Launch of the DIM testing project: when animal testing is difficult, impossible and meaningless (DIM) and the implications for the EU REACH regulation

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Abstract

Under the European Union's REACH Regulation, animal testing is intended to be used for providing information on chemical toxicity only if no other testing approaches can be used and therefore as a last resort option. Yet, despite the availability of non-animal approaches and a growing consensus for their scientific validity, testing requirements often default to traditional *in vivo* methods. This project explores the concept of Difficult, Impossible and Meaningless (DIM) testing within REACH, focusing on cases where animal testing was performed in situations where testing was difficult, technically unfeasible, or scientifically unjustified. Drawing on insights from the Animal-Free Safety Assessment (AFSA) Collaboration and recent literature, the current potential and the limitations of REACH were addressed with a focus on Annex XI, which has been drafted to enable adaptations and waivers from standard testing requirements. Based on the preliminary results, a scientifically driven reinterpretation of regulatory frameworks appears necessary to ensure alignment between regulatory needs and testing strategies, moving beyond checkbox compliance toward robust, substance-tailored, animal-free safety assessments.

Read the full position paper:

Project description

1. Creation of AFSA expert group & project objectives definition

Project objectives

- ✓ To assess how often and under what conditions DIM testing occurs, thereby clarifying the urgency and scale of the problem;
- ✓ To provide practical, science-based recommendations that better align regulatory practice with the last resort requirement and better utilise robust non-animal approaches.

2. Definition of DIM testing

	Difficult	Impossible	Meaningless
Definition	Substances whose properties fall outside the normal applicability domain of the in vivo test methods requested under REACH Standard Information Requirements.	Substance characteristics render the test impossible to conduct.	Any test in which the conduct of the study is of questionable relevance to safety assessment due to the inherent characteristics of the substance.
Examples	Poorly soluble substances requiring extensive use of solvents or emulsifiers to achieve exposure levels, potentially leading to confounding effects.	Chronic toxicity testing of highly volatile substances, where maintaining stable exposure concentrations is unachievable.	Testing of a substance not expected to reach the target compartment (e.g. a chronic test requested for a highly volatile, rapidly degrading substance).

3. Preliminary review of REACH registration data

Based on preliminary DIM criteria developed through consensus, the project has assessed the extent of DIM testing in REACH registration dossiers (particularly post-2009) in combination with ECHA compliance check outcomes.

Search criteria	Range/value
Solubility	< 1 mg/L
Unstable explosive/peroxides	CLP classification: H250, 260, 261, 270; EUH014,029,031,032,071
Unstable ENV – hydrolysis	DT50 < 12h
Unstable ENV – photostability	DT50 < 12h
Corrosive	CLP classification: H290, H314, H318
Volatile	> 0.01kPa
Complex substance	Not mono-constituent substance
Surfactants	< 40 mN/m
Coloured	n/a
Impurities	Purity < 80%

Results

4. Discussion of exemplary real life case studies

Preliminary findings indicate that DIM testing is more common than expected. In several specific cases, hundreds of animals were used per test, even though regulatory conclusions could (and should) have been based on existing *in silico* and *in vitro* evidence.

Case Study 1 – Environmental Toxicity

DIM Category(ies): Difficult/Impossible	**In vivo TGs requested:** OECD TG 203; 305
Chemical(s) tested: 10 substances identified from preliminary DIM screening	
Of 24 DIM substances tested in OECD 203, 10 met criteria (low solubility <0.1 mg/L and/or LogP > 6) for which testing should have been avoided. A similar approach was applied for the bioconcentration testing	

Case Study 2 – Environmental Toxicity

DIM Category(ies): Meaningless	**In vivo TGs requested:** OECD TG 210
Chemical(s) tested: SXS-Sodium (Xylene and 4-Ethylbenzene) Sulfonates	
High-dose in vivo study for a substance with a known mode of action and suitable for REACH read-across was found to be inconclusive due to unquantifiable results from scientifically meaningless test conditions	

5. Preliminary recommendations

Based on the preliminary analysis and additional expert discussions, the project has therefore identified a number of issues and defined a set of preliminary recommendations relevant to the current regulatory context and the ongoing REACH revision, extending also beyond the considerations of the DIM animal tests.

Identified Issues

- ✓ Lack of legal/regulatory certainty that NAMs will be accepted
- ✓ Lack of clear scientific justification when additional data is requested
- ✓ A culture of "checkbox compliance" within regulatory assessment
- ✓ A reliance on arbitrary (high)-dose testing in regulatory frameworks
- ✓ NAMs characterized by their limitations vs *in vivo* studies accepted as gold standard
- ✓ Unclear whether studies were conducted for REACH or other purposes

Technical/Regulatory Recommendations

- **Enhance collaborative exchange** between registrants and regulators
- **Define scientific robustness and adequacy** across all testing sources, including in vivo tests
- **Encourage substance-tailored testing strategy**, science-based justification
- **Improve transparency** in data traceability and regulatory purpose
- **Strengthen the role and incorporation of toxicokinetics** and align testing strategies with meaningful exposure scenarios

Policy Recommendations

- **Level regulations** to the latest state of science and improve the implementation of Annex XI (REACH)
- **Support the legal and cultural transition** to Next-Generation Risk Assessment

Ongoing and Next Steps

6. **Systematic review of REACH** registration data and ECHA compliance check

7. **Scientific publication** incl. description of analysis outcome and final considerations

8. **Strategic dialogue with stakeholders** in combination with AFSA regulatory transformation work

9. **Change to REACH/ Guidance documents** to increase NAM use & the compliance to the last resort requirement

Project partners

dsm-firmenich · GPC Global Product Compliance · iff · innospec · Kenvue · Shell · Merck · P&G · ProtoQSAR · AFSA Collaboration

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