RISE RAPID SUBSTITUTION TOOL

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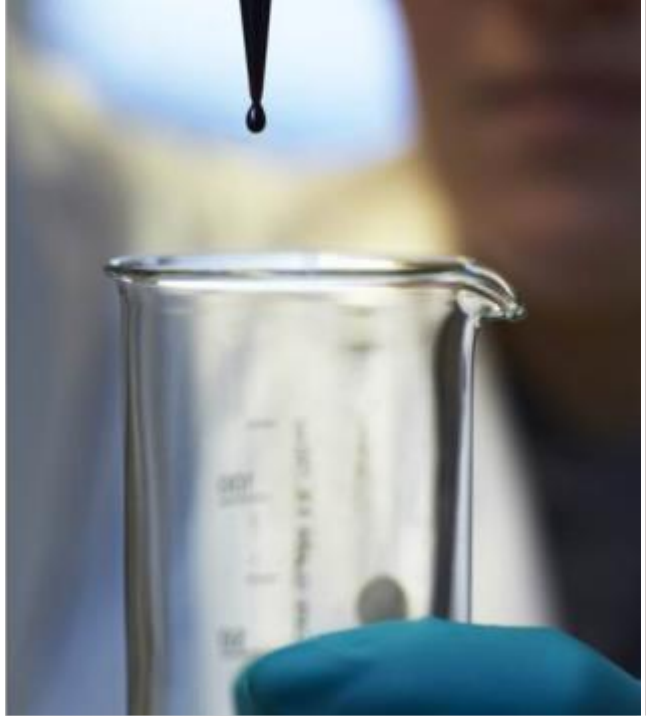
RISE Research Institutes of Sweden

Bioscience and Materials

Surface, Processes and Formulation



HSPiP program – a prolog to RISE rapid substitution tool

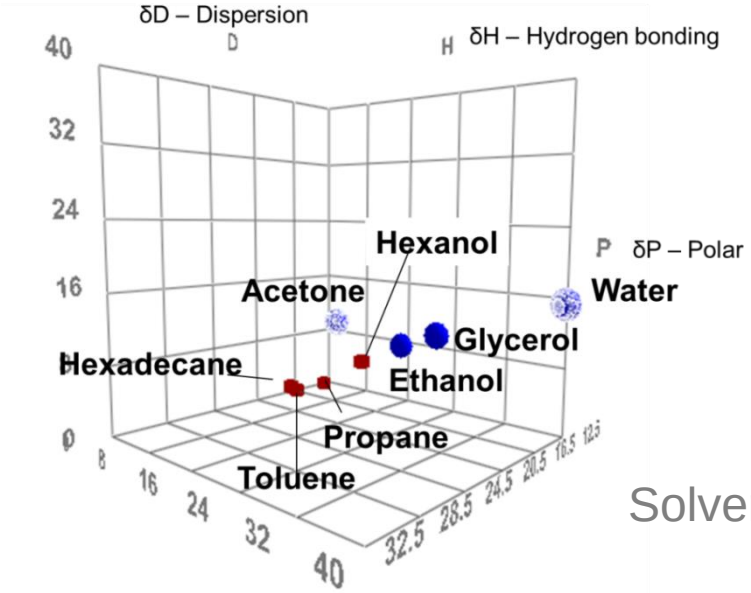
What is HSPiP?... A way to characterize a wide range of chemicals based on 3 parameters only:

•δD →Dispersion - van der Waals forces=the amount of polarizable electrons

•δP →Classic Polarity… dipole moment

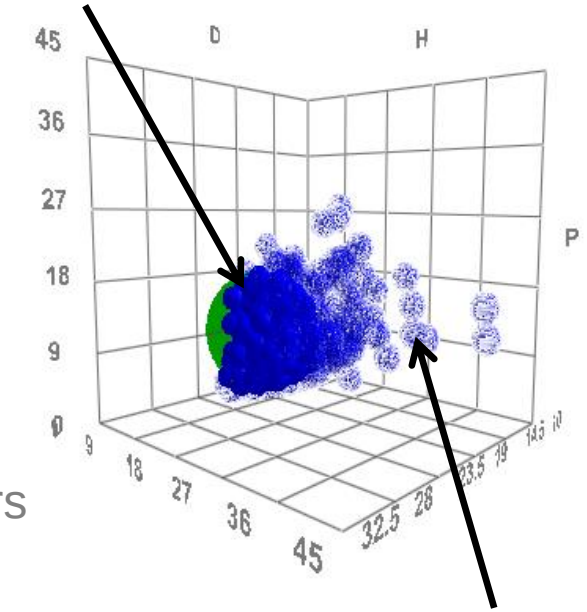
•δH → Hydrogen bonding

- Polymers sphere - is defined based on their interaction with solvents (good/bad)
- The more similar the molecules in the lattice, the easier it is for them to be compatible.
- The further apart, the least alike they are

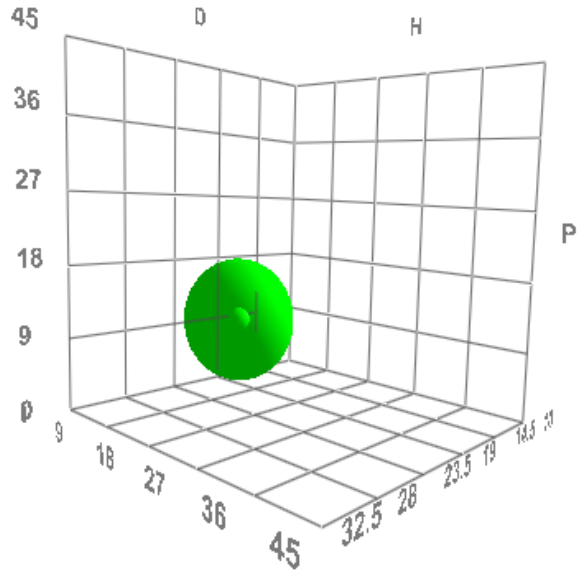


Solvents and polymers

Good solvents



Poor solvents



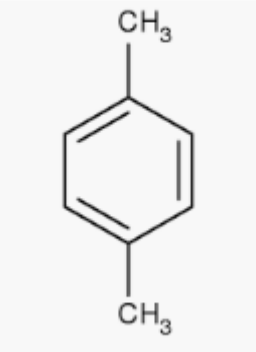
What is RISE Rapid substitution tool?

- ***RISE Rapid substitution tool*** is a database which, for a given chemical, can put at a fingertip information about:

  - **Chemical properties** – via HSPiP program (dD, dP, dH, MWt, Density, Mvol, Bpt, MPt, FPt, VP@25, …)
  - **Chemical Safety** (Harm, CMR[Carc, Muta, Repr], Skin, AcuteTox…) from KEMI (Sweden) and EPA (USA)
  - **Skin permeation** and **Eye irritation** information
  - **Odor** (type and threshold)
  - **Price** (from a common vendor)

This tool can help companies use ***best*** chemical in their products

How it works?



Xylene CAS 108-38-3

- Xylene is used as a solvent in the printing, rubber, paint and leather industries

- Well documented safety issues:

J Oral Maxillofac Pathol. 2010 Jan-Jun; 14(1): 1–5.

- Let´s find a replacement for Xylene
  - Position in the Hansen space
  - Similar Relative Evaporation Rate (RER)
  - Low melting point
  - Good price
  - Less odor
  - Minimal hazards (flammability/health/reactivity)

Use HSPiP program to identify candidates with similar properties

Solvent	δD	δP	δH	δHD/A	MVol	Other I	RER	Weigh	Vol%	S	Distanc	AA	AB	AC	BPt	FPt	VP@25	MPt	MWt	LogS	CAS	SMILES
p-Xylene	17,8	1	3,1	0,4/2,9	121,1	-	80	100	-	True	0	6,995	1456,7	215,7	138	-	8,77	13	106	-1,7	106-42-3	CC1=CC=C
Toluene	18	1,4	2	0,4/3,1	106,6	-	190	100	-	True	1,24	6,938	1334,8	218,4	111	-	28,4	-95	92	-1,27	108-88-3	CC1=CC=C
Ethyl Benzene	17,8	0,6	1,4	0,3/2,8	122,8	-	89	100	-	True	1,75	6,942	1414,5	212,1	136	-	9,47	-95	106	-1,78	100-41-4	CCC1=CC=
Cyclopentyl Methyl Ether (Cpme)	16,7	4,3	4,3	0,2/3,5	116,5	-	343	100	-	True	4,14	6,9647	1300,8	219,2	106	-	43,4	-140	100	0,04	5614-37-9	COC1CCC
Amyl Acetate	15,8	3,3	6,1	0,1/5,6	148	-	67	100	-	True	5,5	6,652	1423,9	228	148	-	10,6	-71	130	-0,76	628-63-7	O=C(OCC
n-Butyl Acetate	15,8	3,7	6,3	0,1/6,1	132,6	-	100	100	-	True	5,79	7,128	1443,3	213,8	126	-	12,1	-74	116	-0,17	123-86-4	CC(OCCC
Methyl Isoamyl Ketone	16	5,7	4,1	0,2/3,9	141,3	-	50	100	-	True	6	6,945	1398,8	199,3	145	-	5,11	-74	114	-0,33	110-12-3	CC(CCC(C
Isobutyl Isobutyrate	15,1	2,8	5,8	0,1/4,1	169,8	-	43	100	-	True	6,3	7,164	1494,9	201,6	148	-	3,69	-81	144	-1,24	97-85-8	O=C(C(C)
n-Butyl Propionate	15,7	5,5	5,9	0,1/5,4	149,3	-	45	100	-	True	6,76	7,156	1489	202,9	145	-	4,19	-90	130	-0,82	590-01-2	O=C(CC)C
n-Propyl Propanoate	15,5	5,6	5,7	0,1/5,7	132,5	-	120	100	-	True	7,01	7,021	1359,2	205,8	123	-	13,5	-76	116	-0,35	106-36-5	CCCOC(=C
Methyl Isobutyl Ketone (MIBK)	15,3	6,1	4,1	0,3/4,1	125,8	-	162	100	-	True	7,21	6,755	1217,8	198,1	116	-	19,8	-84	100	0,28	108-10-1	CC(CC(C)(
n-Propyl Acetate	15,3	4,3	7,6	0,1/6,5	115,8	-	176	100	-	True	7,49	7,066	1304,2	210,1	102	-	33	-95	102	0,18	109-60-4	CC(OCCC
sec-Butyl Acetate	15	3,7	7,6	0,1/5,6	134	-	133	100	-	True	7,67	7,118	1388,4	215,1	112	-	21,6	-99	116	-0,21	105-46-4	CC(CC)OC
Methyl n-Propyl Ketone	16	7,6	4,7	0,4/4	107,3	-	240	100	-	True	7,69	6,917	1255,1	208,6	102	-	35	-77	86	0,74	107-87-9	CC(CCC)=

Similar Relative Evaporation Rate (RER)
Low melting point → Candidates with melting point below zero

RISE Rapid substitution tool - to evaluate hazards

A database on hazardous chemicals from KEMI – The Swedish Chemical Agency

Name	CAS_Nr	EC_No	CMRh	CMRs	Muta	Carc	Repr	RespSens	SkinSens	SkinMildIrrit	SkinIrrit	SkinCorr	AcuteTox	STOT_RE	Hormonstörande	PBT/ vPvB	AqAcute	AqChronic	ED-listan (Kat1-3, Comm)	Hormonstörande - pot (TEDX)	PBT/vPvB - pot (se förklaring)	HazCat_Tkrit
p-Xylene	106-42-3	203-396-5		x			1S				2H		4H	2S				2S				
Toluene	108-88-3	203-625-9	x				2H		1S		2H		4S	2H				2S		x		x
Ethyl Benzene	100-41-4	202-849-4		x		2S					2S		4H	2H				3S				x
Cyclopentyl Methyl Eth																						
Amyl Acetate	628-63-7	211-047-3																3S				
n-Butyl Acetate	123-86-4	204-658-1									2S		2S					1S				
Methyl Isoamyl Ketone	110-12-3	203-737-8											4H									
Isobutyl Isobutyrate	97-85-8	202-612-5									2S		4S					3S				
n-Butyl Propionate	590-01-2	209-669-5									2S											
n-Propyl Propanoate	106-36-5	203-389-7											4H					2S				
Methyl Isobutyl Ketone	108-10-1	203-550-1									2S		4H					2S				
n-Propyl Acetate	109-60-4	203-686-1																				
sec-Butyl Acetate	105-46-4	203-300-1																				
Methyl n-Propyl Keton	107-87-9	203-528-1									2S		3S									

Records on toxic candidates can be evaluated together with our RISE tox team
The higher the value of the recorded number the safer the chemical

X- there are records on hazard

RISE Rapid substitution tool - to evaluate hazards

Positive list☺ Safe Chemical database from EPA – Environmental Protection Agency USA

NAME	Antimicrobial Actives	Chelating Agents	Colorants	Defoamers	Emollients	Enzimes and Stabilizers	Fragrances	Oxidants and Stabilizers	Polymers	Preservatives Antioxidants	Procesing Aids Additives	Skin Conditionings Agents	Solvents	Specialized Industrial	Surfactants	Uncategorized
p-Xylene																
Toluene																
Ethyl Benzene																
Cyclopentyl Methyl Ethe																
Amyl Acetate							Yellow [T									
n-Butyl Acetate																
Methyl Isoamyl Ketone																
Isobutyl Isobutyrate																
n-Butyl Propionate																
n-Propyl Propanoate																
Methyl Isobutyl Ketone																
n-Propyl Acetate													Green [Ci			
sec-Butyl Acetate																
Methyl n-Propyl Ketone																

The positive list from EPA correlated with the Hazard list form KEMI

- Amyl acetate yellow on EPA and 3S on KEMI
- n-propyl acetate green on EPA and no records on KEMI

RISE Rapid substitution tool to evaluate odor

Database from American Industrial Hygiene Association - Oman government, 3M and tgsc.com

Click on CAS

Name	Range of Odor Thresholds (ppm) Am. Ind. Hig. Ass. (Oman)	Odor Character Am. Ind. Hig. Ass. (Oman)	Odor threshold from 3M list (ppm)	CAS
p-Xylene				106-42-3
Toluene			0,16	108-88-3
Ethyl Benzene	<0.002 – 18	oily, solvent		100-41-4
Cyclopentyl Methyl Ether				5614-37-9
Amyl Acetate	0.007 – 43	banana, etherous		628-63-7
n-Butyl Acetate	0.00013 – 368	sweet, banana	0,007	123-86-4
Methyl Isoamyl Ketone	0.0021 – 0.135	sweet, sharp	0,042	110-12-3
Isobutyl Isobutyrate				97-85-8
n-Butyl Propionate				590-01-2
n-Propyl Propanoate				106-36-5
Methyl Isobutyl Ketone (MIBK)			0,121	108-10-1
n-Propyl Acetate	0.048 – 87	sweet, ester	0,575	109-60-4
sec-Butyl Acetate	0.0025 – 4.76	fruity		105-46-4
Methyl n-Propyl Ketone	0.028 – 65	fingernail polish		107-87-9

Odor Type: fruity

Odor Strength: medium ,
recommend smelling in a 10.00 % solution or less
solvent celery fruity fusel raspberry pear
Odor Description: at 10.00 % in dipropylene glycol. solvent celery fruity fusel raspberry pear
solvent pungent fusel sweet fruity
Odor Description: Solvent-like pungency, lifting, fusel, amyl alcohol, sweet and fruity
Mosciano, Gerard P&F 21, No. 5, 49, (1996)

Flavor Type: estery

estery fruity ethereal tutti frutti banana honey
Taste Description: at 10.00 ppm. Estry, fruity, etherial, tutti-frutti, banana and honey
Mosciano, Gerard P&F 21, No. 5, 49, (1996)

Odor and/or flavor descriptions from others (if found).

Frutarom
N PROPYL ACETATE
Odor Description: Fruity, Fusel, Pear
Suggested Uses: Alcoholic Beverages, Hard Fruits, Honey, Melon, Pear, Raspberry, Soft Fruits

Alfrebro
n-PROPYL ACETATE (EU NAT)
Odor Description: Powerful, Celery, Raspberry, Melon, Strawberry

Moellhausen
PROPYL ACETATE
Odor Description: fresh, sweet, strongly fruity, ethereal

Blue Marble Biomaterials
Propyl Acetate - Natural ≥98%
Odor Description: Fruity, pungent, solvent: raspberry, pear, celery
Taste Description: Fruity, estry, etherial: honey, banana, tutti-fruitti

Link to tgsc.com

The ***Goodsensecompany*** is a free online database

RISE Rapid substitution tool to evaluate price

Using a database from a common vendor

Name	CAS	Price danish rule	Function	Safety Code	Color Code	Merck/Sigma code	Price 1 kg	10 kg	20 kg	30 kg	Price 1 kg
p-Xylene	106-42-3	42,69	Solvents		296333-1L	296333-1L	1366SEK				1366
Toluene	108-88-3	24,91			244511	244511	797				797
Ethyl Benzene	100-41-4	57,56			296848	296848	1842				1842
Cyclopentyl Methyl Ether	5614-37-9	95,06	Splvents		791962-1L	791962-1L	3,042.90				3042
Amyl Acetate	628-63-7	24,91			W504009-	W504009-	797				797
n-Butyl Acetate	123-86-4	52,06	Solvents		287725-1L	287725-1L	1666				1666
Methyl Isoamyl Ketone	110-12-3	21,84			8,22E+09	8,22E+09	699				699
Isobutyl Isobutyrate	97-85-8	47,38			537632-1L	537632-1L	1516				1516
n-Butyl Propionate	590-01-2	24,63			W221104-	W221104-	788				788
n-Propyl Propanoate	106-36-5	22,75			W295809-	W295809-	728				728
Methyl Isobutyl Ketone (MIBK)	108-10-1	13,58			360511-2.	360511-2.	434,4				434,4
n-Propyl Acetate	109-60-4	29,47	Solvents	1	8.03183	8.03183	943 SEK	8720 SEK (	5250 SEK(		943
sec-Butyl Acetate	105-46-4	210,94			242594-1C	242594-1C	6750				6750
Methyl n-Propyl Ketone	107-87-9	28,78			W284203-	W284203-	921				921

Price is an important factor in the selection of the best candidate

RISE Rapid substitution tool – records on skin permeation

- This originates from Dr. Hansen work on safe gloves and skin and showed that the correlation between LogP and skin permeation used by pharma and cosmetic is wrong

- The molar volume is important for skin delivery (diffusion coefficients decrease according to $MVol^2$ or $MVol^3$), as is the ability of the solvent to swell the skin

The higher the number the less permeation

Skin Pemiation	CAS	NAME
8,693101	106-42-3	p-Xylene
9,141116	108-88-3	Toluene
10,0439	100-41-4	Ethyl Benzene
5,266878	5614-37-9	Cyclopentyl Methyl Ethe
5,608921	628-63-7	Amyl Acetate
5,209607	123-86-4	n-Butyl Acetate
4,949747	110-12-3	Methyl Isoamyl Ketone
6,80588	97-85-8	Isobutyl Isobutyrate
4,173727	590-01-2	n-Butyl Propionate
4,477723	106-36-5	n-Propyl Propanoate
5,511806	108-10-1	Methyl Isobutyl Ketone
5,040833	109-60-4	n-Propyl Acetate
5,886425	105-46-4	sec-Butyl Acetate
3,879433	107-87-9	Methyl n-Propyl Ketone

https://www.hansen-solubility.com/HSP-examples/skin.php

RISE Rapid substitution tool – records on eye irritation

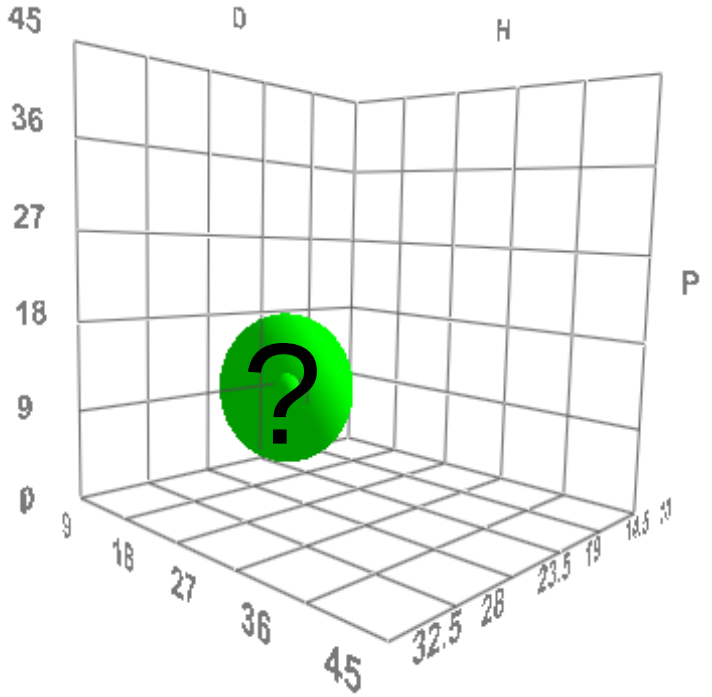
- RISE has developed a model to predict eye-irritation of substances

The higher the number the less irritation

Eye irritation	CAS	NAME
9,64	106-42-3	p-Xylene
10,44	108-88-3	Toluene
11,32	100-41-4	Ethyl Benzene
7,48	5614-37-9	Cyclopentyl Methyl Ethe
6,93	628-63-7	Amyl Acetate
6,63	123-86-4	n-Butyl Acetate
7,95	110-12-3	Methyl Isoamyl Ketone
8,14	97-85-8	Isobutyl Isobutyrate
6,68	590-01-2	n-Butyl Propionate
7,07	106-36-5	n-Propyl Propanoate
8,61	108-10-1	Methyl Isobutyl Ketone
6,20	109-60-4	n-Propyl Acetate
6,84	105-46-4	sec-Butyl Acetate
7,57	107-87-9	Methyl n-Propyl Ketone

A new method for *in-silico* prediction of eye-irritation using Hansen Solubility Parameters Idea:

Could we treat the cornea as a polymer…
…and use a Hansen approach?



Selection of

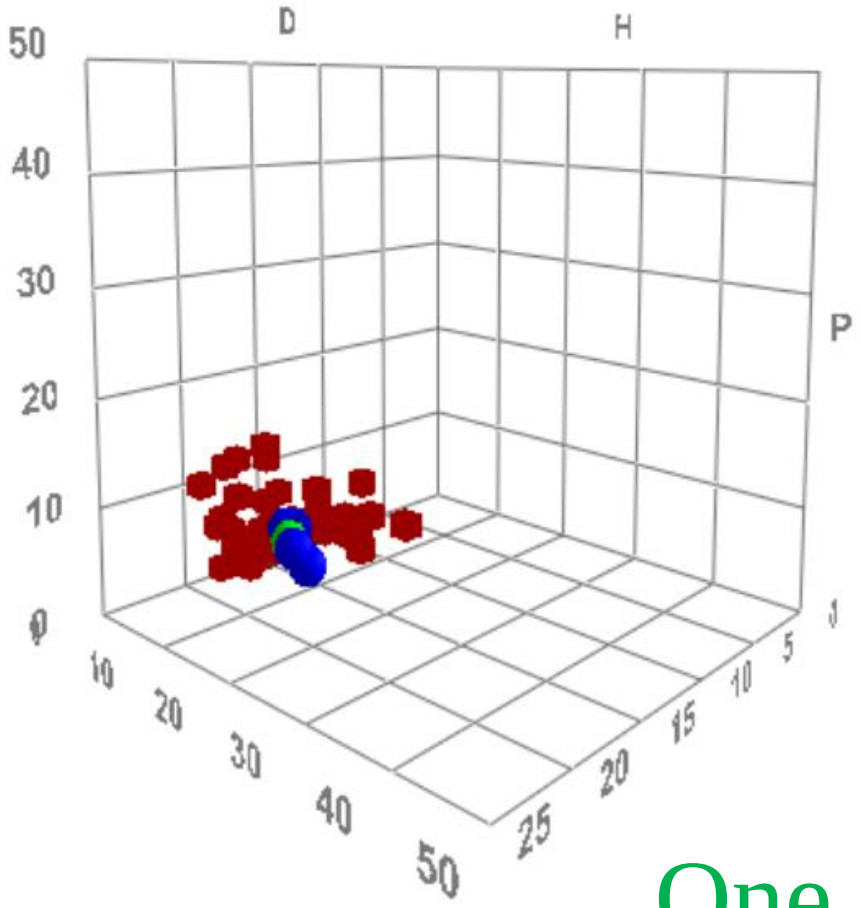
- **62 non-irritants (”No Cat”, ”CO=0”)**
- **4 strong irritants (”Cat 1”, but non-acidic, non-alkaline, non-reactive, no particles etc)**

from (”The Draize eye test Reference Database (DRD)”, Arch Toxicol (2017) 91:521–547)

2-Hydroxy iso-butyric acid ethyl ester
Cyclohexanol
1-Chloroctan-8-ol
Benzyl alcohol (neat)

Thanks to Cosmetics Europe and Dr. Bertrand Desprez for providing us access to the underlying data in "The Draize eye test Reference Database (DRD)", Arch Toxicol (2017) 91:521–547

- **The 4 irritants are positioned within a well-defined sphere in Hansen space**
- **ALL 62 non-irritants fall outside the sphere**



One can we treat cornea as a polymer!

OK!
So which synthetic polymer is most similar to the cornea?

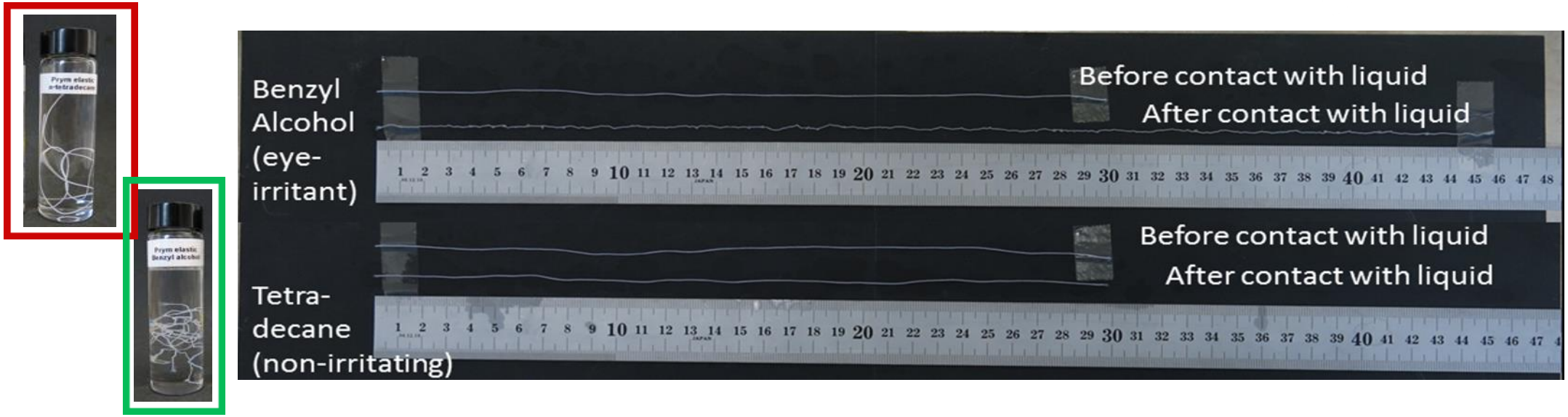
?

?

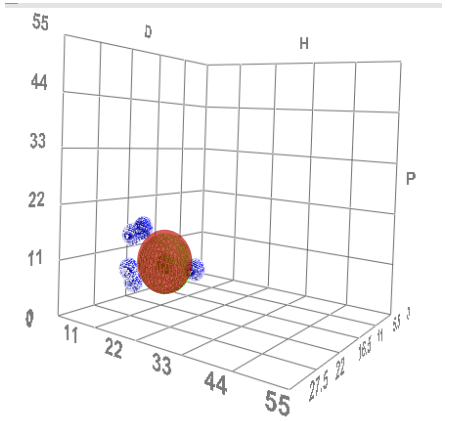
Elongation of a elastan/polyamid thread dipped in a liquid seemed to correlate with its eye-irritation!

- **Up to ca 50% elongation in irritants**
- **No elongation in non-irritants**
- **Equilibrium after 3 hours.**

(Small dataset,
4 irritants + 3 non-irritants)

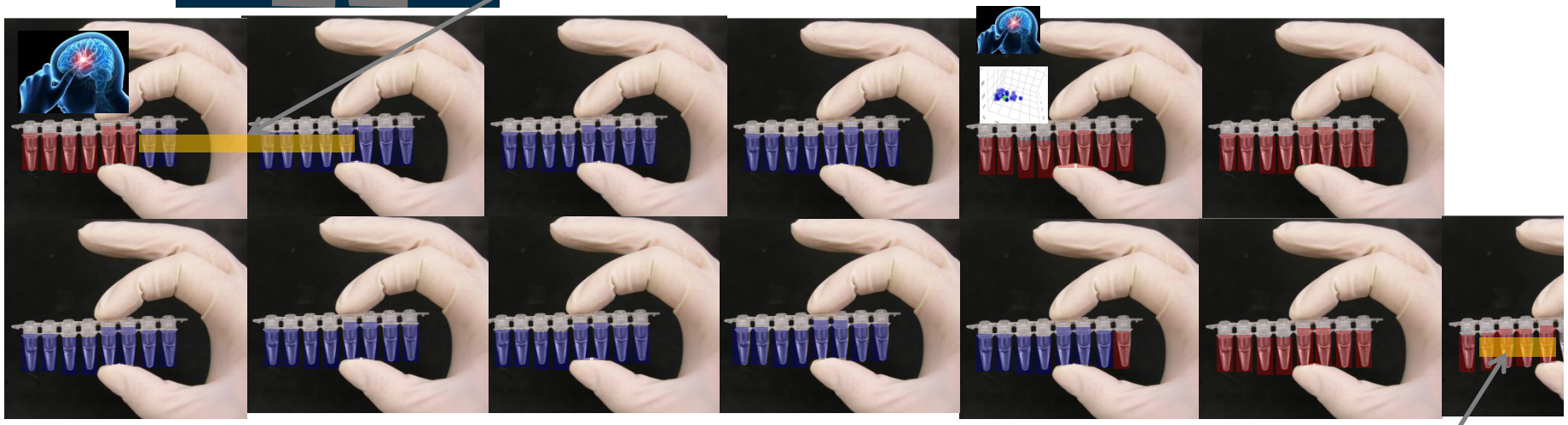


Hi! I have 101 compounds in my lab. Which are eye-irritants and which are not?



These 7 are irritants
(all close to the irritation sphere)

Correct answer:



In 90 of 101 cases the model gives a correct answer

~ 9/10

The method is still under development and will thereafter be validated

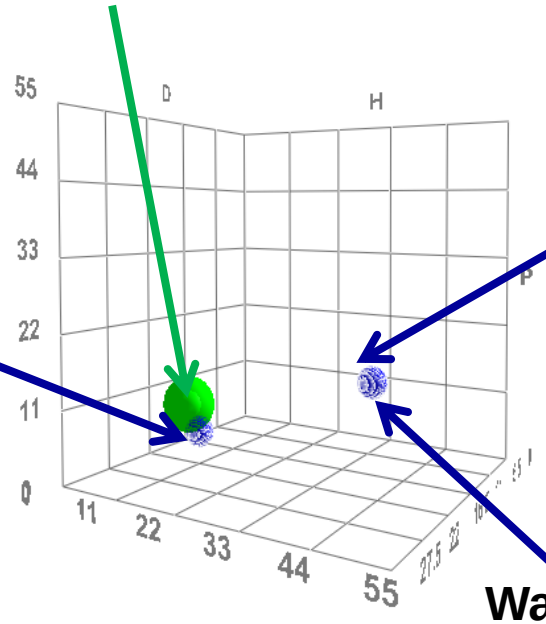
These four are non-irritants
(surface active EO-ethers, and EO gas)

Can our threads pick up ”formulation scalping”?

(15 cm)

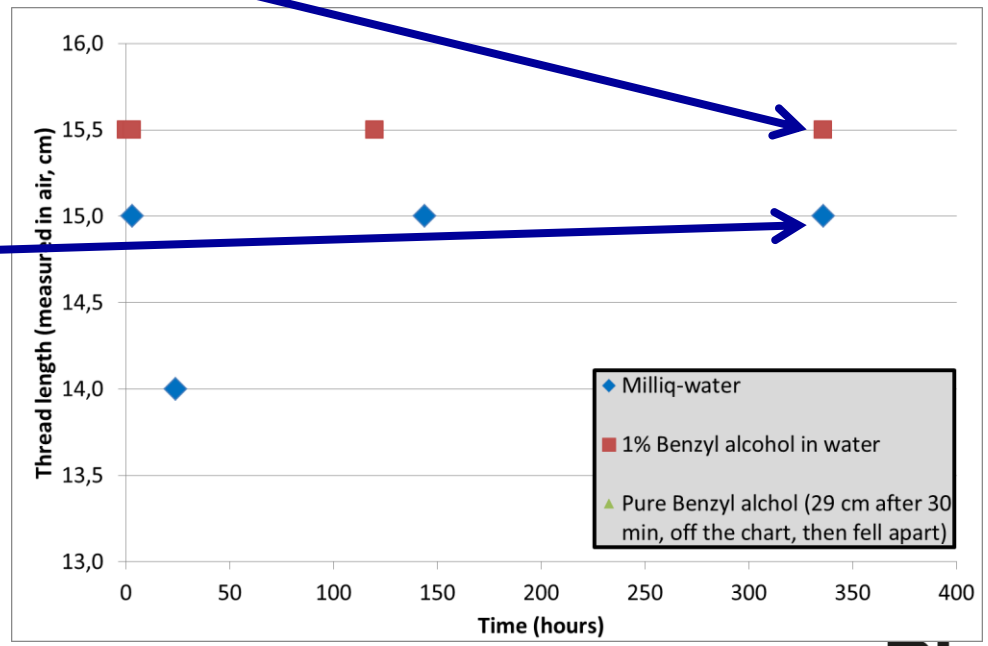
Benzyl alcohol (BA)
Swells the thread almost 100%

Thread material



1 vol-% BA in water

Water



Summary

- One can easily use ***RISE rapid substitution tool*** for quick screening of chemicals based on:
  - Chemical ***properties*** and ***safety***
  - ***Eye*** irritation and ***skin*** sensitivity
  - ***Odor*** and ***price***

- For the example of Xylene substitution, the best replacing candidate can be chosen based on the chosen application and the following arguments:
  - Amyl Acetate or n-Propyl Acetate
    - Good price but the slight odor must be tolerated
    - Aquatic toxicity is not relevant for the chosen application
    - It may be more sensitive to the eye or to the skin than Xylene

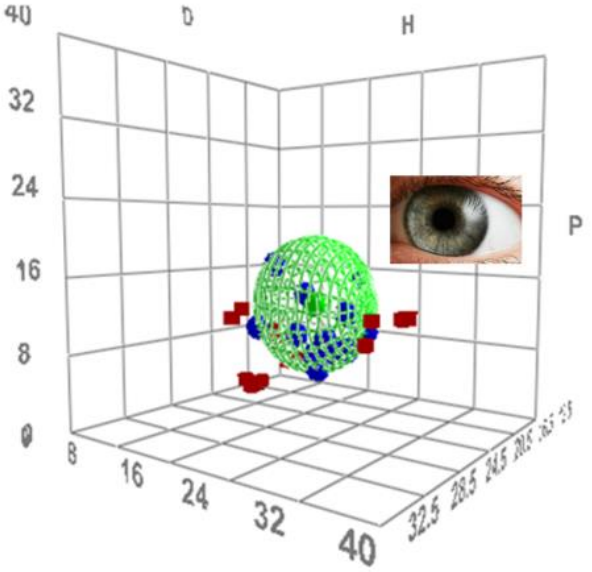
- Promising eye irritation tool under development!

Acknowledgement

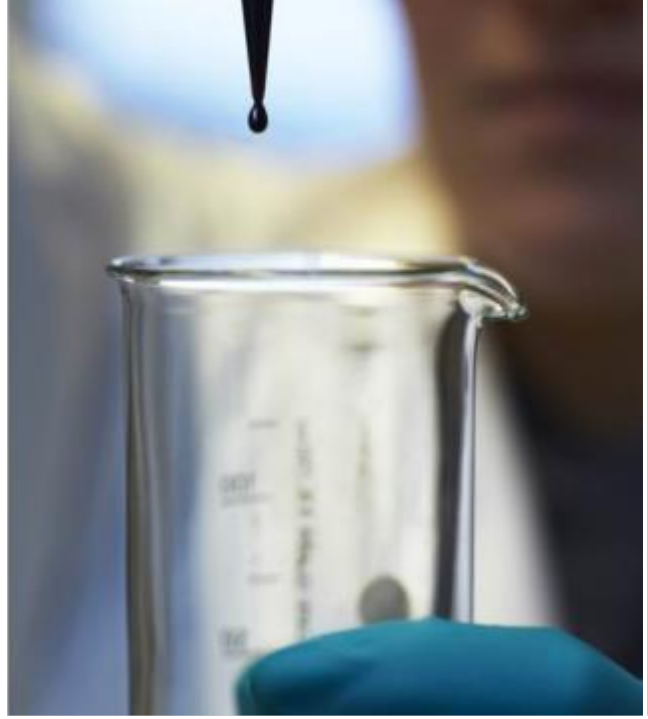
Financial support for Eye irritation tool:
Swedish Fund for Research Without Animal Experiments

RISE

+ Thanks to
Prof. Steven Abbott and Dr Charles Hansen for support!



THANK YOU



Contact: petru.niga@ri.se

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Bioscience and materials

Surfaces processes and formulation