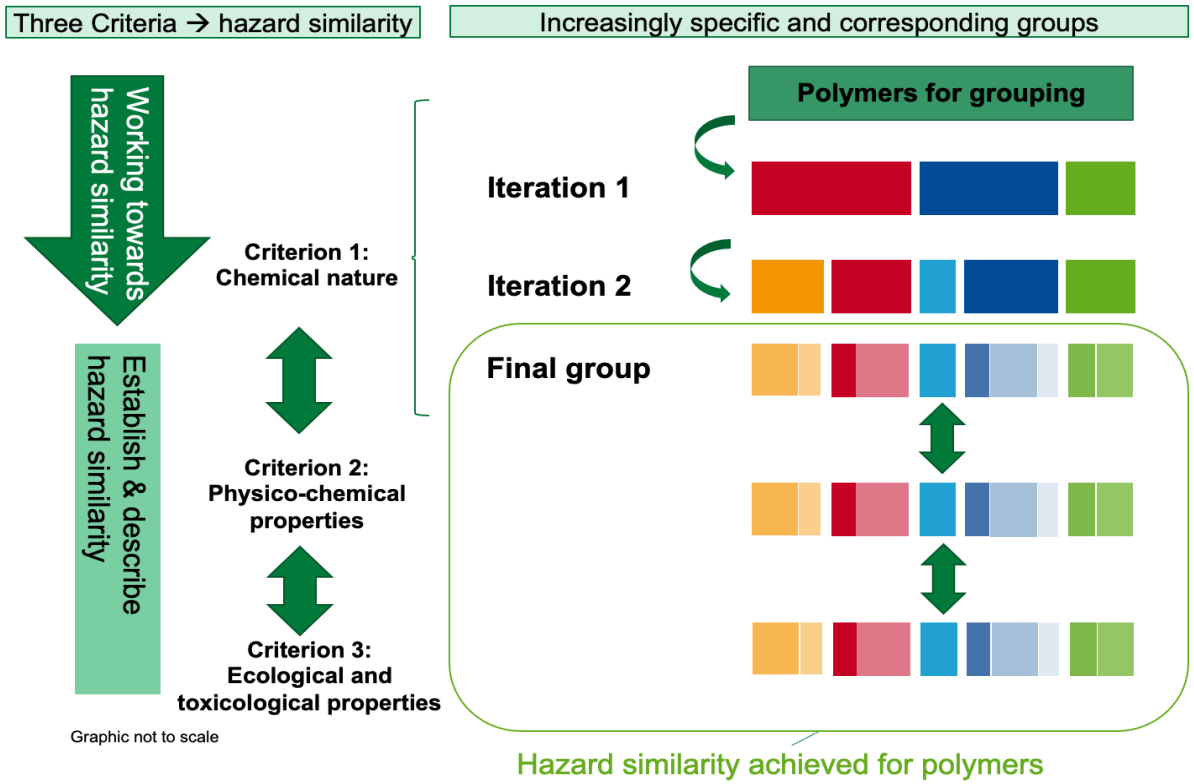
- The basic principle for polymer grouping
  - is following **three Criteria**
  - is **balanced** of aspects represented therein.
- All Criteria serve to establish **hazard similarity** of the group.

Further details on the three Criteria to enhance grouping approach evaluation



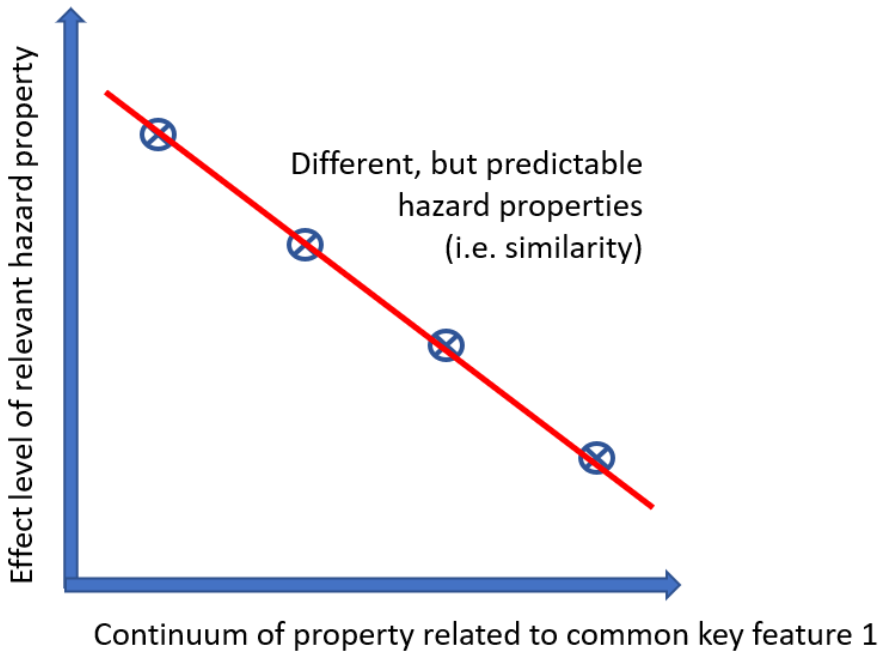
- All three Criteria are indispensable to describe the *hazard similarity* of the group.
- While hazard similarity is taken as the central element and the ultimate goal when defining and justifying the polymer group.

Overall concept to enhance grouping for polymers



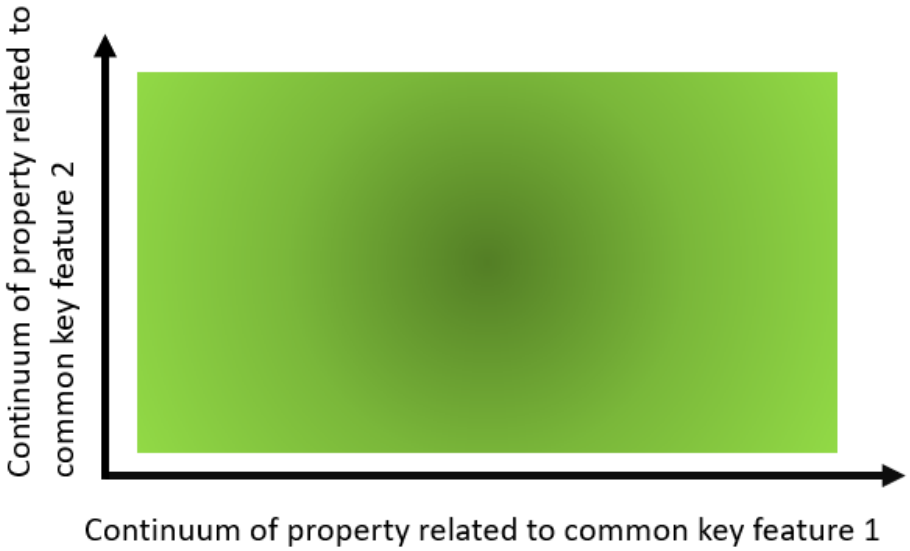
- Within the polymer grouping approach, the stepwise narrowing down of a particular group is described as different iterations until a final group is identified.
- Criterion 1 includes the identification of ***common key features*** of all members of the (preliminary) group
- The definition of the group is further substantiated in Criterion 2 by identifying relevant physico-chemical properties and in Criterion 3 by hypothesising **relevant hazard properties.**

Level of similarity



- The effect level of **relevant hazards properties** of group members from one end of the group do not necessarily have to be the same as those for group members at the other end.
- The relevant hazard properties *as such* (e.g. acute oral toxicity) need to be the same for the entire group
- A continuum and predictivity of the relevant hazard property should be established and justified.

How does a data matrix help to visualize hazard similarity?



- A data matrix supports evaluation of the polymer grouping approach, the common key feature(s) as well as the corresponding relevant hazard property/ies.
- Consistency and predictability of the relevant hazard properties along the common key feature can be assessed and documented.

Summary

- The building block nature and resulting complexitiy and versatility of polymer chemistry serves a dedicated concept for grouping
- The polymer grouping approach described here should be viewed as a targeted and flexible framework.
- The **internationally agreed grouping concepts has been further advanced and the concept of hazard similarity has been added to cope with the complexity**
- **The description along three criteria also allows the description of polymer groups and polymer identity**
- Certain steps of the grouping approach may be of higher or lower importance for some types of polymers, whereas other types of polymers may benefit from adding specific aspects

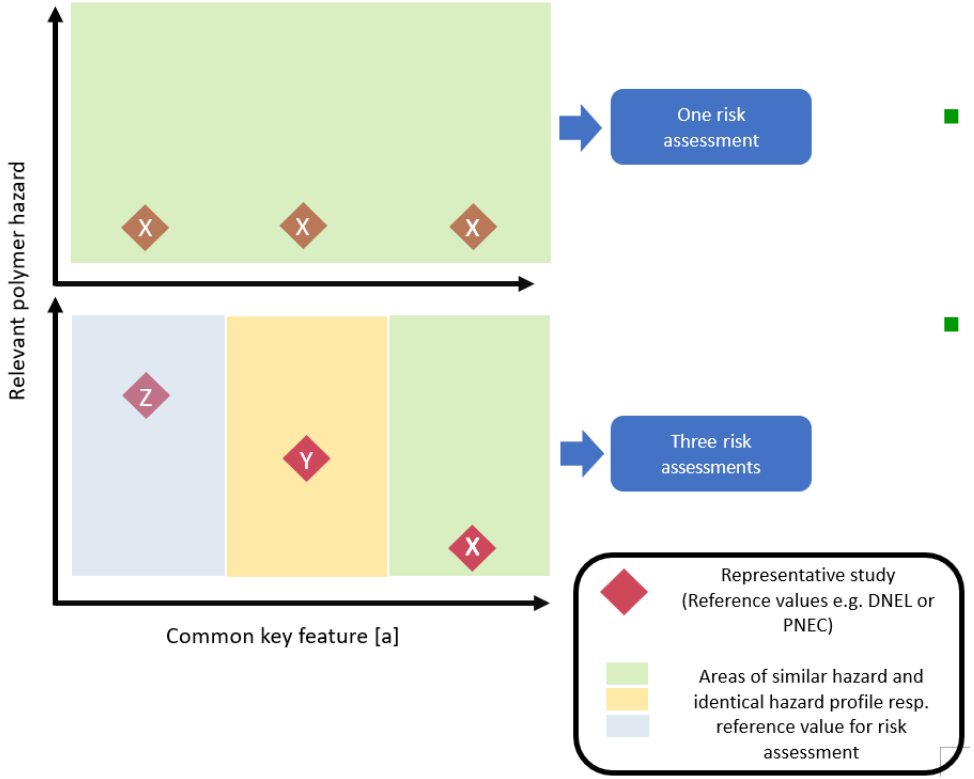
Bracket testing hazard data

- To cover the variety of polymers, so-called bracket testing can be applied when additional endpoint data are required to characterise the hazards of a group of polymers.
- Some different test materials out of the group are selected for testing and subsequent read-across of the properties across the group members.
- This requires selecting those test materials which are at the boundaries and in the middle of the group in terms of chemical nature and physico-chemical properties
- The number of test items in the bracket test necessary to adequately represent the entire group of polymers will depend upon
  - the range and consistency of Criterion 1 and 2 properties
  - and the available data on effects within the polymer group
  - as well as the concordance of the findings of any bracket testing.

Options for risk characterization of the final group

Same & similar hazard or uses

Similar hazards and / or uses

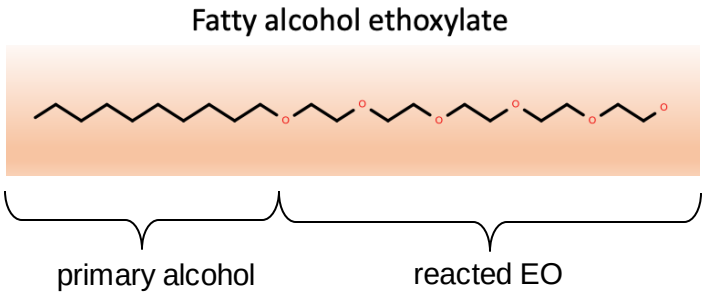


- The final polymer group may also be subject to risk characterisation.
- This is founded on the common key feature and relevant hazard properties.
- It may be necessary to subdivide the final group to further refine the exposure or hazard assessment depending upon
  - the margin of safety
  - or different uses and associated exposure

Example 1:
Grouping across a continuum of polymers:
Alcohol ethoxylates

ECETOC TR 133-3

Introduction to Alcohol Ethoxylates



Use

- AEs are excellent surfactants, emulsifiers, wetting agents, and moderate foamers.

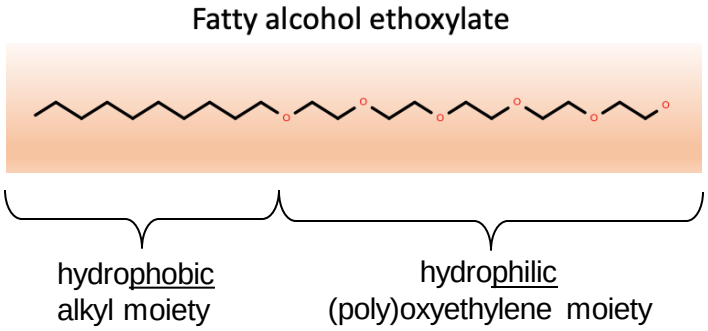
Descriptors

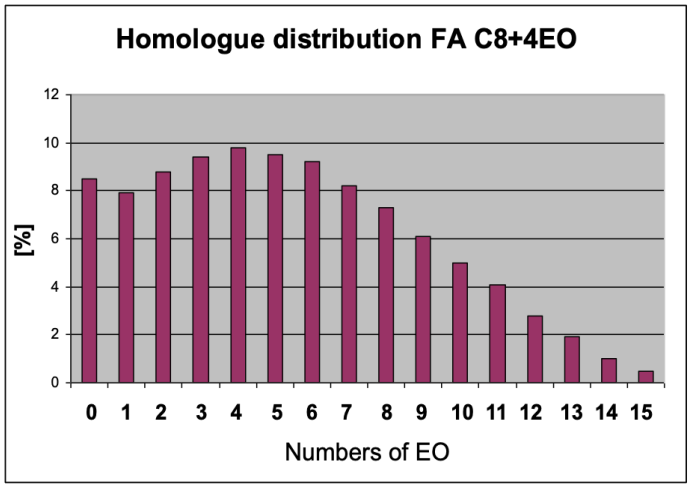
- Standard chemical descriptors (e.g. CAS) are not sufficiently specific for the identification of AEs.

Chemistry

- Alcohol Ethoxylates (AE) are surface active non-ionic polyethers composed of a long-chain primary alcohol reacted with ethylene oxide (EO).
- They can be linear, quasi-linear, or branched.
- For the commercially available AEs, the degree of branching as well as their chain length distribution varies by the feedstock source and by the method used to produce the alcohols.

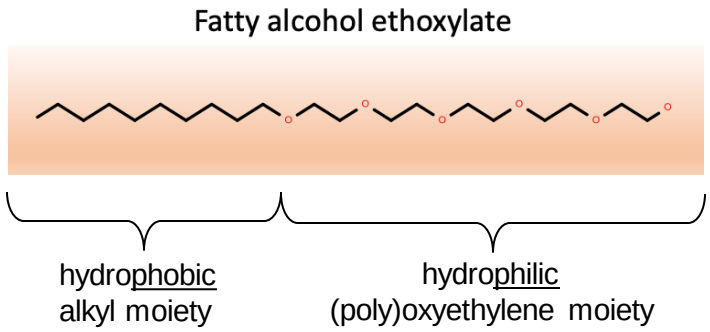
Step 4.1. Use expert judgement to identify key parameters / Criterion 1: Chemical Nature





- The AEs considered here all have the same **structural key element (common key feature)**: hydrophobic alkyl moiety (C) linked via an ether linkage to a hydrophilic (poly)oxyethylene moiety (EO)
- General structure Cx-y EOn (x-y = 8-18; n = 1-50)
- Molecular weight ranges from approx. 200 to 2,500 Da
- Although different by C-chain and degree of ethoxylation, they can be considered similar: They share the same structural key element!

Step 4.2: Use expert judgement to determine polymer similarity / Criterion 2: Physico-chemical and fate properties



- The common key feature of the linear AEs triggers Criterion 2 (physico-chemical and fate properties):
  - reduce the surface tension below 45mN/m at 5g/L
  - rapid biodegradability

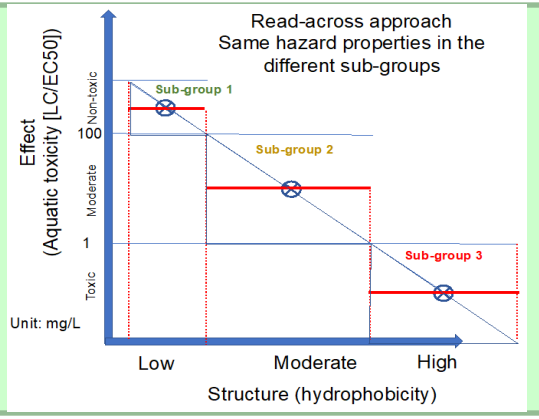
- Summary of Step 4.1 & Step 4.2: AEs included are defined as being linear, as having the general chemical structure Cx-yEOn (x-y = 8-18; n = 1-50), as reducing the surface tension of water, and as being readily biodegradable. The additional consideration of surface activity and ready biodegradability for grouping safeguard a clear definition of the group.

Step 4.4: Identify available ecotoxicity and toxicity data / Criterion 3: Ecotoxicological and toxicological data

- There is an existing comprehensive dataset on the acute aquatic toxicity available. Also, an abundance of chronic aquatic toxicity data is available.

Background for grouping by aquatic hazard similarity:

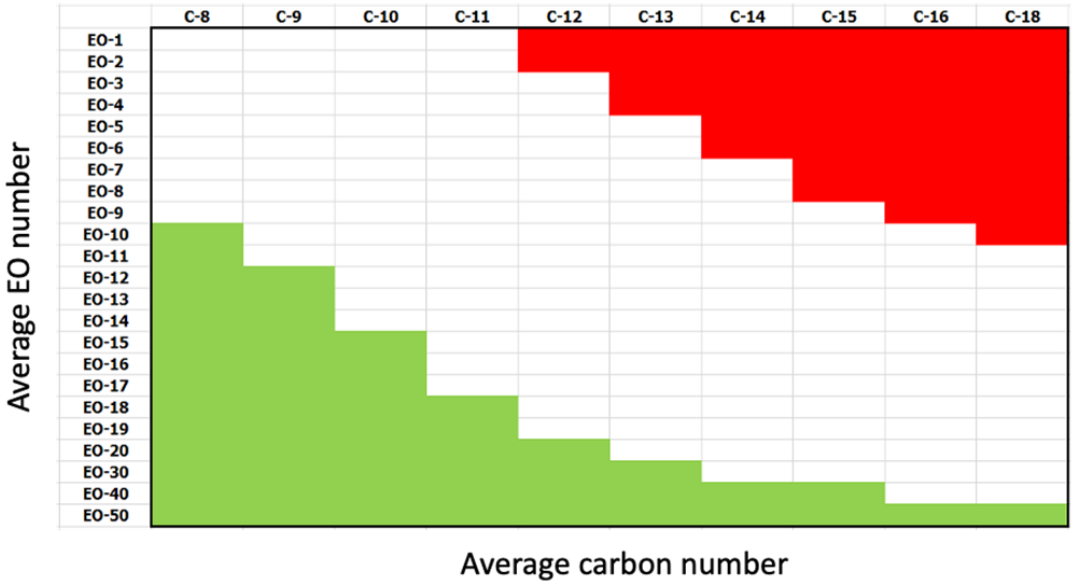
- Aquatic toxicity of the AEs is driven by their non-polar narcotic mode-of-action resulting in a strong, structure-dependent increase in aquatic toxicity potential with increasing overall hydrophobicity of the AEs.



- Other ecological endpoints, e.g. biodegradation and bioaccumulation, are mainly determined by the metabolic pathways of the AEs. Due to same common key feature, AE are easily biodegraded and/or metabolised and excreted.
- Therefore, regardless of their precise structure, the AEs are readily biodegradable and have a low tendency to bioaccumulate.

Step 4.4: Identify available ecotoxicity and toxicity data / Criterion 3: Ecotoxicological and toxicological data

- A hazard matrix was derived based on the existing data on aquatic toxicity.
- The data matrix includes all commercially available AEs based on the *Recommendations for the harmonised classification and labelling of surfactants* (CESIO, 2017).



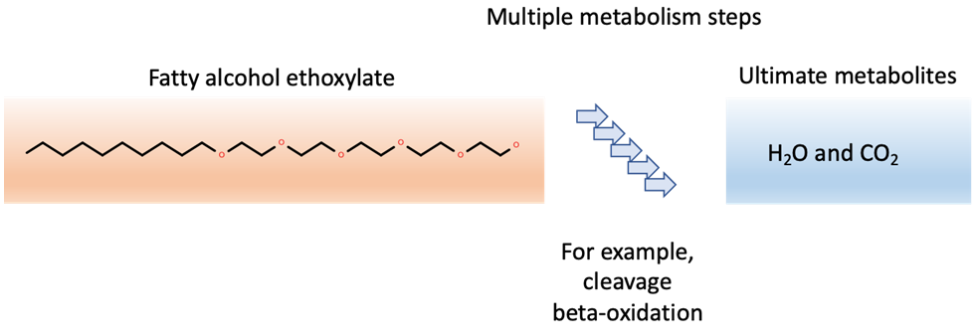
- Acute aquatic toxicity depends both on the length of the C-chain and on the degree of ethoxylation.
- Different levels (i.e. hazard classifications) can be demonstrated for different AE subgroups when applying the limit values for acute aquatic toxicity implemented in GHS.

Step 4.4: Identify available ecotoxicity and toxicity data / Criterion 3: Ecotoxicological and toxicological data

- There is a comprehensive database available on acute and long-term systemic toxicity as well as local endpoints (Yam et al., 1984; Talmage, 1994; Danish EPA, 2001; HERA, 2009; Section 7.8.3 of TR 133-3)

Background for grouping by toxicological hazard similarity:

- The major hazard potential presented by AEs is characterized by local action / local irritation
- AE are either metabolised to physiologically occurring metabolites (fatty acids), or to compounds of low toxicity.



Step 4.4: Identify available ecotoxicity and toxicity data / Criterion 3: Ecotoxicological and toxicological data

- In consideration of the toxicological profile, human health hazard matrices were prepared to address acute oral toxicity and eye irritation:

A: Human health data matrix for linear and branched alcohol ethoxylates:
AEs that elicit severe eye irritation and AEs that elicit acute oral toxicity

Blue outline: AEs that elicit eye irritation

Average EO number	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16	C-17	C-18
EO-1											
EO-1,5											
EO-2											
EO-3											
EO-4											
EO-5											
EO-6											
EO-7											
EO-8											
EO-9											
EO-10											
EO-11											
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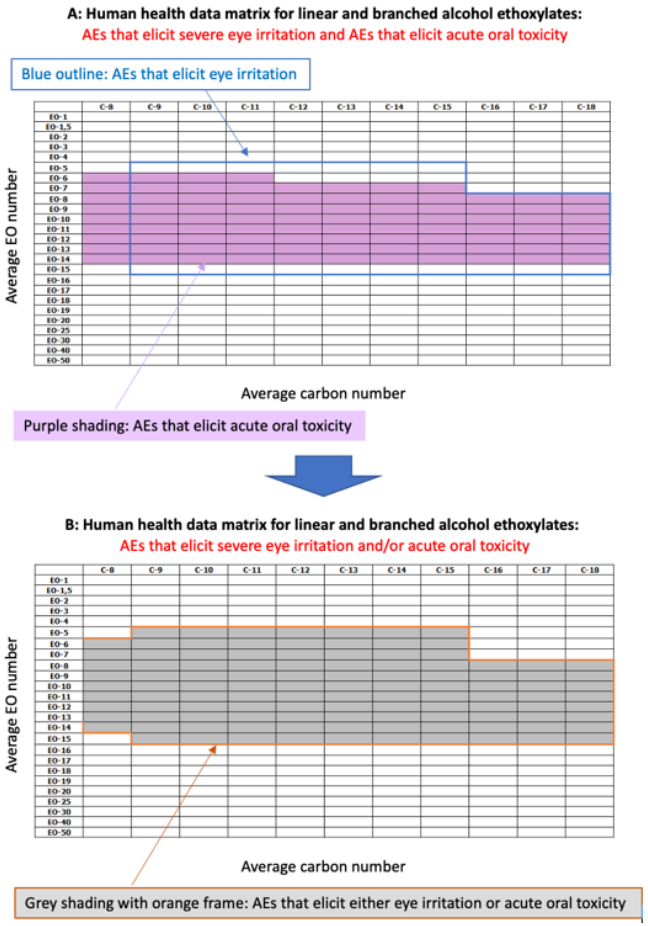
EO-16											
EO-17											
EO-18											
EO-19											
EO-20											
EO-25											
EO-30											
EO-40											
EO-50											

Average carbon number

Purple shading: AEs that elicit acute oral toxicity

Step 4.4: Identify available ecotoxicity and toxicity data / Criterion 3: Ecotoxicological and toxicological data



- The data matrix shows a trend for linear and branched AEs both for
  - eye irritation
  - acute oral toxicity
- This is dependent on C-chain length and degree of ethoxylation, which is widely concordant
- A common area for acute oral toxicity and eye irritation can be identified

Step 4.3: Define hypothesis for grouping and read-across and determine relevant approach

Guiding hypothesis for CF4Polymers (Step 4) grouping approach evaluation on AEs:

- The magnitude of ecotoxicity (**relevant hazard property**: acute aquatic toxicity) and toxicity (**relevant hazard properties**: acute oral toxicity and eye irritation) changes in a predictable manner as their C-chain length (C8 – C18) and degree of ethoxylation changes (EO 1-50).

- A hazard-similarity-based approach is suggested as relevant to subgroup AEs if they exhibit the same hazard classification (relevant hazard properties).
- Thereby, read-across can be performed for those AEs that are within the sub-group to fill data gaps for target substances using available data.

Step 4.5: Use expert judgement to justify grouping and to fill data gaps by read-across

All AEs (C8-18; EO 1-50) are considered a *SINGLE* overarching group

- Based on **similarity** in (1) amphiphilic structure **(common key feature)**; (2) trend behaviour of physico-chemical properties; and (3) similar mechanisms for (3a) biodegradation and acute ecotoxicity, as well as (3b) metabolism in mammals and systemic toxicity / local effects **(relevant hazard properties)**
- Their hydrophobic part strongly interacts with biological membranes, leading to a non-polar narcosis mode-of-action in aquatic organisms (Boeije et al., 2006).

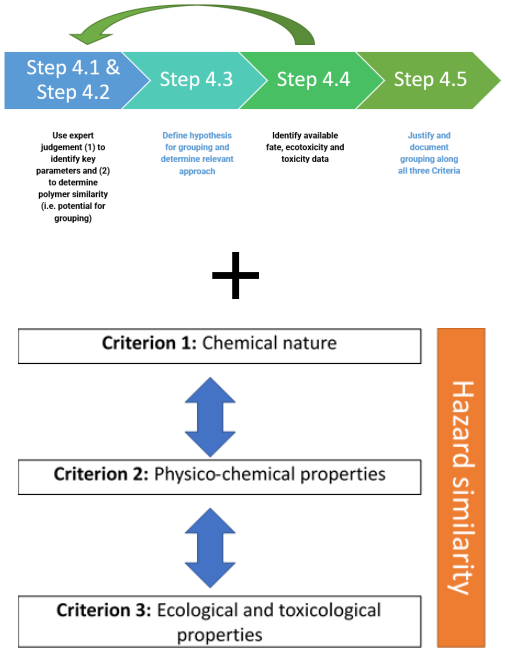
Considerations for the foundation to fill data gaps for some group members:

Environmental fate (particularly biodegradability and bioaccumulation): the AE structure is generally accessible for rapid metabolism.

Acute aquatic toxicity: Trends due to membrane interaction of the AEs could be established and suspected to be dependent on the hydrophobicity of the AE.

Human health effects: The major toxicological effects elicited by AEs are due to local action caused by membrane interaction. AEs generally present a low systemic toxicity potential. Trends in eye irritation potential of the AEs could be established.

Summary



- The amended grouping scheme presented has proven useful for the grouping of AEs
- The description along three criteria also allows the description of polymer groups and polymer identity
  - **Criterion 1**: structure **(common key feature)**
  - **Criterion 2:** trend behaviour of physico-chemical properties
  - **Criterion 3**: **relevant hazard properties** with similar mechanisms for (3a) biodegradation and acute ecotoxicity, as well as (3b) metabolism in mammals and systemic toxicity / local effects

By identifying the **key components** and a coherent **"hazard similarity" hypothesis**, an Alcohol Ethoxylates (linear, quasi-linear, and branched) polymer group was built which is **fit for purpose.**

Epoxy resin polymer grouping

Presented by Dr. Philippe G. Gottis

Risks posed by polymers in comparison with other substances (REACH Article 138)

BADGE Epoxy resin chemistry: from substance to polymers

ECETOC/CEFIC tiered grouping (Chemistry, Phys-Chem, Hazard)

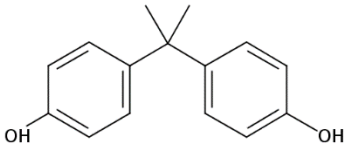
Key common constituent (KCC) for identification/grouping

Dr. Philippe G. Gottis

- 1982: Diploma of Chemie ParisTech (master degree in Chemistry)
- 1988: Paris VI/French Petroleum Institute: PhD. Physical chemistry and Petroleum Science. Structural Characterization of Asphaltenes with IR light and small-angle diffusion
- 1988-2011: Ciba and Huntsman: Various leading roles in R&D and Technical Service
- 2011-present: Huntsman: REACH and global risk manager.

BADGE Epoxy resin identification
1) 2 processes (2 CAS#) / 1 architecture

Monomers BPA & EPI

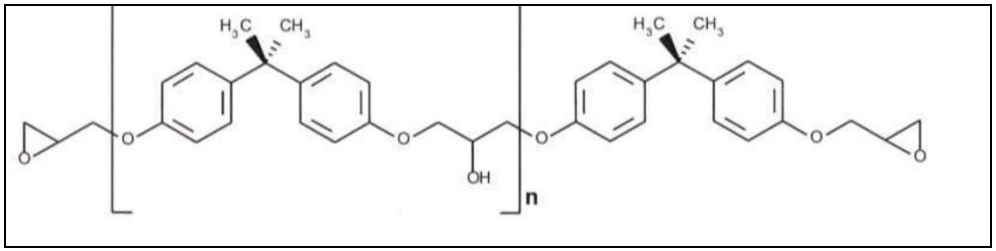


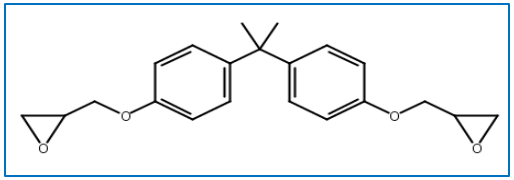
BPA

+

EPI

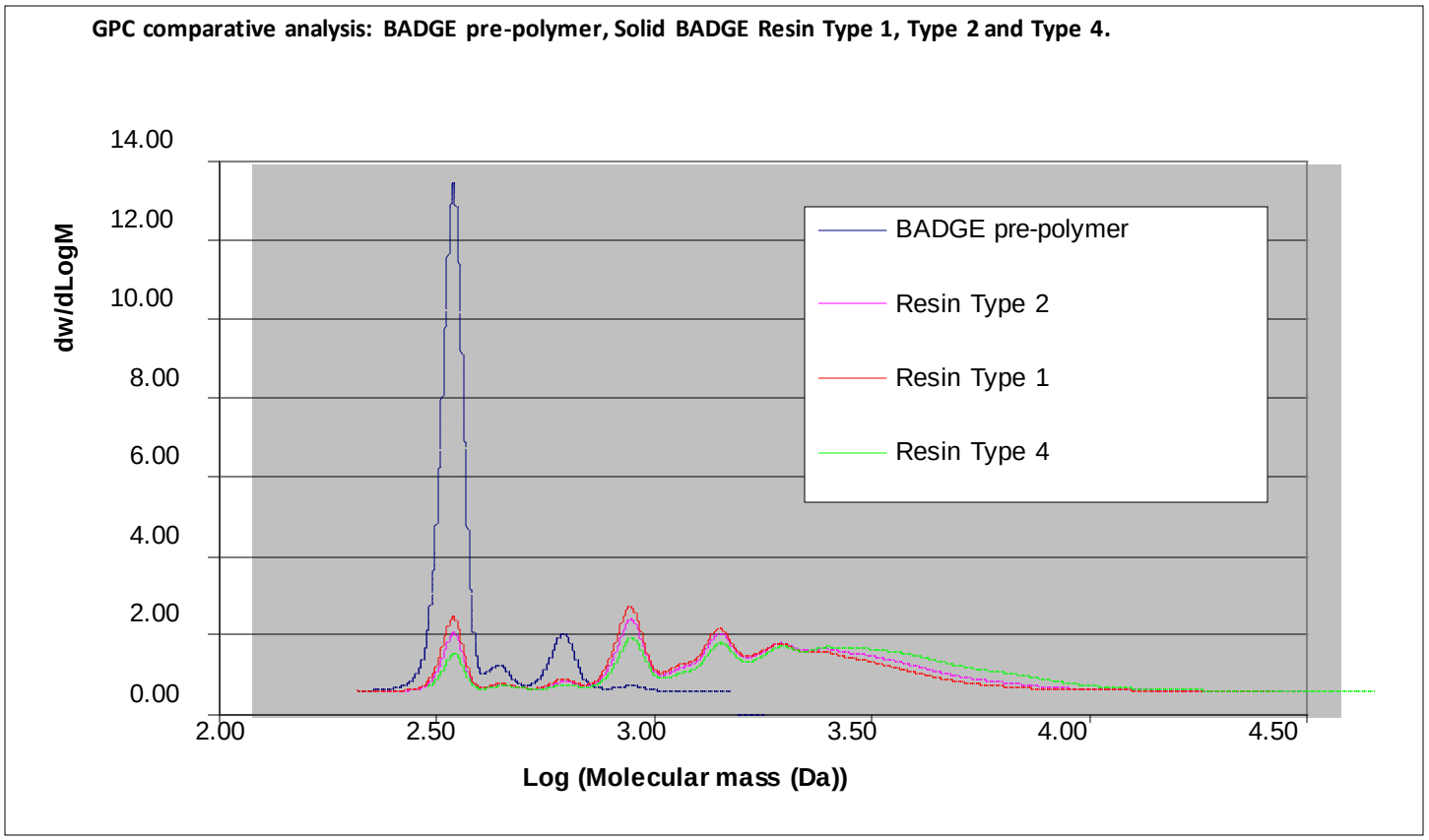
EPOXY RESIN OLIGOMER





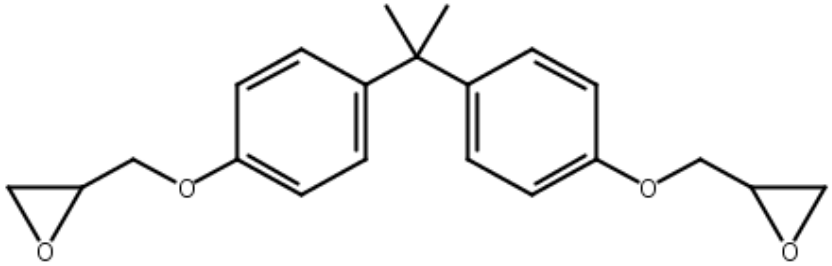
BADGE PREPOLYMER n=0

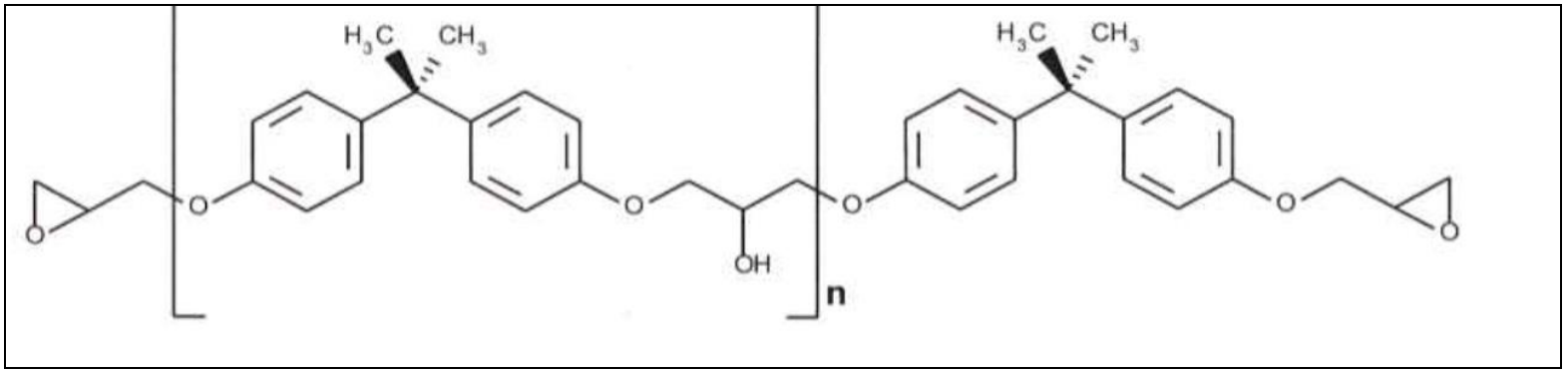
GPC spectra of BADGE solid epoxy resins: BADGE vs. type 1, 2 and 4 polymer resins



BADGE Epoxy resin identification
2) Key common constituent: BADGE

REACH substance and **prepolymer** intermediate:





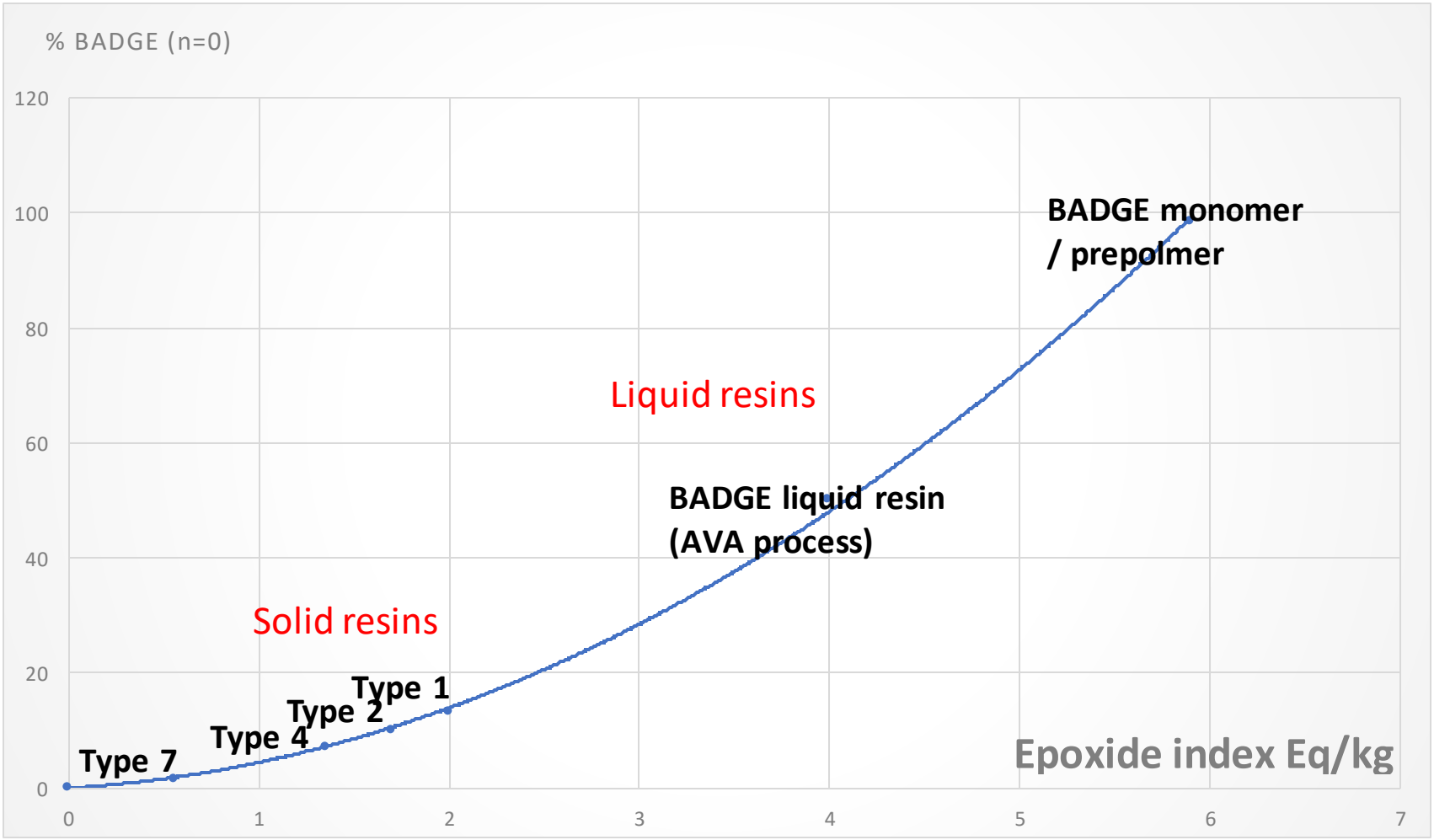
→ BADGE is a registered REACH substance with full data set

→ Epoxy resins are linear polymeric substances, which differ only in the number of BADGE links in the chain and in the unreacted BADGE ratio.

Key common constituent
(Low Molecular fraction < 800-1000Da)

- Present in every polymer of a group
- *Or a polymer group can be identified with a group of key common constituents*
- Soluble in a GPC solvent
- Easiest and most accurate substance type analytical identification
- Best manageable with Chesar tool
- Highest probability of physical- (water/fat solubility) and bio-availability
  (systemic effect / cell membrane permeability)
- Highest probability to drive toxicity & ecotoxicity
  >> Reactivity, mobility and accessibility of reactive groups
- Data set likely available
  >> Registered monomers and prepolymers substances, additives, etc.
- Way of group identification
  >> Common “active” constituents

Epoxy resin BADGE content vs. Epoxide index



Solid epoxy resin types, BADGE%
BADGE physical availability (water extraction)

GPC values	BLR	BSR Type 1	BSR Type 2	BSR Type 4	BSR Type 7
Mn (Da)	359	969	1079	1476	3211
Mw (Da)	379	1931	2269	3085	9702
Polydispersity (-)	1.057	1.992	2.104	2.090	3.021
GPC components distribution:					
Monomer BADGE (N=0) (% surf.) [M=342]	**83**	**13**	**10**	**7**	**1.4**
Monochlorhydrine of the BADGE (% surf.)	4.4	1.6	1.5	1.4	1.1
Dimer BADGE (N=1) (% surf.) [M=625]	11.5	2.6	2.0	1.4	2.7
Trimer BADGE (N=2) (% surf.) [M=909]	1.4	19.1	16.4	12.2	3.1
Oligomer BADGE (N=3) (% surf.) [M=1194]	-	20.4	18.7	15.0	3.7
Oligomers BADGE (N>3) (% surf.)	-	43.6	51.4	63.3	88.0
Water extraction test (30°C, powder, 20h) BADGE (ppm)		**31**	**3**		**0.5**
Dimer (ppm)		**< 0.5**	**Not detected**		**Not detected**

BLR: BADGE Liquid Resin / BSR: BADGE solid resin

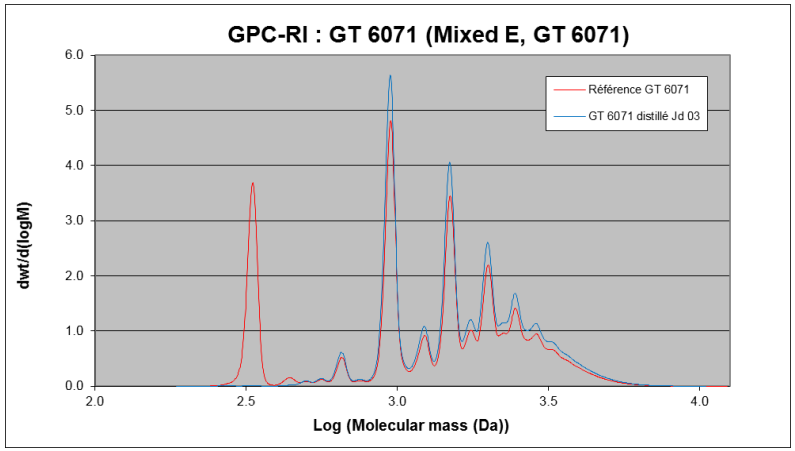
BADGE substance bioavailability

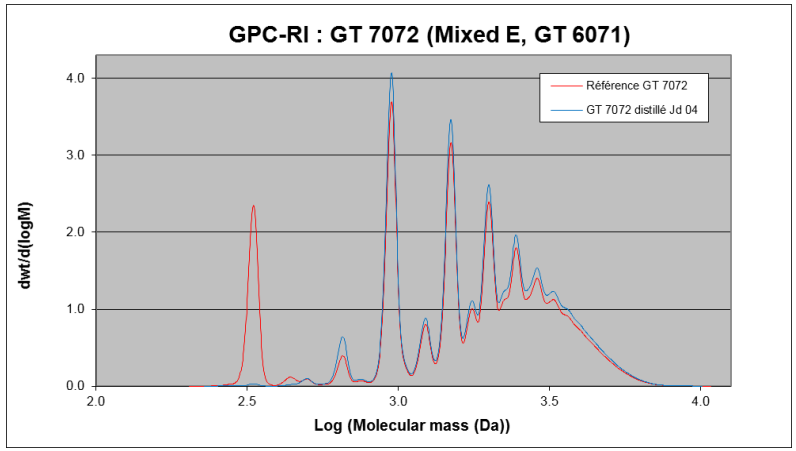
- BADGE is the only physically available fraction from solid epoxy resins
- Tox and ecotox hazard properties of selected solid epoxy resins are evaluated against BADGE = bioavailability of BADGE
- Studies launched by Huntsman
  - >> Subgroups segmentation
  - >> PLC clear limit

	Study	**OECD**
1	Water solubility	OECD 105, EEC A6
2	In vitro skin irritation	OECD 439
3	If (2) positive → In vitro eye irritation	OECD 437
4	Skin sensitisation / Local lymph assay	OECD 429
5	Aquatic tox (Daphnia)	OECD 202

Tier 1 studies launched by Huntsman
Study material: 2 LMW solid resins
with & without the reference substance

Samples	% BADGE (HPLC)
Type 1 (Original)	17.1
Type 1 (Distillation residue)	0.2
Type 2 (Original)	11.3
Type 2 (Distillation residue)	0.1





Tier 1 studies: 2 low MW BSR with & without the key common constituent - Results

Property		Type 1 and Type 2 resins as produced and purified				BADGE
		Type 1 as produced	Type 1 purified	Type 2 as produced	Type 2 purified	Substance
Physical state		Solid				Viscous Liquid
Number average molecular weight (M_n; Da)		928	1426	1174	1621	359
Weight average molecular weight (M_w; Da)		1575	1822	1990	2121	379
Polydispersity (no unit)		1.7	1.28	1.7	1.33	1.057
Epoxide groups content						
Functional group equivalent weight (g/Eq.)		455	725	581	840	183--189
Epoxy index (Eq./kg)		2.2	1.38	1.72	1.19	5.30-5.45
Component distribution, as measured by gel permeation chromatography (% surf.)						
BADGE (n = 0)		15.7	0.1	9.9	0.2	83
Monochlorohydrin of BADGE		0.8	< 0.1	0.6	< 0.1	4.4
BADGE oligomer (n = 1)		2.2	2.6	1.7	2.8	11.5
BADGE oligomer (n = 2)		21.3	25.6	16.2	17.9	1.4
Higher oligomers		60.0	71.7	71.6	79.1	
Tier 1 test results						
Water solubility	OECD 105	< 2mg/l	< 2mg/l	< 2mg/l	< 2mg/l	6.9 mg/l
In vitro skin irritation	OECD 439	Not irritating MTV 15 min* 78.56%	Not irritating MTV 15 min* 98.49%	Irritating MTV 15 min* 10.37%	Not irritating MTV 15 min*70.07%	Irritating
Skin sensitisation LLNA	OECD 429	Not sensitising	EC3 54.5 SI values 1.06-3.28 Weak sensitiser	Not sensitising	Not sensitising	EC3 5.7 SI values 0.9-11.8 Moderate sensitiser
Acute Aquatic Toxicity to Daphnia (Tween 80)	OECD 202	EC50 6.51 mg/l	EC50 31.64mg/l	EC50 12.97 mg/l	EC50 39.40 mg/l	EC50 1.8 mg/l

* Main Tissue Viability 15 min

** Daphnia: Type 1 and 2 resins with Tween 80; BADGE tested in fresh water

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BADGE polymer grouping
Conclusion

Group identification layers

1) Chemistry

- Chemistry well defined --> first layer grouping prioposal
- 2 processes → 2 CAS# and 2 sets of monomers / 2 polymer limits

→ Usefulness and limitations of CAS identifiers (one BADGE polymer group)

- Continuously varying compositions from BADGE substance to BADGE polymers (no tipping point)

→ Polymer Mol weight limit for classification, PLC/PRR boundaries
→ low molecular fraction (well-defined)
→ incl. Key Common Constituent (main tox driver)
→ high molecular fraction (Repeat unit, mol weight distribution, reactive functional groups)
→ multi-constituent type approach

- BADGE polymer low boundary → low molecular range BADGE solid resins (type 1)

2) KCC physical availability (water extraction)

- Low physical availability / Only BADGE monomer identified (ppm level)

3) KCC bioavailability

- Selected 2 low molecular solid resins with Mol weight just below and just above Mn 1000Da
- No further hazard as the BADGE hazard expected (similarity of hazard, only differences of extent/intensity)
- Low bioavailability of BADGE
- Solid resins test methods merit some development work

Grouping of polymers and read-across to corresponding oligomers: Polyetherols (PEOLs)

Presented by Dr. Isabel D. Krug

Isabel D. Krug (Dr. rer. nat.)

- Diploma in Food Chemistry at the department of Food Chemistry and Toxicology at TU Kaiserslautern (2009 – 2014)
- PhD thesis as WWU Münster at the Institute for Food Chemistry with focus toxicology (2015 – 2018) (“In vitro-studies on the effects of selected mycotoxins and marine biotoxins at the blood-brain barrier”)
- Regulatory Toxicologist at BASF SE (2018 – now)

Focus of CS5: Polyetherols - PEOLs

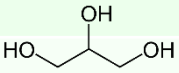
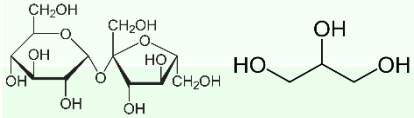
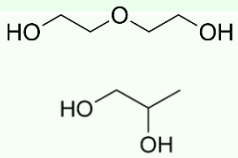
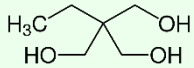
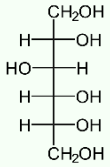
Definition

- Polymers based on initiator molecules containing multiple OH- or NH_2- functional groups (**e.g. simple molecules like glycerol, diethylene glycol, or more complex molecules like sugars or sugar alcohols** to linear amines and aromatic amines)
- Initiator molecules are alkoxylated with ethylene oxide (EO) or propylene oxide (PO) to varying degrees
- Result: polyetherols with varying chain lengths, fulfilling polymer criteria

Use

- Further processed downstream: e.g. undergo futher reactions with diisocyanates to form foams (mattresses, insulation boards…)
- Mainly handled in a controlled, industrial setting, followed by further processing downstream
- Formation of other polymers out of them (not considered in this CS)
- In general, no consumer use or professional use is anticipated → exposure or wide dispersive use considered unlikely

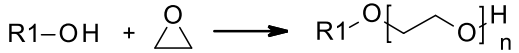
PEOLs included in CS5

Initiator molecule (R1)	Chemical structure	Alkoxylation variants (repeating units)
1,2,3-Propanetriol (i.e. glycerol)		EO PO EO-PO
Saccharose / glycerol (mixture for co-initiated PEOLs)		PO EO-PO
Diethylene glycol (i.e. 2,2'-oxydiethanol)		EO-PO PO (only NLP)
Propane-1,2-diol (i.e. monopropylene glycol)		PO EO-PO
Propylidynetrimethanol (i.e. trimethylol propane)		EO PO EO-PO
Glucitol (i.e. D-sorbitol)		PO EO-PO

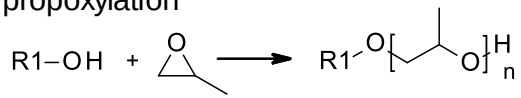
R1 = Initiator molecule. Alkoxylation of the hydroxyl functional group of the initiator molecule with ethylene oxide (EO) or propylene oxide (PO): 1. Ethoxylation (EO) 2. Propoxylation (PO) 3. Ethoxylation and propoxylation (EO-PO)

Alkoxylation

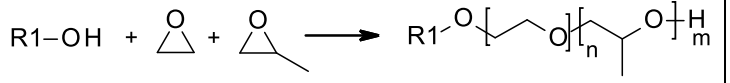
1. ethoxylation



2. propoxylation



3. ethoxylation and propoxylation



Grouping basis

- Chemical nature, physico-chemical properties, and hazard similarity & application domain
- Basic acute and local toxicity data for selected PEOLs available
- Data gaps filled by read-across from corresponding NLPs*. NLPs with same/similar initiator molecules serve as appropriate data source for read-across

***NLP polyols (NLPs) = oligomeric PEOLs**

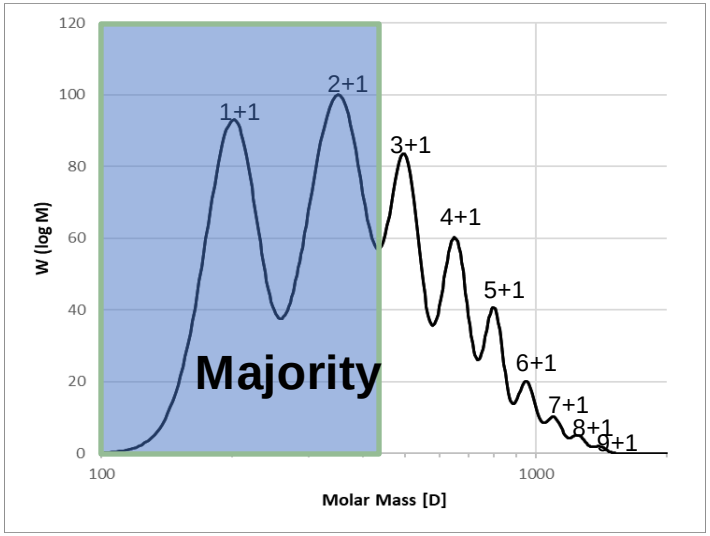
- Constituents of PEOLs have intersection with NLP polyols constituents. Continuum of alkoxyl ation chain lengths. Artificial cut-off between NLP polyols and PEOLs ("3+1 rule")

Hypothesis:

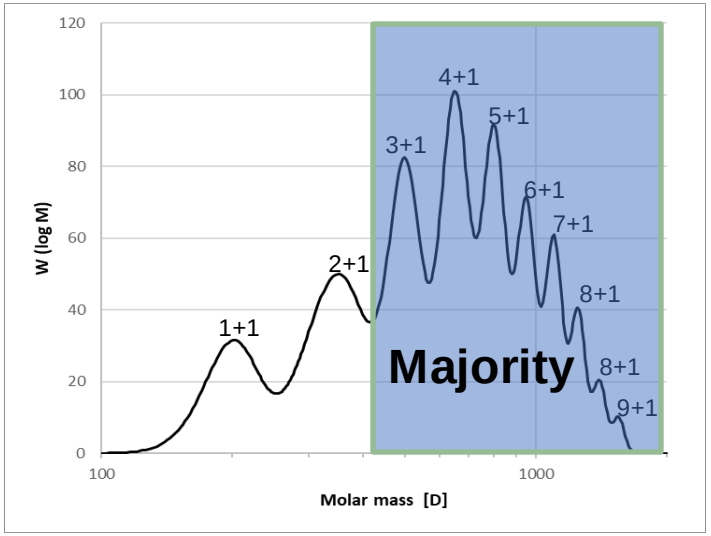
- Grouping of PEOLs of this CS in one group, potential subgrouping by initiator molecule
- Alkoxylation ↑ (increasing repeating units) → influence of initiator molecule ↓
- Generally accepted concept: Systemic bioavailablity decreases with increasing molecular weight (Lipinski rules/Rule of 5). If no/low effects seen for smaller, more bioavailable corresponding NLP polyols, systemic effects are expected **not** to be higher for larger PEOLs

NLP Polyols vs PEOLs

oligomeric Polyols (NLP)



polymeric Polyols (PEOLs)



Schematic illustration of gel permeation chromatograms of oligomeric no-longer polymer (NLP) polyols and polymeric polyols (PEOLs) resulting from alkoxylation of the initiator molecules and differentiation

- Regulatory cut-off but rely on same principle
- structures of NLPs equivalent to PEOLs, only difference: chain lengths resulting in different molecular sizes

NLP polyols are suitable data source for polymeric PEOLs

Data situation PEOLs

- PC data: available
- ENV data:
  - very little data available for polymers
  - Basic data set available for NLP polyols
- HH data:
  - PEOLs: acute and local toxicity data for selected PEOLs available
  - NLP polyols: basic data set available + limited repeated dose data

PEOLs: Physico-chemical properties

Endpoint	Data
Molecular weight range	LMW 500 – 800 Da, medium range 800 – 3,000 Da, HMW up to 18,000 Da
Viscosity	Highly viscous liquids > 10,000 mPa*s (100 mPa*s – 40,000 mPa*s at 25°C)
Water solubility	High (1 – 1,000 g/L at 20°C)
n-octanol/water partition coefficient	Mostly logK_{ow}<1 (few PEOLs >1 <2)
Surface activity	In general not surface active (> 45 mN/m)
Vapour pressure	Low (< 0.10 mbar at 20°C)

Physico-chemical data support boundary description of PEOLs as group

PEOLs: Environmental properties

- Robust, publicly available fate data are scarce
- NLP polyols: mostly readily biodegradable (Not considered for grouping)
- NLP polyols:
  - No acute aquatic toxicity up to 100 mg/L: NLP polyols highly water soluble
  - (few) chronic studies confirm low aquatic toxicity
  - No concern for bioaccumulation identified

Hypothesis:

Corresponding PEOLs, which are based on same/similar initiator molecule and alkoxylation but have longer chains, (i.e. higher MW) do not exhibit more pronounced toxicity than their lower molecular weight and shorter-chained NLP counterparts.

→ NLP counterparts did not raise concerns

→ The few studies that have been performed on PEOLs support the hypothesis

No environmental hazard for PEOLs expected

PEOLs: Human health properties

- Low potential for systemic bioavailability of PEOLs
  - > 500 Da: limited passive diffusion in GI-tract expected
  - In regulatory setting: molecules > 1,000 Da have a low likelihood of becoming systemically bioavailable
- ↑ molecular weight → systemic bioavailability ↓

Hypothesis:

Corresponding PEOLs, which are based on same/similar initiator molecule and alkoxylation but have longer chains, (i.e. higher MW) do not exhibit more pronounced toxicity than their lower molecular weight and shorter-chained NLP counterparts.

- NLP polyols: No local and acute toxicity. Limited toxicological data for systemic toxicity endpoints indicate low systemic toxicity.
- PEOLs: Low to absent local and acute toxicity for acute dermal toxicity, skin/eye irritation, mutagenicity in bacteria, and skin sensitization
  - In general, no acute oral and acute pulmonary toxicity for **majority** of tested PEOLs
  - Limited data indicate slightly more pronounced acute oral and inhalation toxicity for Gly- and PG-initiated PEOLs (MW-range of 500 – 2,000 Da) → further elaboration ongoing

PEOLs show low to absent local and acute toxicity. No inherent potential to induce systemic toxicity is assumed.

Summary

- Use in industrial setting and further processed
- Generally low hazard potential of PEOLs (ENV and HH)
- Grouping within PEOLs and read-across to NLP polyols based on
  - chemical nature ✓
  - physico-chemical properties ✓
  - hazard similarity ✓

no hazard identified for NLP polyols → no hazard assumed for PEOLs

- **PEOLs can be grouped in one group of hazard similarity**
- **NLP polyols serve as suitable source to fill data gaps**