

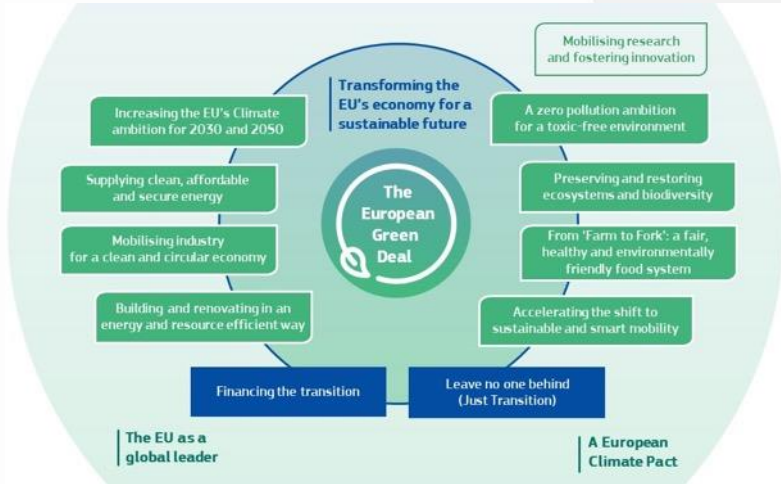


# Automated sustainability screening of natural substances used for biocontrol

Sarah Croonenborghs, Sabine Navis, Frederick Verdonck, Karel Viaene

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## ► Background



⇒ using **natural substances** is a logical choice

## ► Background

- Natural substance **not per definition safe** substance

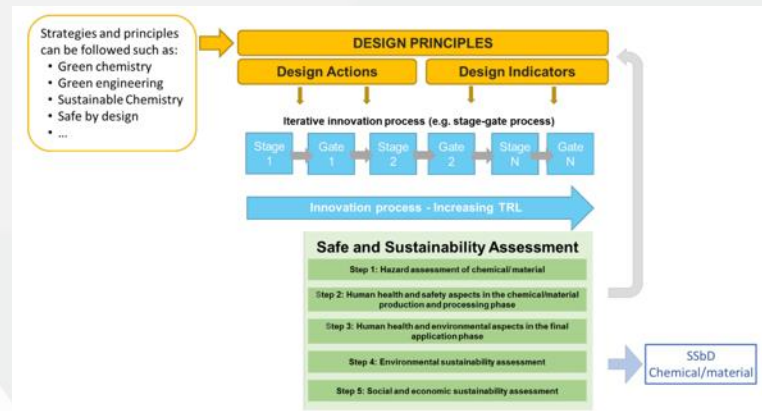


- JRC has developed framework  
**Safe and Sustainable by Design**  
⇒ aims for early assessment of  
all substances involved

- Avoid or be prepared: the sooner, the better!



<https://op.europa.eu/en/publication-detail/-/publication/eb0a62f3-031b-11ed-acce-01aa75ed71a1/language-en/format-PDF/source-285338970>



## ▶ Background

- ▶ Natural substances typically **more complex** than conventional substances

### **Natural** substances

- Mixture of components
- Exact composition not always known or variable (time of harvest, growing conditions & location, ...)

### **Conventional** active substances

- Monoconstituents where different batches are very similar

- ▶ Assessment of natural substances **more time consuming**

⇒ high potential for **automated screening tools**

## ▶ Data input

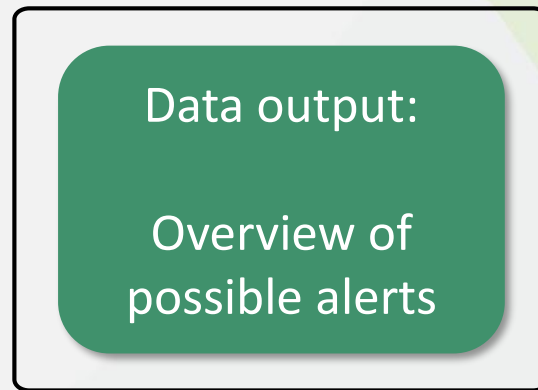
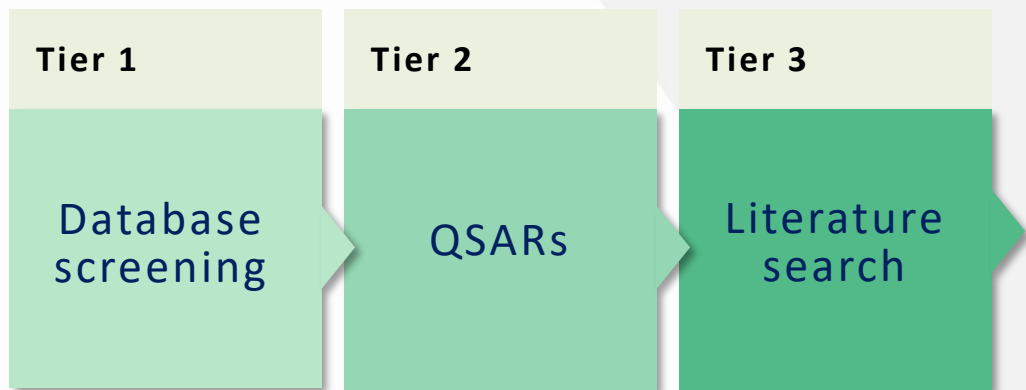
### Example: Lavender oil

- ▶ List of (known) components
- ▶ For natural substances:  
Multiple lists depending on growing conditions
- ▶ Approach also valid for lists of coformulants

Known constituents					
	Chemical name EC CAS IUPAC other	Number EC CAS	Mol. Formula Hill method	Typical conc. % (w/w)	Conc. range % (w/w)
A	<b>EC</b> linalyl acetate <b>CAS</b> 1,6-Octadien-3-ol, 3,7-dimethyl-, acetate <b>IUPAC</b> 3,7-Dimethyl octa-1,6-dien-3-yl acetate	<b>EC</b> 204-116-4 <b>CAS</b> 115-95-7	C <sub>12</sub> H <sub>20</sub> O <sub>2</sub>	33	28 - 38
B	<b>EC</b> linalool <b>CAS</b> 1,6-octadien-3-ol, 3,7-dimethyl- <b>IUPAC</b> 3,7-Dimethyl octa-1,6-diene-3-ol	<b>EC</b> 201-134-4 <b>CAS</b> 78-70-6	C <sub>10</sub> H <sub>18</sub> O	29,5	24 - 35
C	<b>EC</b> Bornan-2-one <b>CAS</b> Bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl- <b>IUPAC</b> 1,7,7-Trimethylbicyclo[2.2.1]-2-heptanone <b>Other</b> camphor	<b>EC</b> 200-945-0 <b>CAS</b> 76-22-2	C <sub>10</sub> H <sub>16</sub> O	7	6 - 8
D	<b>EC</b> Cineole <b>CAS</b> 2-oxabicyclo [2.2.2]octane, 1,3,3-trimethyl- <b>IUPAC</b> 1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane <b>Other</b> 1,8-cineole	<b>EC</b> 207-431-5 <b>CAS</b> 470-82-6	C <sub>10</sub> H <sub>18</sub> O	5,5	4 - 7
E	<b>EC</b> P-menth-1-en-4-ol <b>CAS</b> 3-Cyclohexen-1-ol, 4-methyl-1-(1-methylethyl)- <b>IUPAC</b> 1-(1-Methylethyl)-4-methyl-3-cyclohexen-1-ol <b>Other</b> terpinene-4-ol	<b>EC</b> 209-235-5 <b>CAS</b> 562-74-3	C <sub>10</sub> H <sub>18</sub> O	3,25	1,5 - 5
F	<b>EC</b> 2-Isopropenyl-5-methylhex-4-enyl acetate <b>CAS</b> 4-Hexen-1-ol, 5-methyl-2-(1-methylethenyl)-, acetate <b>IUPAC</b> 2-(1-Methylethenyl)-5-methylhex-4-en-1-ol <b>Other</b> (±)-Lavandulol acetate	<b>EC</b> 247-327-7 <b>CAS</b> 25905-14-0	C <sub>12</sub> H <sub>20</sub> O <sub>2</sub>	2,25	1,5 - 3
G	<b>EC</b> DL-borneol <b>CAS</b> Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, (1R,2S,4R)-rel- <b>IUPAC</b> (1R,2S,4R)-rel-1,7,7-trimethyl bicyclo[2.2.1]heptan-2-ol <b>Other</b> borneol	<b>EC</b> 208-080-0 <b>CAS</b> 507-70-0	C <sub>10</sub> H <sub>18</sub> O	2,25	1,5 - 3
H	<b>EC</b> Caryophyllene <b>CAS</b> Bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methylene-, (1R,4E,9S)- <b>IUPAC</b> (1R,4E,9S)-4,11,11-trimethyl-8-methylene bicyclo[7.2.0]undec-4-ene <b>Other</b> trans-beta-caryophyllene	<b>EC</b> 201-746-1 <b>CAS</b> 87-44-5	C <sub>15</sub> H <sub>24</sub>	1,75	1 - 2,5

## ► Screening process

### Tiered approach



## ▶ Tier 1: Automated database screening

- ▶ Check of existing databases and lists for specific endpoints:
  - CLP
  - CMR
  - ED
  - PBT
  - ...
- ▶ Wide array (ministries, EU, NGO, companies,...):
  - US EPA
  - EU REACH
  - SVHC
  - EU ED priority list
  - CORAP
  - ...

**Time consuming to check manually**

**⇒ Automated screening**

# ► Tier 1: Automated database screening



From BAuA

[https://www.subsportplus.eu/subsportplus/EN/Substances/Data-base-of-restricted-and-priority-substances/restricted-priority-substances\\_node.htm/](https://www.subsportplus.eu/subsportplus/EN/Substances/Data-base-of-restricted-and-priority-substances/restricted-priority-substances_node.htm/)

**Search for**  
Search term (CAS-No. or EC-No.)

Substance list  
all 38 lists

SEARCH

Search results 1 to 2 from a total of 2

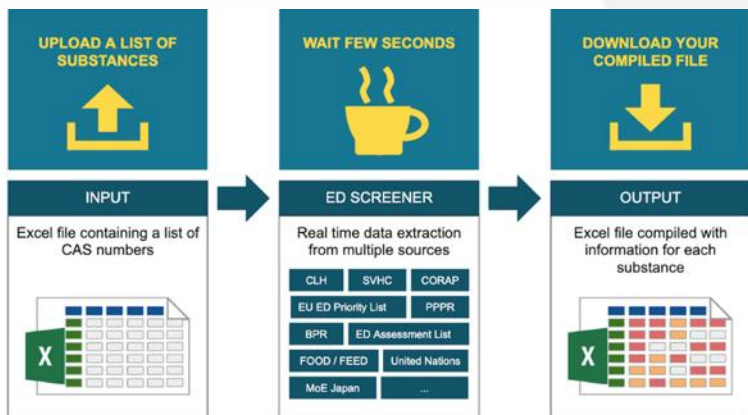
No.	Substance/group name	CAS No.	EC No.	List of Substances	Property of Concern
1	Linalool	78-70-6	201-134-4	<a href="#">KEMI: PRIO Phase-Out Substances</a>	Allergenic
2	linalool; 3,7-dimethyl-1,6-octadien-3-ol; dl-linalool [1] coriandrol; (S)-3,7-dimethyl-1,6-octadien-3-ol; d-linalool [2] licareol; (R)-3,7-dimethyl-1,6-octadien-3-ol; l-linalool [3]	78-70-6 [1] 126-90-9 [2] 126-91-0 [3]	201-134-4 [1] 204-810-7 [2] 204-811-2 [3]	<a href="#">SDSC: Substance List according to Screening Criteria</a>	CLP Regulation: sensitiser (H317, H334)



# Tier 1: Automated database screening

Already developed at ARCHE for CMR, PBT and ED endpoints

Automated batch screening e.g ED endpoints together with My Chemical Monitoring BV



Output: matrix of substances versus lists

Substances

Lists/Databases

Substance no.	CAS number	Classification	ED assessment	REPPPR	REACH Candidate List of SVHC	CORAP	EU ED Priority List	SVHC List	MoE Japan	SVHC Intention	Dev.	AR
Substance 1	30082-29-4	H002.H013.H013.H003.HM11	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 2	7732-18-7	H019.H032	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 3	1888-23-9	H002	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 4	8143-5	H002.H014	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 5	307-51-4	H002	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 6	8143-5	H002.H012.H014.H032	No	No (BPR); No (P)	No	No	No	No	No	NO (CORAP for other concerns than ED)	2	2
Substance 7	71-42-2	H002.H015.H015.H003.HM11	No	No (BPR); No (P)	No	No	No	No	No	YES (for other related concerns, CMR/expected CMR)	1	1
Substance 8	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 9	101-12-2	H019.HM12	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	2	2
Substance 10	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 11	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 12	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 13	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 14	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 15	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 16	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 17	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 18	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 19	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 20	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 21	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 22	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 23	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 24	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 25	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 26	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 27	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 28	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1
Substance 29	100-27-5	H026.H015.H017.H004.H000.HM1	No	No (BPR); No (P)	No	No	No	No	No	Yes (for other related concerns, CMR/expected CMR)	1	1

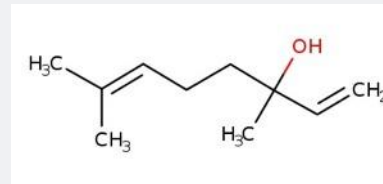
⇒ alerts identified

## ► Tier 2: Automated QSAR screening

- Screen large volumes of structures using QSARs
  - ⇒ “batch mode”
- Predictions for endpoints based on chemical structure
  - Human toxicity (CMR, ED)
  - Fate & ecotoxicity (PBT)
- Uncertainty on predictions (e.g. applicability domain) critical: important to also report/quantify

- Screening of available databases for similar structures ⇒ potential for read-across

linalool



Classification	
Hazard Class and Category Code(s)	Hazard Statement Code(s)
Skin Sens. 1B	H317

source: ECHA  
<https://echa.europa.eu>

## ► Tier 2: Automated QSAR screening

### ► Different automated QSAR packages exist e.g.:

- **VEGA** (<https://www.vegahub.eu/portfolio-item/vega-qsar/>)
- **Janus** (<https://www.vegahub.eu/portfolio-item/janus/>)
- **OECD** (<https://qsartoolbox.org>)

⇒ “batch mode” available

### ► Models have different applicability domains

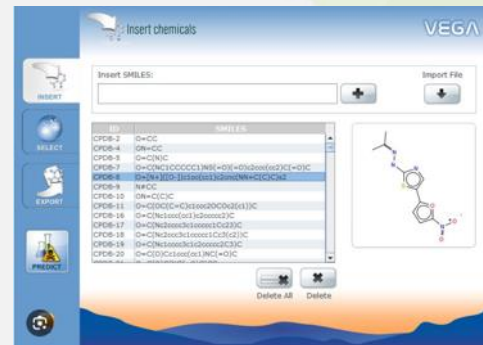
Today: user needs to check manually for each component

⇒ automate process

### ► Target: provide consolidated overview based on different packages

⇒ QSAR screener for R&D phase company

⇒ applied for KEMI on 1-10 tpa REACH substances



## ► Tier 3: Literature search

### Data-poor substances

- Manual check  
e.g. Web of Science



The screenshot shows the Information Discovery dashboard with a list of publications. The text is highlighted in yellow, and there are blue circles (1, 2, 3, 4) indicating specific features. A blue sticky note is overlaid on the bottom right of the screenshot with the following text:

1. Auto-classification
2. Confidence values
3. Filters ready to use
4. Safety highlights

Filtering and indexing: Publications and articles get sorted into topics and relevant text is highlighted automatically (Screenshot taken from the Information Discovery dashboard)

<https://averbis.com/information-discovery/>

### Data-rich substances

- Use text mining to develop filters to organise manuscripts
- Use AI to pre-process manuscripts as relevant or non-relevant
- Semi-automatic check of literature

## ▶ Screening advantages

- ▶ Identify alerts for natural substances
  - ⇒ stop in early phase (discard as “low-risk substance”)
  - ⇒ be prepared for higher-tier testing
- ▶ Identify best time to harvest, growing locations/conditions for natural substances
  - ⇒ be mindful about impact on efficacy!
- ▶ Identify sustainable co-formulants with automated screening (cfr. DG SANTE call regarding co-formulants in biocontrol products)



## ► Challenges and limitations

- Only info on components, not on natural substance as a whole
- Not to identify safe compounds
  - ⇒ No data ≠ safe
  - ⇒ Remains a screening: false negatives/false positives possible
- Possibly still unknown components in the composition

## ► Acknowledgements

- Thank you!



*Sabine Navis*



*Frederik Verdonck*



*Karel Viaene*

Visit us at **BOOTH 94!**



[Sarah.Croonenborghs@arche-consulting.be](mailto:Sarah.Croonenborghs@arche-consulting.be)



[www.arche-consulting.be](http://www.arche-consulting.be)

