Predictive methods for determining the decomposition properties of hazardous substances: from development to experimental verification – HAZPRED Project

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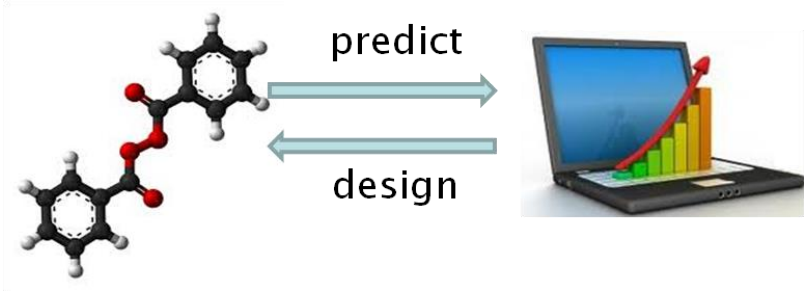

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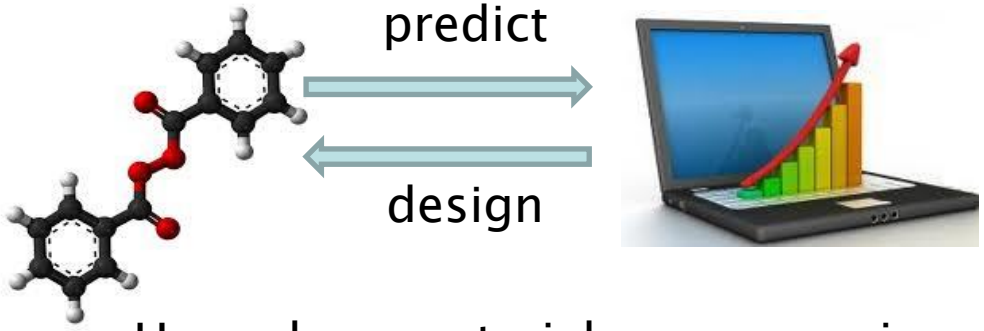
Overall description of the HAZPRED project

1rst July 2015-2018, budget ca. 320k€ including a PhD

CONCEPT



Hazardous materials e.g. organic peroxides, self-reactive materials

NEW IDEAS

Prediction of (complex) macroscopic properties from knowledge of substance's molecular structure

Novel tools for assessment of risks and understanding of physico-chemical behaviour of hazardous substances

OBJECTIVES

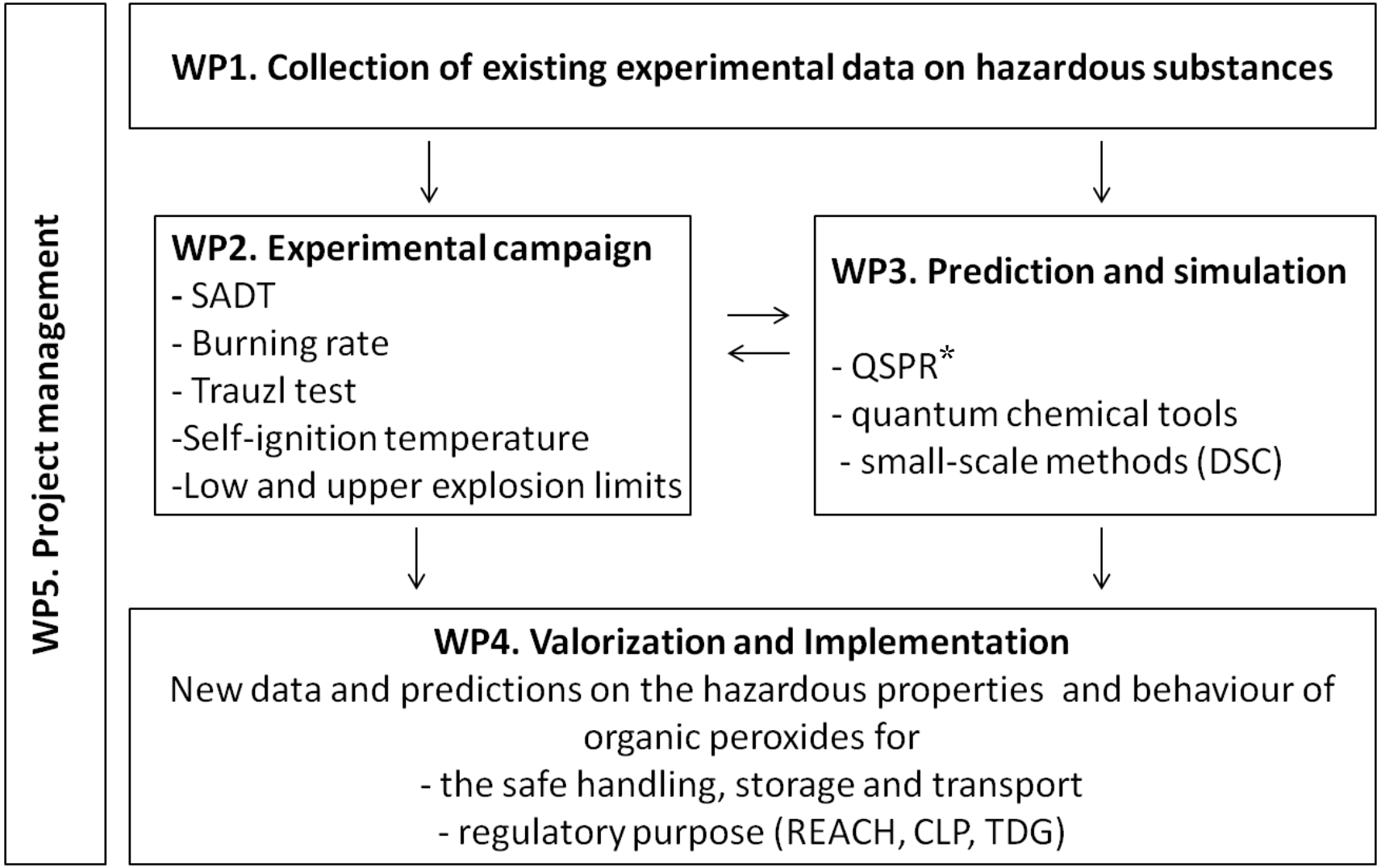
- Development and use of predictive methods, QSPR* and small-scale tests, for investigating hazardous properties in regulatory and risk assessment purposes but also screening purposes in R&D

*QSPR = Quantitative Structure-Property Relationships

Expected impact of HAZPRED

- Reduce costs for experimental testing
- Increased safety for people and environment during transport, handling and storage
- Guide R&D of new (hazardous) substances, **early hazard identification**
- Assess missing or “difficult-to-measure” properties required for REACH
- Enhance competitive advantage of industry

HAZPRED WP structure



*QSPR = Quantitative Structure-Property Relationships

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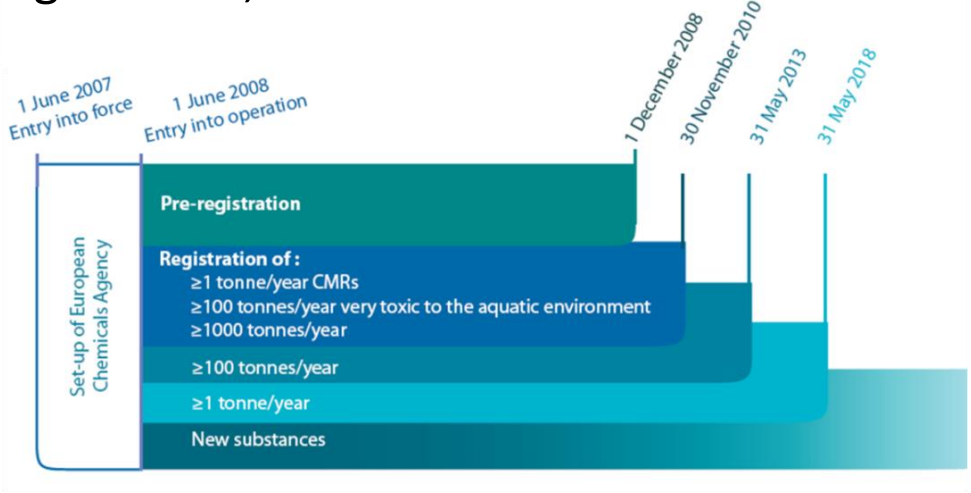
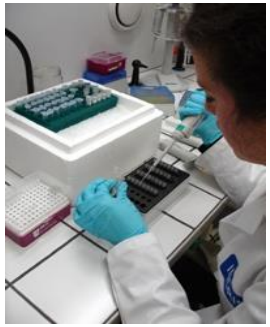
Context of HAZPRED-The use of molecular modeling

To serve the identification and control of chemical risks and to anticipate earlier pitfalls related to product safety and chemical reactions in development phase.

Fast development of molecular modeling (and diversity of methods) can solve the lack of data on chemicals.

- Chemical Information contained in Safety Data Sheets
- REACH: Registration, Evaluation and Authorization of Chemicals





http://echa.europa.eu

- More than 140 000 substances under concern
- Toxicological, ecotoxicological, physico-chemical properties
- Ethics (animal tests), cost, availability of labs, hazards…

↳ Alternative methods

QSAR/QSPR*

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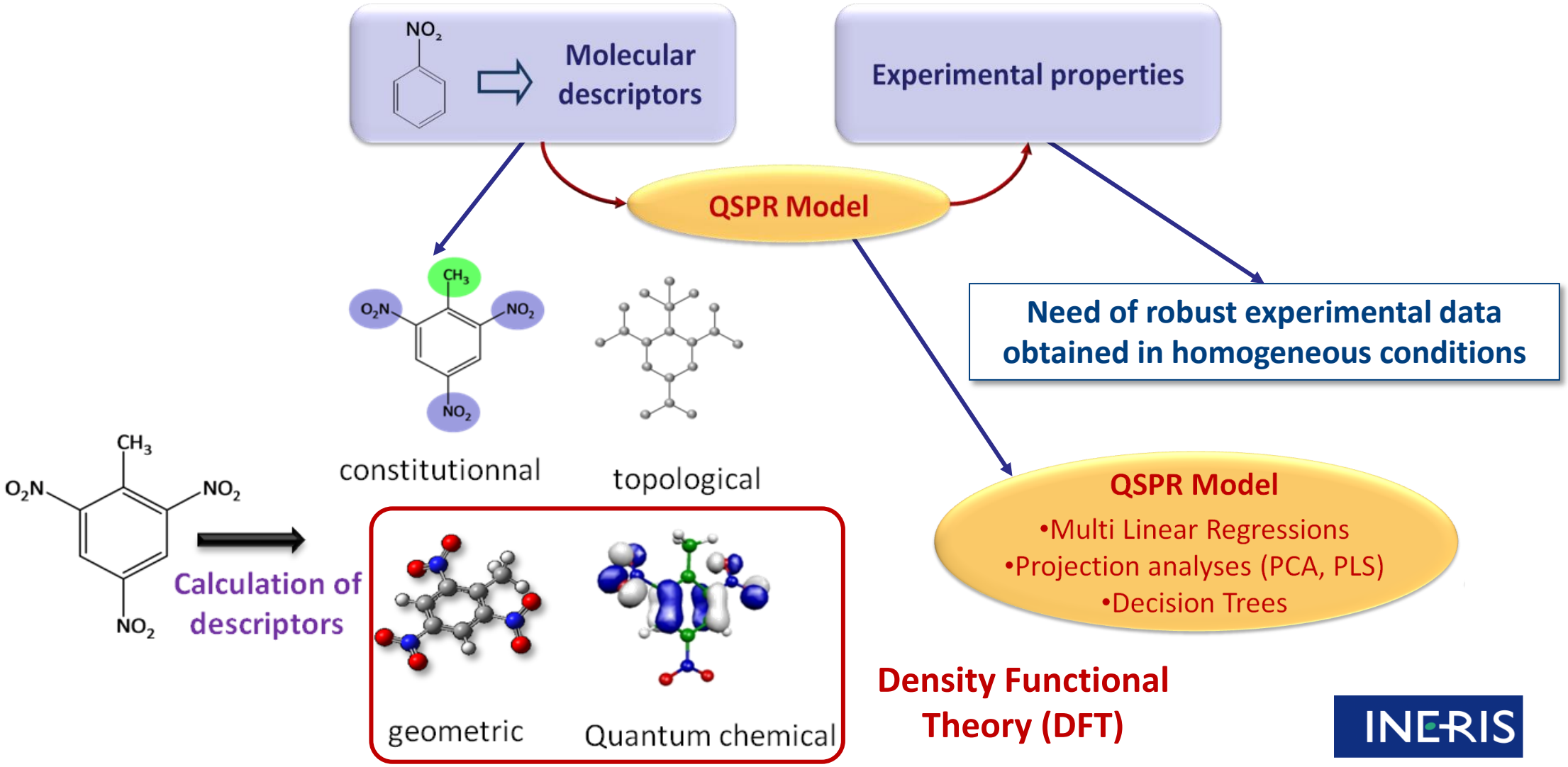
Quantitative Structure-Property Relationships

➪ **QSPR models** allow **predicting the physico-chemical hazards** of chemical substances only based on their molecular structures



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Validation of QSAR/QSPR for regulatory purpose/REACH

1- a defined endpoint

2- an unambiguous algorithm

3- a defined domain of applicability

4- appropriate measures of goodness-of-fit, robustness and predictivity

5- a mechanistic interpretation, if possible

Principles, for Regulatory Purposes of (Quantitative) Structure-Activity Relationship Models

Organisation for Economic Co-operation and development (OECD)

Paris, 2009

Substances and properties

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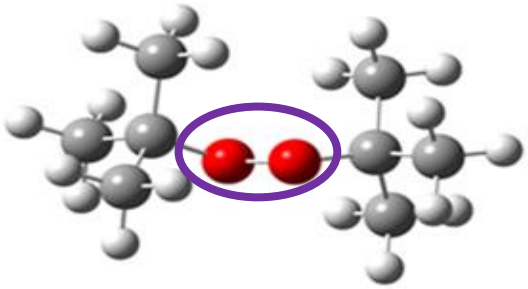
Organic peroxides (OPs) and Self-reactive substances (SRs)

« Organic peroxides are liquid or solid organic substances which contain the bivalent -O-O- structure and may be considered derivatives of hydrogen peroxide, where one or both of the hydrogen atoms have been replaced by organic radicals.. », Class 5.2



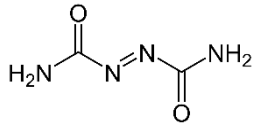
Di-tert butyl peroxyde

« Self-reactive substances are thermally unstable substances liable to undergo a strongly exothermic decomposition without participation of oxygen (air). Class 4.1

-aliphatic azo compounds (-C-N=N-C-)

-organic azides (-C-N_3)

-diazonium salts (-$CN_2^+Z^-$)



-N-nitroso compounds (-N-N=O)

-aromatic sulphohydrazides (-SO_2-NH-NH_2).

-Hazardous properties : thermally unstable → decomposition

(i) liable to explosive decomposition; (ii) burn rapidly; (iii) sensitive to impact or friction; (iv) react dangerously with other substances

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SADT-self accelerated decomposition temperature

SADT is an important thermal hazard parameter for risk assessment and safe management of OPs and SRs during storage and transport (to determine control and emergency temperatures).

SADT is the lowest temperature at which self-accelerating decomposition may occur with a substance in the packaging as used during carriage.

Measured by 4 regulatory tests (H1 to H4) and calorimetric methods

- one of criteria to decide if a substance can be a self-reactive substance

  →,If SADT<=75°C for a package of 50kg

- Involved in the procedure of classification of OPs according to TDG and GHS

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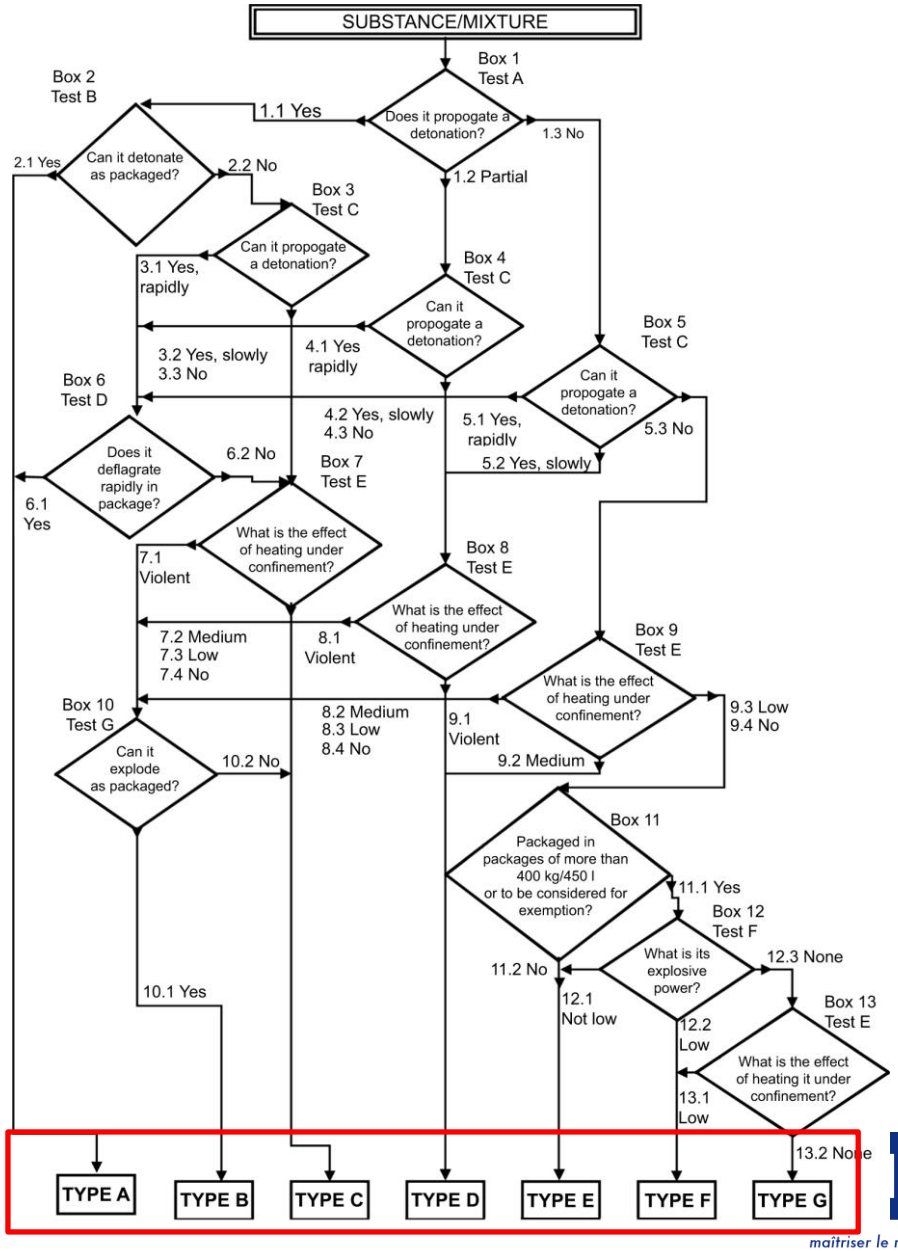
Characterization of OPs

Properties
Detonation, deflagration
Heat under confinement
Explosive power
SADT
Impact sensitivity
Friction sensitivity

Recommendations on the Transport of Dangerous Goods: Manual of Tests and Criteria, ST/SG/AC.10/11/Rev.5; Nations Unies, 2010



Existing QSPR models for the SADT of organic peroxides

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Pan et al. (2014)

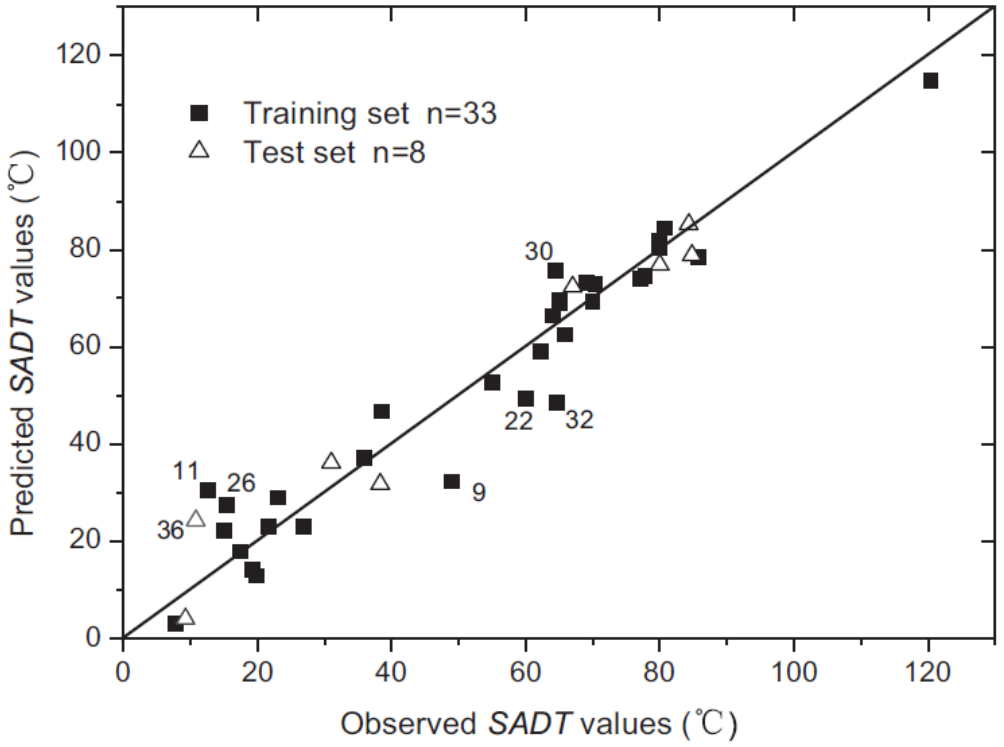
Pan et al., Journal of Loss Prevention in the Process Industries 31 (2014) 41-49

Based on 41 data taken from literature (Yu et al. 1996, Bosch et al. 2001, Sun et al. 2001, Ding et al. 2009)

$$SADT = -14.627(\pm 1.693)MAXDP + 3.006(\pm 0.672)RDF095v + 286.743(\pm 53.963)R2m + +6.962(\pm 1.666)nHDon - 18.457(\pm 2.917)C-004 - 7.052(\pm 2.698)C-006 + 80.091(\pm 7.170)$$

Molecular descriptor	Type	Definition	ME value
MAXDP	Topological indices	Maximal electrotopological positive variation	−7.679
RDF095v	RDF descriptors	Radial Distribution Function − 095/ weighted by van der Waals volume	3.397
R2m+	GETAWAY descriptors	*R* maximal autocorrelation of lag 2/ weighted by mass	106.265
nHDon	Functional group counts	Number of donor atoms for H-bonds (N and O)	5.673
C-004	Atom-centered fragments	CR4	−12.752
C-006	Atom-centered fragments	CH2RX	−6.118

Descriptors calculated by Dragon software



Training: R^2=0.93 RMSE=7.3°C

Test: R^2=0.95 RMSE=6.6°C

NB. 6 decriptors for 33 training data → maybe over parameterized

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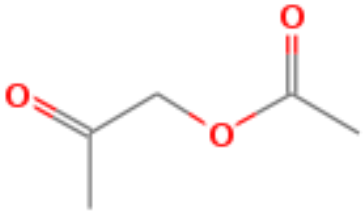
Pan et al. (2014)

Pan et al., Journal of Loss Prevention in the Process Industries 31 (2014) 41-49

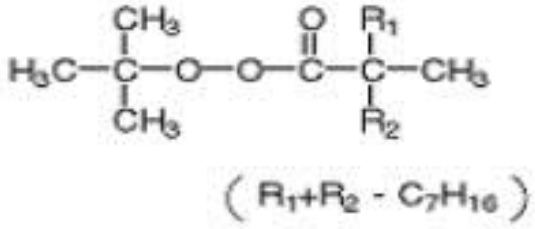
Detailed analysis of the dataset

Based on 41 data taken from literature (Yu et al. 1996, Bosch et al. 2001, Sun et al. 2001, Ding et al. 2009)

⇨ 1 data does **not concern an organic peroxide**: 1-(Acetyloxy)-2-propanone



⇨ 9 data concern **possible mixtures**, e.g. tert-Butyl peroxyneodecanoate



⇨ **Lack of information about experimental protocols,** in particular on the size of package

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Gao et al. (2015)

Gao et al., Process Safety and Environmental Protection 94 (2015) 322-328

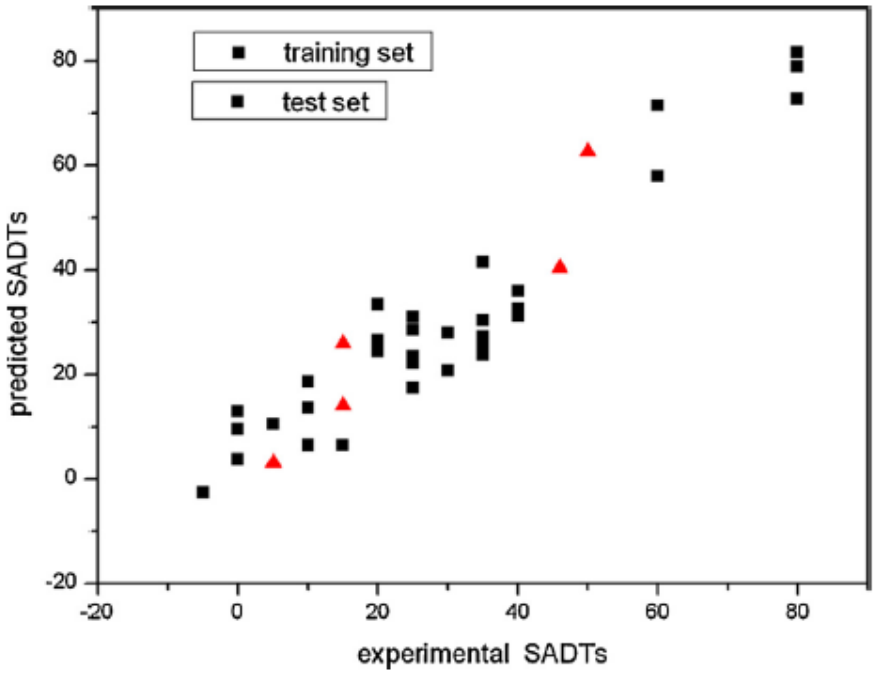
Based on 34 data taken from TDG **(but not found !)** and 5 data from new experiments

⇨ **including 7 possible mixtures**

$$Y = 136.476 - 179.676 \times Qneg - 28.082 \times Mor20v - 57.247 \times MATS3e - 94.15 \times R2u+$$

Name	Meaning
Qneg	Total negative charge
Mor20v	3D-MoRSE-signal20/weighted by atomic van der Waals volumes
MATS3e	Moran autocorrelation-lag 3/weighted by atomic Sanderson electronegtivities
R2u+	R maximal autocorrelation of lag 2/unweighted

Descriptors calculated by Dragon software



Training: R^2=0.90 RMSE= 6.2°C

Test: R^2=0.86 RMSE= 6.4°C ⇨ **Only 5 molecules**

The applicability domain was not defined

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Towards new QSPR models for the SADT of organic peroxides

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Objectives

Development of new robust QSPR models for the prediction of SADT of organic peroxides

- From a larger and curated experimental dataset (key point in our study)
- Satisfying OECD principles, in particular definition of an applicability domain
- With different types of descriptors
  - From quantum chemical descriptors to describe reactivity of OPs
  - With simple descriptors (constitutional and topological) to facilitate the use by industry

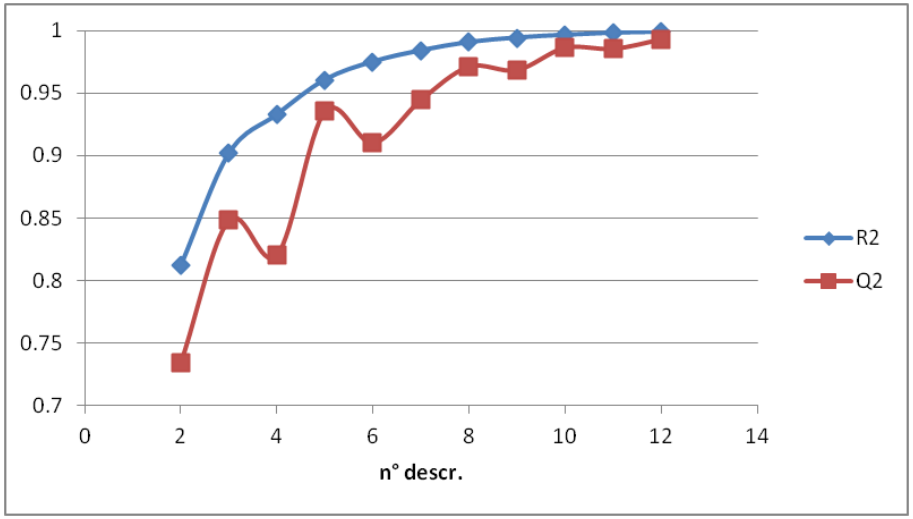
Preliminary results based on Pan's dataset

Best model, obtained with partition P1

Training set : 21 molecules ; validation set : 10 molecules

more than 300 descriptors including quantum chemical descriptors using Codessa and Gaussian09 programs

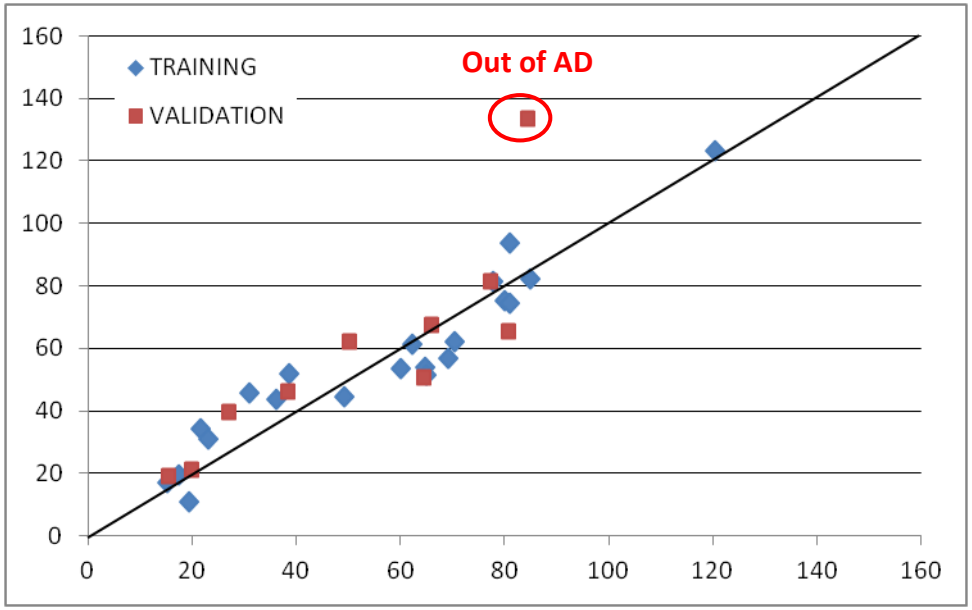
use of the BMLR technique as implemented into Codessa software



$$SADT = 585.9 - 368.5\ E_{O,max} - 252.1\ V_{O,avg} + 16.8\ RPCS$$

$R^2 = 0.90$; $Q^2 = 0.85$

$R^2_{IN} = 0.84$; $MAE_{IN} = 8.0°C = 18.8\%$



$E_{O,max}$ - Max electroph, react, index for a O atom
$V_{O,avg}$ - Avg valency of a O atom
RPCS - Relative positive charged surface area

Performances are not increased after curation the dataset
→ consolidation of another database

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Consolidation of a robust dataset

- **Some drawbacks were observed in the datasets of Pan and Gao:**
  - lack of details on experimental protocols (in particular the size of package)
  - lack of information on concentrations (in solvent)
  - no identification of mixtures (within commercial OPs)

- **Compilation of available data with all available details:**
  - DATATOP supported by TNO
  - Catalogues of suppliers (Arkema, Akzo Nobel)
  - Literature

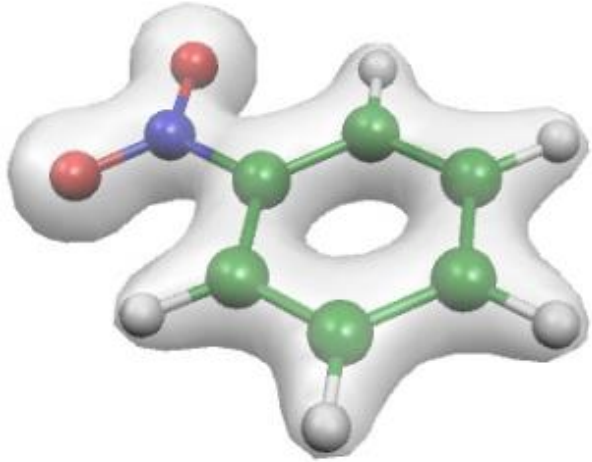
A total of 545 data have been yet gathered and are **under investigation to check their relevance and define a robust database**, suitable for the development of QSPR models

Perspectives

- Develop QSPR models for SADT of OPs
  - Based on consolidated databases (in progress)
- Towards QSPR models for SADT and thermal stability of **self-reactive substances**
  - **No QSPR model exist for SRs**, probably due to the lack of available experimental data in literature limited to some particular molecules and their chemical diversity
  - **First step: consolidation of a robust dataset** on properties of SRs obtained from
    - literature, industrial suppliers (contact with Bayer, BASF…)
    - new experimental data measured within HAZPRED project

Such database will be useful not only for the development of QSPR models in HAZPRED project but also in the future to give reference data to support expert and regulatory discussions

Thank you for your attention



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Objectives

- Develop theoretical models (e.g. QSPR, Quantitative Structure Properties Relationship) and small-scale tests to predict complex properties such as flammability, thermal stability, explosivity of hazardous substances (in particular organic peroxides and self-reactive substances)

- Quickly complete the lack of knowledge on hazardous substances and better understand their decomposition behavior

- Improve the safety of people and the environment as knowledge of these hazardous properties will contribute to the safety of these materials during transport, handling and storage

- Guide the research and development of new (hazardous) substances and help that chemicals become REACH-compliant

Valorization and implementation

Datatop will be completed

QSPR models respecting OECD principles of validation will be proposed to regulatory agencies of chemicals (JRC, ECHA and OECD)

Proposition of an informal paper will be submitted to the UN Sub-Committees of Experts on the Transport of Dangerous Goods as well as on the Globally Harmonized System of Classification and Labelling of Chemicals about these promising alternative screening methods

Peer-reviewed journal papers and communications

Preliminary results based on Pan's dataset

- Use of the only 31 data of OPs presenting no doubt of mixtures
- Study on 4 different partitions to define an external validation set
  - ⇨ 3 partitions defined by distributed selection of data ordered by incresing magnitude of property (1/3 or 1/4)
  - ⇨ Based on the partition of Pan (26/5)

Models	n	R^2	R^2_{ext}	$RMSE_{ext}$
Pan	*33/8*	*0.93*	*0.95*	*6.6°C*
Gao	*34/5*	*0.90*	*0.86*	*6.4°C**
New P1	21/10	0.90	0.84	8.0°C
New P2	21/10	0.92	0.84	11.3°C
New P3	23/8	0.95	0.79	9.5°C
Reduced Pan's partition	26/5	0.94	0.99	4.2°C

*MAE