Bundesanstalt für Arbeitsschutz und Arbeitsmedizin

Workshop on SID and Substance Sameness

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From substance identification to experiences from SID checks

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Outline

1. Identifying complex substances
2. Experiences from substance identity checks

What is a substance?

Chemical Abstract Service

- **Ideal substance** (100%)
- Structural formula
- Molecular formula
- Unambiguous chemical name
- CAS no.
- **No information about purity and impurities**

REACH

- **Real substance** (Article 3(1))
- Substance as manufactured including
  - impurities
  - if necessary, stabiliser

⇨ Intended manufactured substance

However in daily practice: (ideal) CAS no. is used for identification of real substances

Substance ID - defined substances

Example

2-chlorotoluene is registered with CAS no 95-49-8

- mono-constituent substance
  - Manufacturer A: 2-chlorotoluene purity 87%
  - Manufacturer B: 2-chlorotoluene purity 99%

General agreement:
CAS no. (ideal substance) is a unique identifier for mono-constituent (real) substances with a purity of at least 80%).

ID guidance derived consequences:

- **Real substances** (main constituent ≥80%) are
  - identified by the same CAS no, irrespective of the impurity profiles
  - the same as the main constituents are identical
- **Manufacturers A and B**
  - in the same SIEF
  - members of a joint dossier, although different purities

Substance ID – UVCB

Example:
EC no 273-579-2, CAS no 68990-11-4, Arnica montana, ext.
Extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc., obtained from Arnica montana, Ericaceae

For UVCBs no such rule as 80/20% or 80/10% for defined substances

Extraction process:
- manufacturer A: solvent ethanol
- manufacturer B: supercritical CO_2

⇨ Both processes are covered by the EC no. / CAS no.

- Are substances A and B the same, although different processes?
- Joint dossier?
- Is EC no. / CAS no. sufficient to decide about sameness **and** joint dossier?

SIEF – joint dossier (I)

Formation of a **SIEF**

•Basis: same phase-in substance (art. 29 REACH)

→ EINECS entry (EC no., CAS no.)

Compilation of the **joint dossier**

•Basis: EINECS entry (EC no., CAS no.)

•Sufficient? If not, what else? Criteria?

Mono-constituent substances:

•application of 80/20% rule

•Joint dossier, yes, but taking into account the different impurity profiles

Multi-constituent substances:

•application of 80/10% rule

•Joint dossier, yes, but taking into account the variations of the main constituents and the different impurity profiles

SIEF – joint dossier (II)

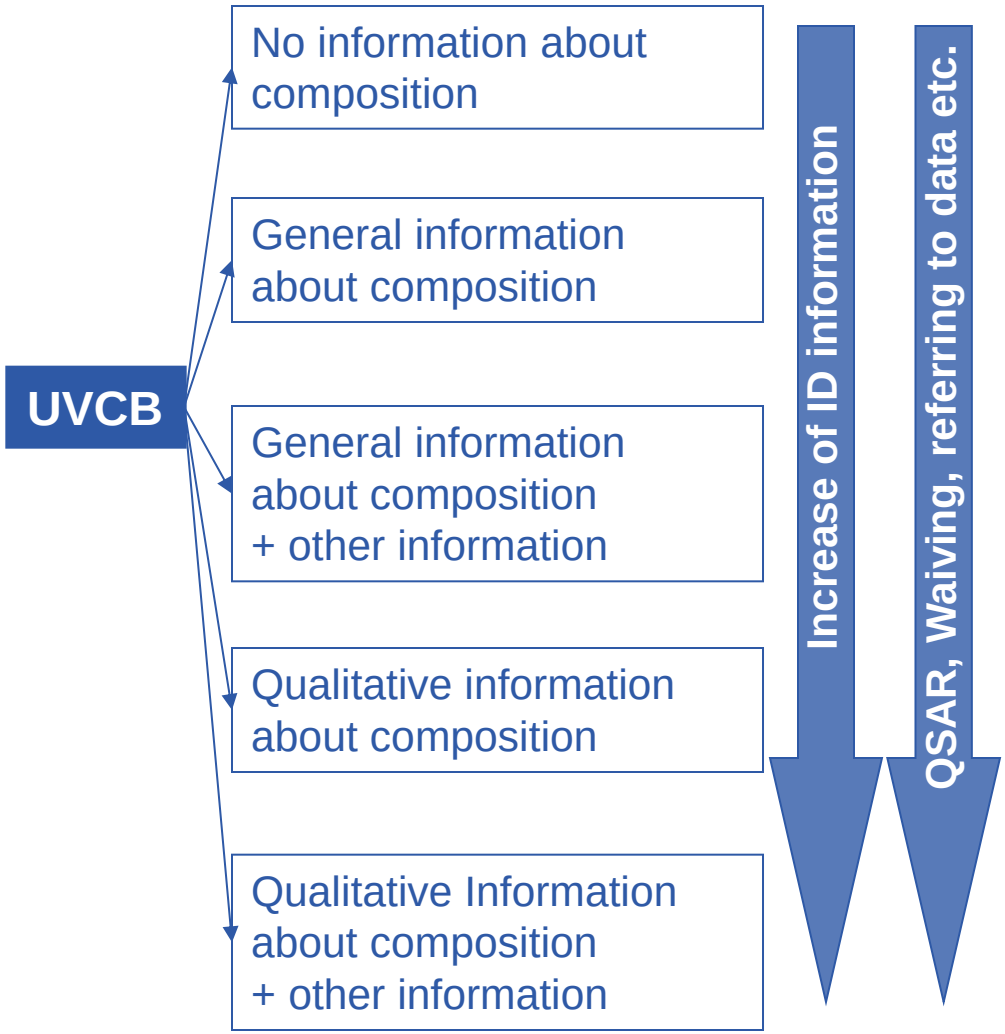
UVCB – How to decide on sameness and joint dossier?

- Starting point for sameness: pre-registrants of UVCBs with same CAS/EC no. join the same SIEF
- Is it justified to submit a joint dossier **only** on the basis of a CAS/EC no.?
  - **No**, a decision about a joint UVCB dossier requires very detailed considerations about the data set

We assume that the industry considers the question about compliance of the data set before a joint dossier project is started

= responsible care

UVCB – details of composition



CAS no. 100403-20-1, Coconut oil, distn. residues

CAS no. 97615-94-6, Fish, ext.
Extractives and their physically modified derivatives such as proteins, carbohydrates, lipids, nucleic acids, inorganic ions, etc. obtained from (mixed fish).

CAS no. 92045-74-4 Paraffin waxes (petroleum), low-melting
A complex combination of hydrocarbons obtained from petroleum fractions by solvent crystallization (solvent deoiling), by sweating or an adducting process. It consists predominantly of straight chain saturated hydrocarbons having carbon numbers predominantly greater than C12.

CAS no. 91845-18-0, Glycerides, C14-22

CAS no. 8021-99-6, Charcoal, bone
A fine black powder obtained by burning animal bones in a closed container. It consists primarily of calcium phosphate and carbon.

Outline

1. Identifying complex substances
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Sameness of substances

Sameness of substance on basis of CAS/EC no.

Clear for defined substances

CAS no. 64-17-5: ethanol

80/20% rule →sameness

Clear for UVCBs?

CAS no. 100765-57-9 Pyridinium, 1-(phenylmethyl)-, alkyl derivs., chlorides

Manufacturer A: analytics show “heptyl octyl derivs.”

Manufacturer B: analytics show “ethyl methyl derivs.”,

Manufacturer C: analytics show broader distribution, e.g. methyl to octyl derivs.

Joint submission?

Sameness of substances

Clear for UVCBs – probably not always

SID guidance chapter 4.1:

"The basic rule is that substances are defined as much as possible by the chemical composition and the identification of the constituents. Only if this is not technically feasible other identifiers should be used, as specified for the various types of UVCB substances."

→UVCB names should contain generated information about the substance

main identifiers for UVCBs are related to:

- source of the substance
- process used
- or to a group of "other main identifiers" (e.g. "chromatographic or other fingerprints").

→ **similarity is no criterion for sameness and a joint submission**

→ similarity may in some cases be a criterion for data sharing

Sameness of substances

Pyridinium, 1-(phenylmethyl)-, alkyl derivs., chlorides
Manufacturer A: analytics show “heptyl octyl derivs.”
Manufacturer B: analytics show “ethyl methyl derivs.”,
Manufacturer C: analytics show broader distribution, e.g. methyl to octyl derivs.

100765-57-9 Pyridinium, 1-(phenylmethyl)-, alkyl derivs., chlorides
70914-44-2 Pyridinium, 1-(phenylmethyl)-, C_{7-8}-alkyl derivs., chlorides
68909-18-2 Pyridinium, 1-(phenylmethyl)-, Et Me derivs., chlorides

→ different registrations

SID guidance chapter 4.3:

“Where the chemical composition of e.g. a complex reaction product or a substance of biological origin is known, substance identification should be identified either as a mono- or multi-constituent substance, as appropriate.”

Experiences from SID checks

SID deficiencies make sameness discussion difficult:

General:

- CAS-No. and (EC/CAS/IUPAC) name inconsistent
- mixture registered
- stereoisomers
- other general errors

Analytics

- inadequate or no analytical data
- analytical data and registered substance inconsistent
- Joint dossiers: same analytical data for different registrations

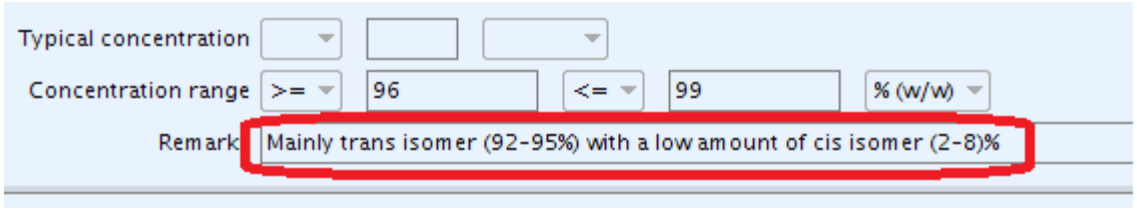
UVCB

- UVCB names
- UVCB vs. multi-constituent substance

Examples of inconsistencies

Stereoisomer:

- e.g. cis/trans
- two options possible
  - racemate: multi-constituent substance
  - 80/20% rule: one of the diastereomer is main constituent →mono-constituent substance + *trans* or *cis* must be in the chemical name, other isomer is impurity



Examples of inconsistencies

UVCB:

Chemical name: Hydrocarbons, Cx-unsaturated, polymerized

IUPAC name: Hydrocarbons, Cx-unsaturated, polymerized

Constituent	Constituent	Constituent	Constituent
Dimers of Cx-monomers Typ. conc. ca. 28% Range >= 20 %	Trimers of Cx-monomers Typ. conc. ca. 23% Range >= 10%	Highers of Cx-monomers, Typ. conc. ca. 49 % Range >= 15 %	Monomers Typ. conc. <0.1% Range < 1 %

- general name to take part in joint submission. Problem of data sharing.
- identity unclear, although structure of constituents are basically known.

Examples of inconsistencies

UVCB:

Chemical name: Hydrocarbons, Cx-unsaturated, polymerized

IUPAC name: Hydrocarbons, Cx-unsaturated, polymerized

- structure of constituents are basically known
- chemical name should comprise manufacturing process, educts & identified structural groups

Examples of inconsistencies

UVCB vs. multi-constituent substance

- sum of constituents ≥ 80%

I	Constituent	Constituent	Constituent	Constituent
Type	UVCB	defined	defined	defined
content	>30 – <75% (38%)	>10 – <40% (17%)	> 5% - < 45% (40%)	>1 – <10% (2%)

→ UVCB substance, if one constituent is UVCB

II	Constituent	Constituent	Constituent	Constituent
Type	defined	defined	defined	defined
content	>30 – <75% (38%)	>10 – <40% (17%)	> 5% - < 45% (40%)	>1 – <10% (2%)

→ All constituents defined, but UVCB because of great variability of constituents?

→ Are there criteria?

Examples of inconsistencies

UVCB vs. multi-constituent substance

- Substance ID guidance chapter 4.1:
  "It is recognized that there will be borderline cases between well defined substances (reaction products with many constituents, each within a broad range) and UVCB substances (reaction products with variable and poorly predictable composition). It is the responsibility of the registrant to identify a substance in the most appropriate way."
- no criteria, therefore both options possible; **test requirements remain the same.**
- strong recommendation: test substance should be defined more precisely (no variation). Otherwise SID of test substance is unclear and data sharing problematic.
- responsibility of industry to take sample of appropriate substance as test substance.

Summary

- Substance ID means composition of a substance
- Industry obliged to identify substance as much as possible
- Substance ID basis of a registration / joint submission
- Proper SID enables sameness discussion (and joint submissions)
- Proper SID enables data sharing
- Proper SID enables read-across, …

Finally

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Thank you for your attention!