The contribution of *in silico* methods to qualify non-genotoxic impurities in drugs

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S-IN Soluzioni Informatiche S.r.l.

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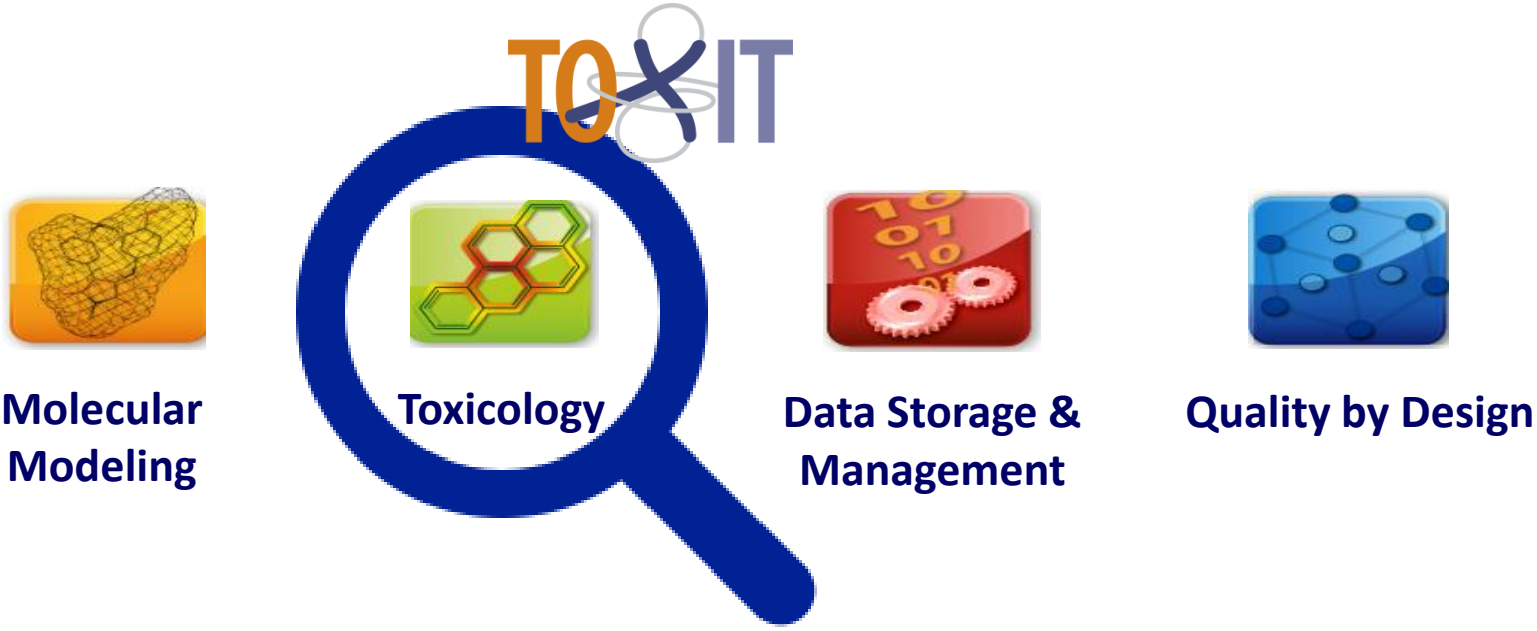
- **S-IN Soluzioni Informatiche** offers a wide range of services in chemistry and life sciences: consultancy, contract research, training, *in silico* predictions and studies, software solutions.



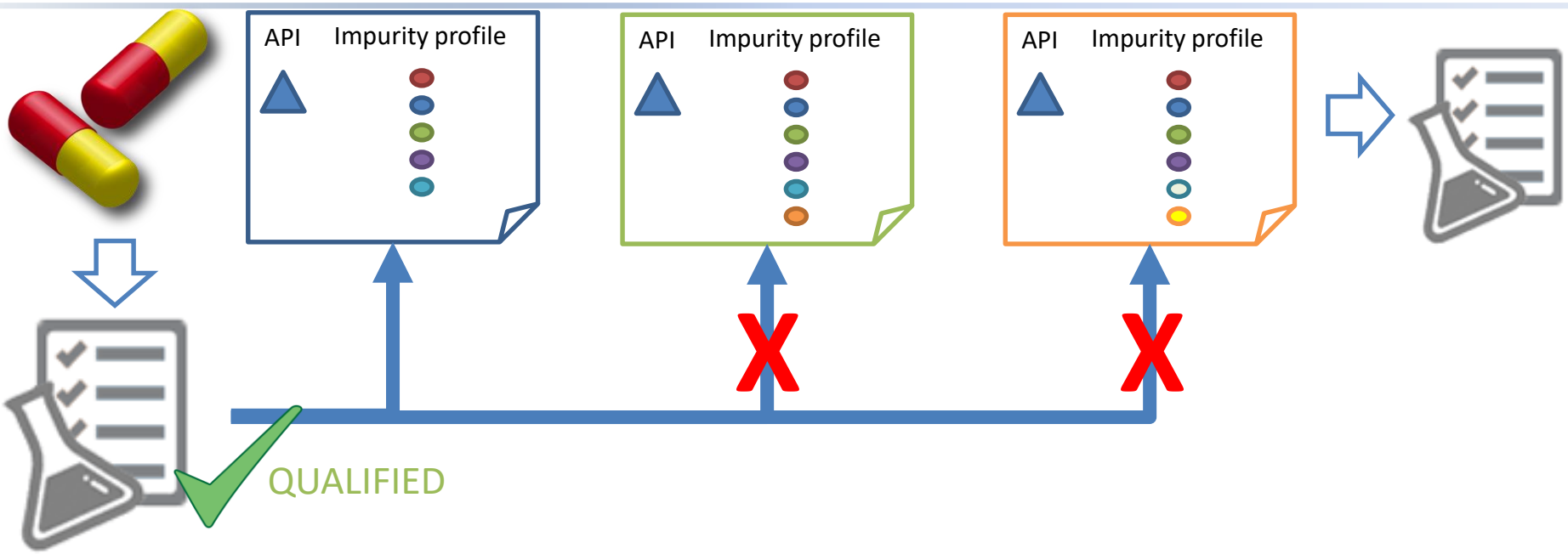
Objective

- Definition of a workflow for the safety assessment of non-genotoxic impurities (NGI) present in drug substances/products at levels > qualification threshold, based on non-testing methods.

The context

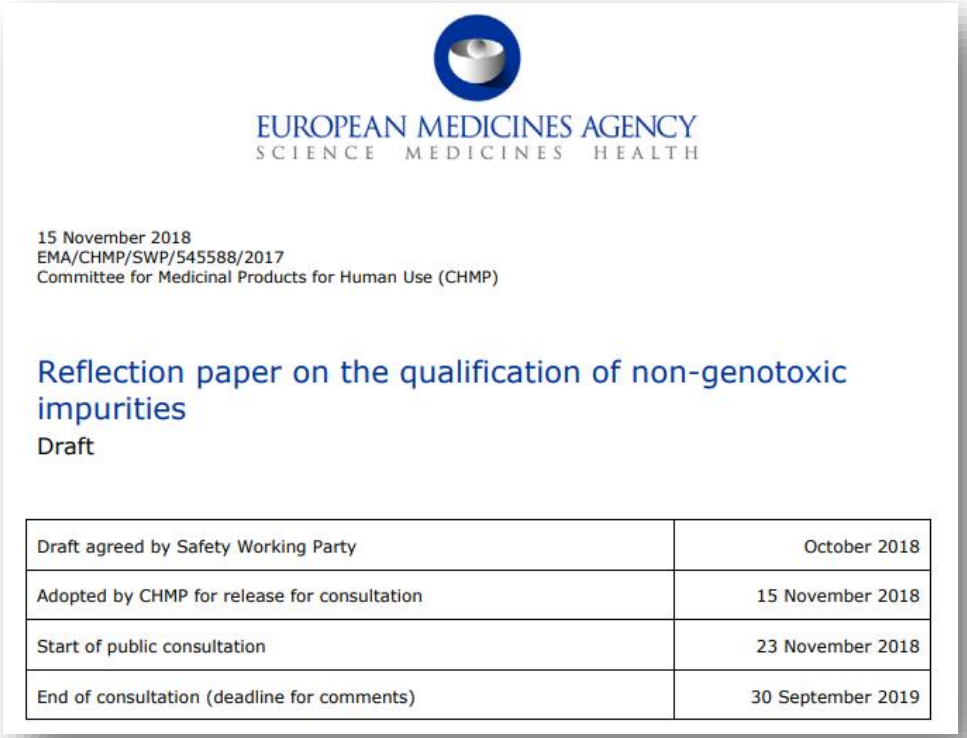
- Qualification of impurities addressed by ICH Q3A/Q3B guidelines
  - *The qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified*
  - Do not provide details on how NGI should be qualified
  - Specific guidelines for DNA reactive (mutagenic) and elemental impurities and residual solvents (ICH M7/Q3D/Q3C), not for NGI.

Concerns



- The level of any impurity in a new drug substance that has been tested in safety and/or clinical studies would be considered qualified
- Qualification is establishing biological safety of a drug substance/product with a given impurity profile (NOT safety profile of individual impurity)
  - Not possible to extrapolate the safety of a drug with a given impurity profile to a drug with the same API but with an increased level of an impurity/new impurities (with levels > qualification threshold)
  - Not possible to discriminate between toxicity attributable to the API and those attributable to the impurities.

EMA reflection paper



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 November 2018
EMA/CHMP/SWP/545588/2017
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on the qualification of non-genotoxic impurities
Draft

Draft agreed by Safety Working Party	October 2018
Adopted by CHMP for release for consultation	15 November 2018
Start of public consultation	23 November 2018
End of consultation (deadline for comments)	30 September 2019

No specific recommendations are made on which *in silico* tools to use/non-clinical approaches are most suitable.

- From a 3R's perspective no animal studies should be performed if they are unlikely to provide relevant information
- An impurity-specific evaluation could be followed making use of the non-animal testing strategies
  - Threshold of toxicological concern, TTC
  - (Quantitative) Structure Activity Relationship, (Q)SAR
  - Read-across
  - Toxicological databases
  - *In vitro* assays (if insufficient information or concerns are identified).

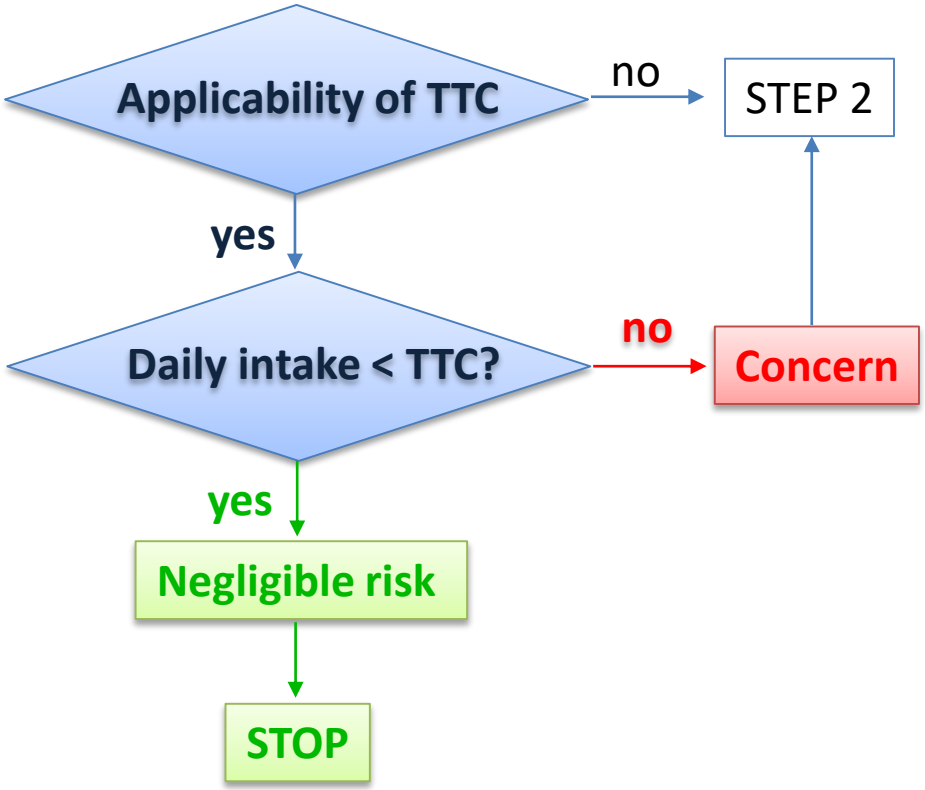
Qualification of impurities - STEP 0

Genotoxicity assessment of impurities (ICH M7) → classification

- Identify NGI (classes 4, 5)
  - NGI with levels > qualification threshold
  - NGI with levels ≤ qualification threshold, but a toxicological concern may exist
    - High dose pharmaceuticals
    - The impurity involved is unusually potent, producing toxic or pharmacological effects at a level ≤ that of the identification threshold.

Qualification of impurities - STEP 1

Dose considerations



Qualification of impurities - STEP 2

In silico assessment

- Definition of the endpoints *
  - Genotoxicity
    - Mammalian *in vitro* mutagenicity
    - Chromosome aberration *in vivo*
    - Microucleous *in vivo*
  - General toxicity
    - Acute oral toxicity
    - Repeated dose toxicity
    - Carcinogenicity
    - Reproductive and developmental toxicity
  - Other specific endpoints
    - Skin/eye irritation-corrosion
    - Skin/respiratory sensitization
    - Target-organ toxicity
      - Neurotoxicity
      - Hepatotoxicity
      - Nephrotoxicity
      - Cardiotoxicity

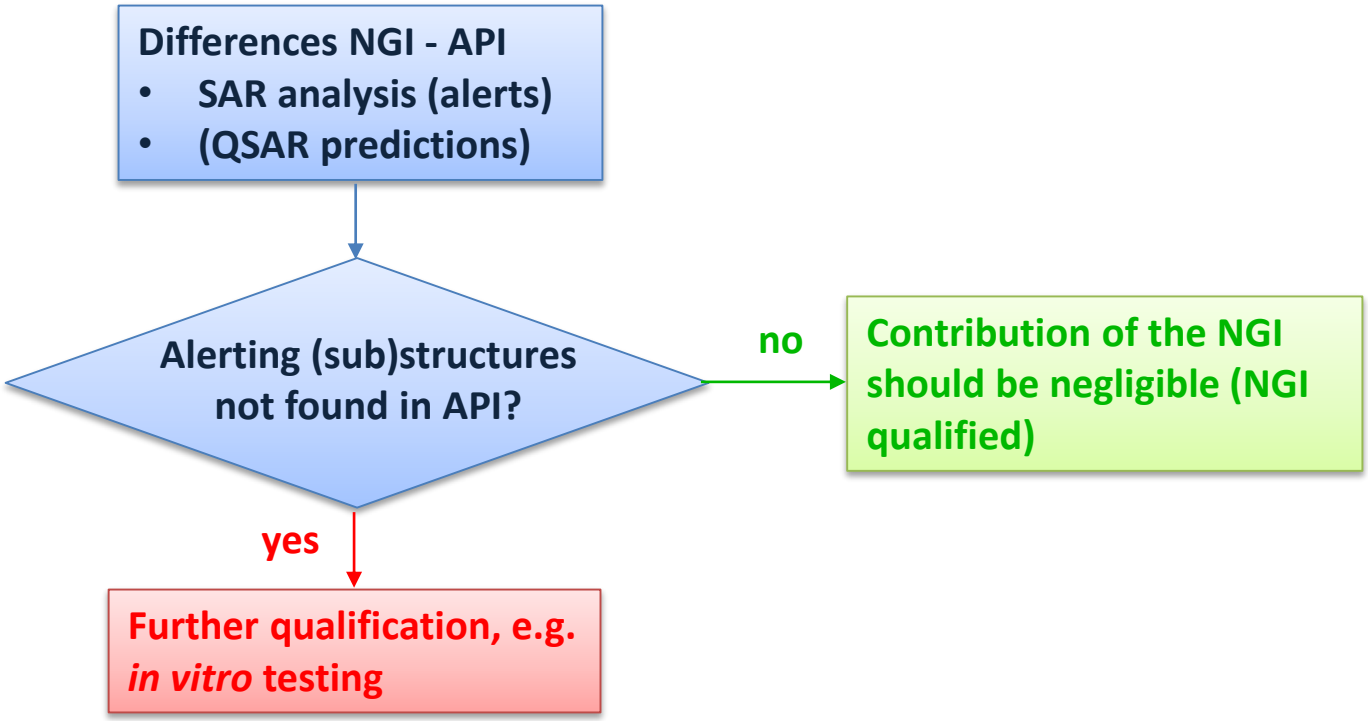
* They can be affected by intended use, route/duration of administration, existing knowledge on comparable compounds, organ-specific toxicity.

- Comparison with API
  - NGI structure related to the API → 2a
  - NGI structure ***not*** related to the API → 2b

Qualification of impurities - STEP 2a

- NGI structure related to the API, only having a deviating substructure

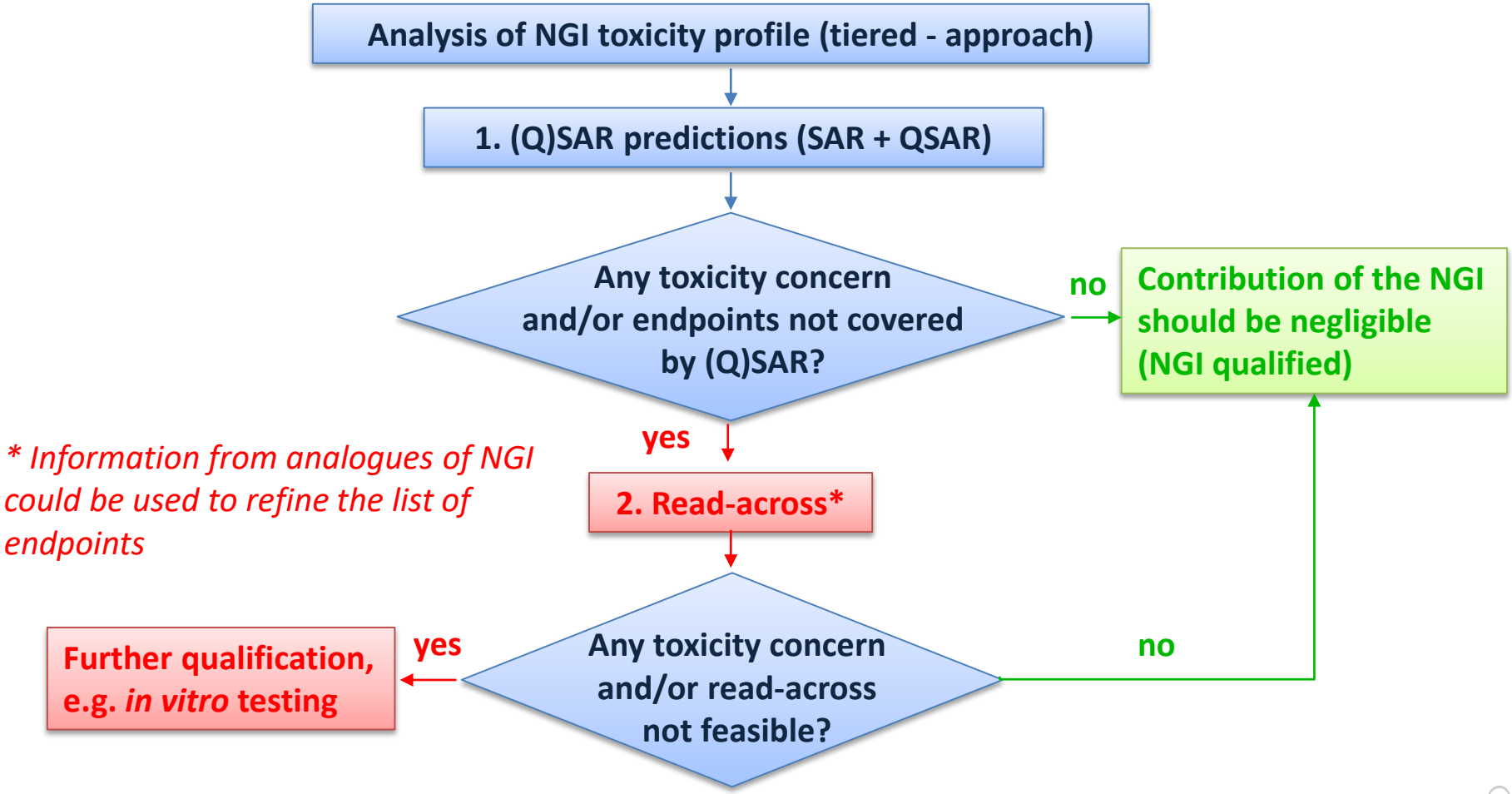
→ The goal would not be to predict the similarity in toxicity profile with the API but to determine whether any substructures that have not been identified in the API alert for specific types of toxicity.



Qualification of impurities - STEP 2b

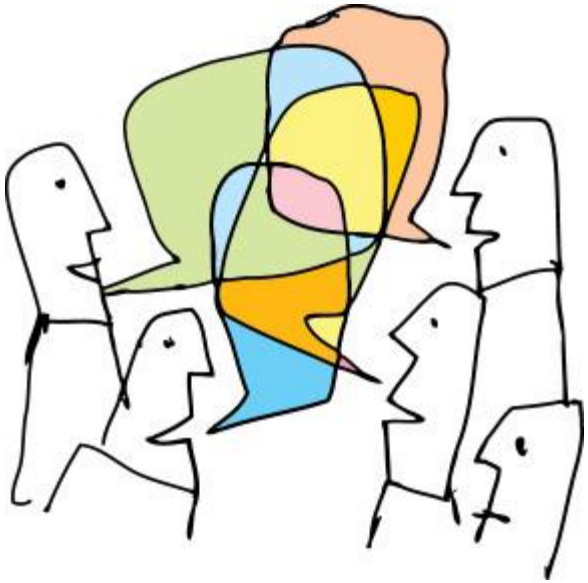
- NGI structure ***not*** related to the API

→ Read-across may provide relevant safety information when sufficient compounds with similar structure as the NGI exist for which toxicological data are available.



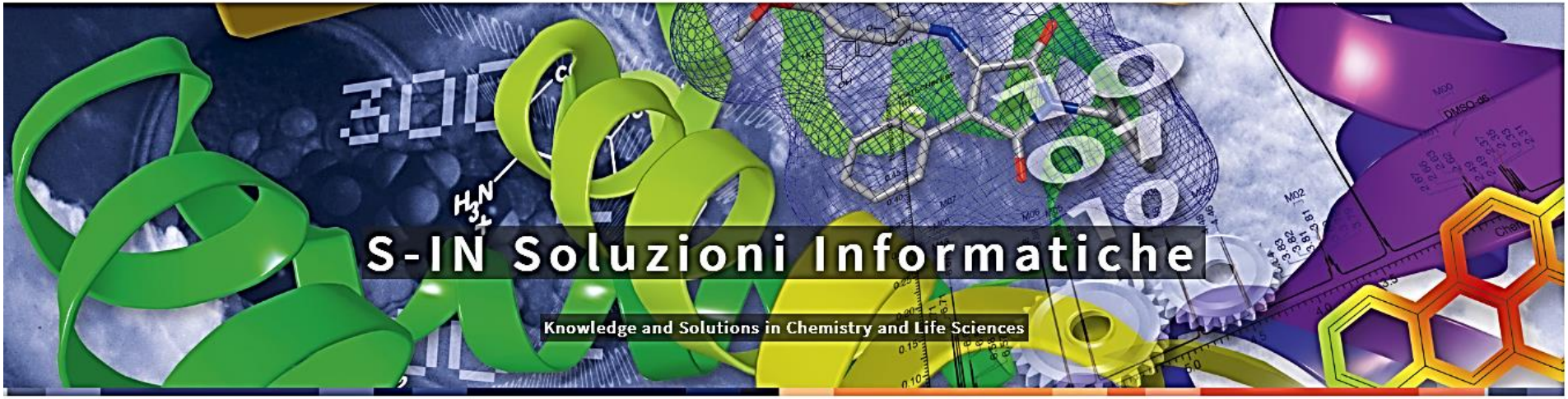
Conclusion & perspectives

- For NGI qualification, the only requirement is to determine whether at the specified level no adverse effects are expected
- When impurity-specific safety information is required, TTC, (Q)SAR, read-across and *in vitro* strategies may be used in a weight-of-evidence approach, including an assessment of uncertainty level
- By integrating impurity-specific data with existent knowledge, these approaches may provide a better understanding of NGI safety than by following the approach of testing an active substance batch containing the NGI in an animal study.



Thank you!

Special thanks to Simona Kovarich and Luca Sartori



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