IPA
Institute for Prevention and Occupational Medicine
of the German Social Accident Insurance
Institute of the Ruhr-Universität Bochum

RUHR UNIVERSITÄT BOCHUM RUB

Cohort Study: Evaluation of the Diisocyanate Restriction

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April 22, 2021

Diisocyanates (DII) & Health Effects

- Important substances in industry
  - manufacture of PU-based products
- DII cause respiratory and lung diseases
  - not common
  - persons are usually forced to discontinue all activities
  - no. of unreported cases?
- REACH restriction since 08/2020
  - teaching safe handling of DII

1315 | Diseases caused by isocyanates

Notifications of suspected cases of occupational disease

2005	2010	2015	2018	2019
99	119	103	108	92

Recognized cases of occupational disease

2005	2010	2015	2018	2019
35	30	38	35	16

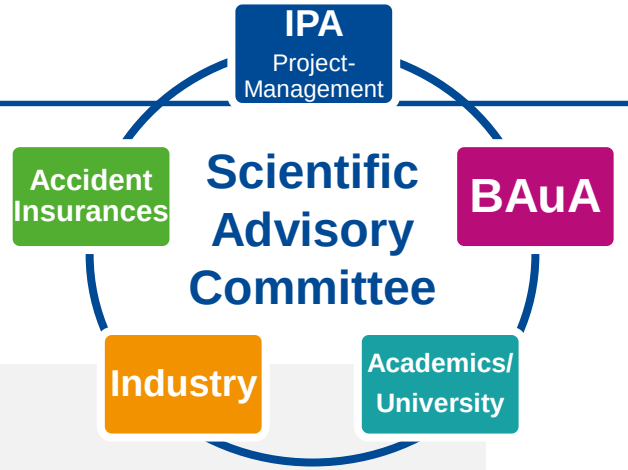
New occupational disease pensions

2005	2010	2015	2018	2019
22	13	21	15	12

Open Questions / Issues

- What is the prevalence / incidence of DII-induced respiratory diseases?
- Does skin exposure contributes to DII-induced sensitization and respiratory disease?
- Is there an association between exposure level and duration with sensitization and or respiratory disease?
- How can the effectiveness of the REACH restriction be evaluated?

Overall Aims of the Study



- To record the number of DII-related respiratory and lung diseases caused by diisocyanates (prevalence, incidence)
- To determine the amounts of DII which are taken up by employees (external exposure, biological monitoring)
- To describe the relationship between exposure and respiratory and lung diseases (dose-response relationship, case studies)
- To systematically check the effectiveness (*i.e.*, reduction of exposure and diseases) of protective measures which are specified in the REACH restriction regulation

Challenge: Cohort Size

Limiting factor: To record the incidence of DII-induced respiratory disease

- Evaluation of 8 studies (5 US, 1 JP, 1 SWE, 1 UK) in workers exposed to TDI´s
- Cases were based on ´self-reported symptoms´, ´decisions by occupational physician´ and ´diagnosis by one or more clinical test´

➔ **~1 case / 100 person-years**
(~**50 cases** in **1,000 persons** in **5 years**)

Daniels *et al.* **2018** (*Am. J. Ind. Med.* 61: 282)

REVIEW ARTICLE

WILEY

Occupational asthma risk from exposures to toluene diisocyanate: A review and risk assessment

Robert D. Daniels PhD

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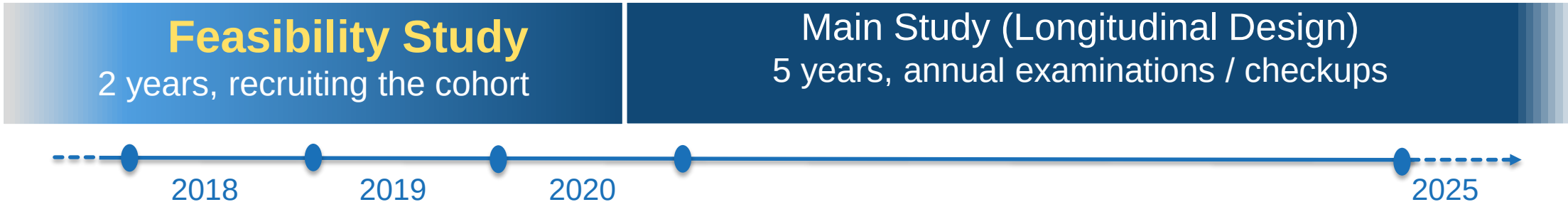
Funding information
No funding.

Background: Toluene Diisocyanate (TDI) is a known respiratory sensitizer linked to occupational asthma (OA). To better manage worker risks, an appropriate characterization of the TDI-OA dose-risk relationship is needed.
Methods: The literature was reviewed for data suitable for dose-response modeling. Previous study data were fit to models to derive prospective occupational exposure limits (OELs), using benchmark dose (BMD) and low-dose extrapolation approaches.
Results: Data on eight TDI-exposed populations were suitable for analysis. There were 118 OA cases in a population contributing 13 590 person-years. The BMD-based OEL was 0.4 ppb. The OEL based on low-dose extrapolation to working lifetime extra risk of 1/1000 was 0.3 ppb.
Conclusions: This study synthesized epidemiologic data to characterize the TDI-OA dose-risk relationship. This approach yielded prospective OEL estimates below recent recommendations by the American Conference of Governmental Industrial Hygienists, but given significant study limitations, this should be interpreted with caution. Confirmatory research is needed.

KEYWORDS
dose-response, epidemiology, isocyanates, occupational asthma, risk assessment

Study Implementation – A 2-Step Process



- Recruiting of ~1.500 exposed individuals and 200 controls
- Developing study design and study measures (*i.e.*, assessing exposure and health effects)

Funded by:
- Federal Institute for Occupational Safety & Health (**BAuA**)
- European Diisocyanate and Polyol Producer`s Association (**ISOPA / ALIPA**)
- Selected Statutory Accident Insurance Institutions (**BGRCI**, **BGHM**, **BGBAU**, **BGETEM**)

Recruiting Process

First Contact

e.g., ISOPA / ALIPA Accident Insurances

Notification of IPA

incl. contact person at company

First Information

Schedule appointment

Meeting at the Company

Noncommittal

Basic information

- Type of diisocyanates
- Working tasks
- No. of exposed persons

…

Decision Making

with regard to participation

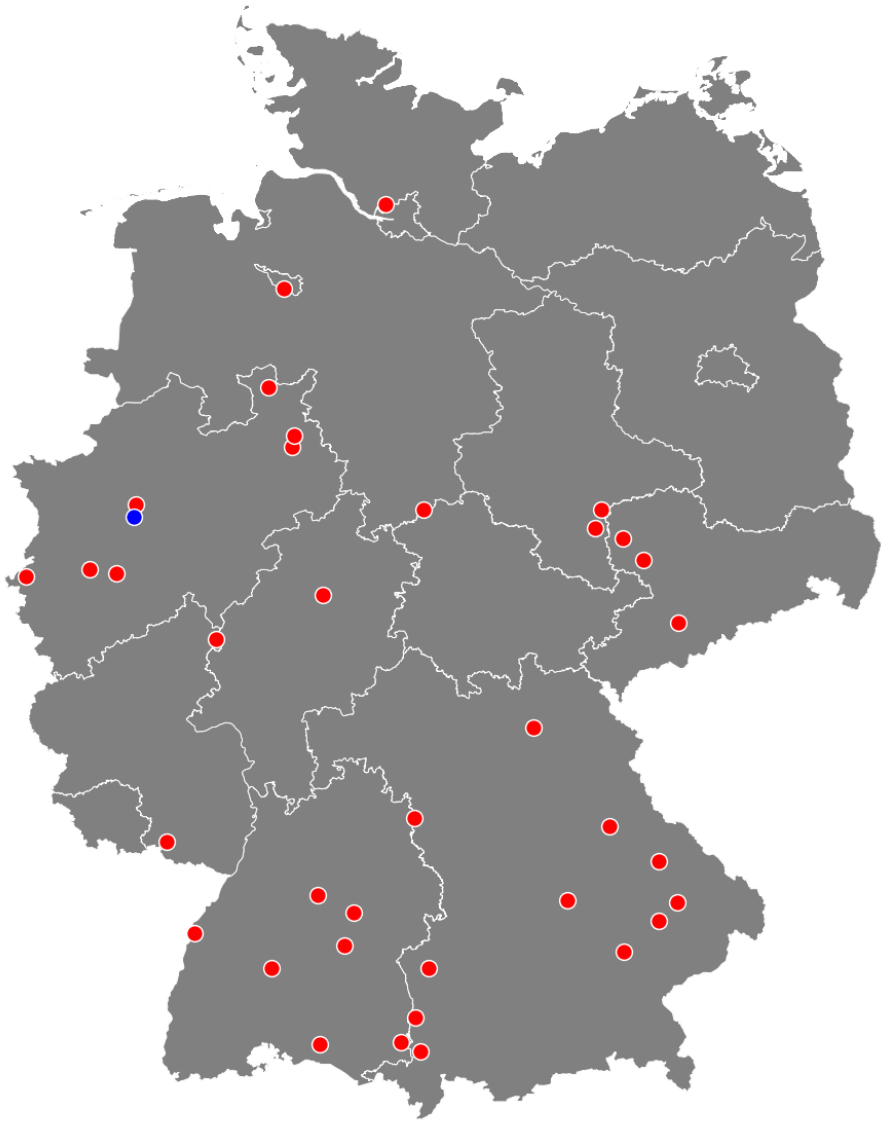
- Management
- Unions
- Occupational Physicians

Current Status

Contact with **80** companies

- **6** Currently without feedback
- **14** Cancellations / Rejections
- **35** Commitments to participate
- **25** Interested in participation

1,320 exposed employees in 28 companies



Industrial Sectors

Manufacturers of **Diisocyanates**
Raw Materials

Use of diisocyanates for PU-based…

- **Adhesives & Sealants**
- **Coatings**
- **Flexible Foam**
- **Binders**
- **Elastomers**
- **Rigid Foam**

Users of PU-based Products
End-Use Markets

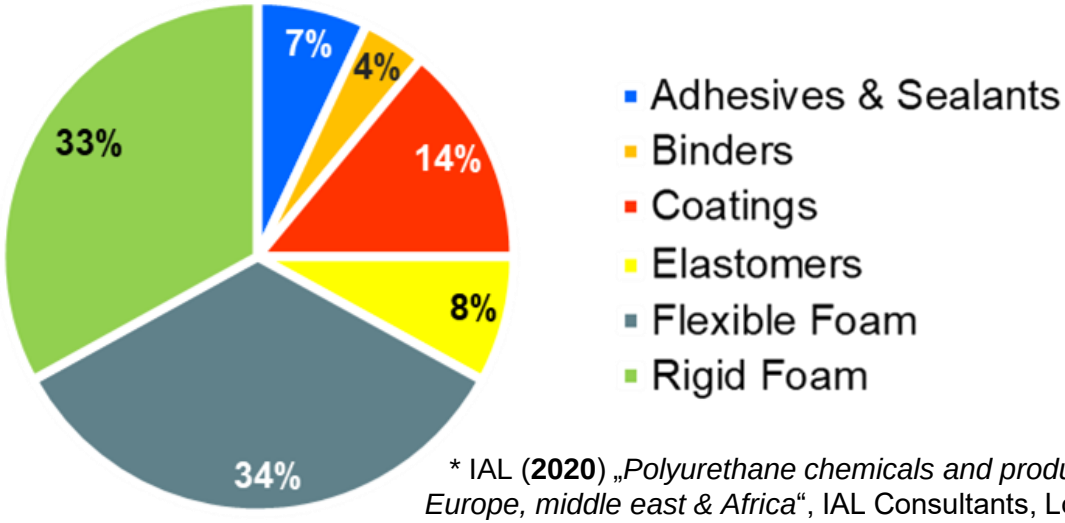
DII Consumption in Europe*

- MDI (2019) 1,64 Mill. tonnes
- TDI (2019) 0,57 Mill. tonnes

~3:1

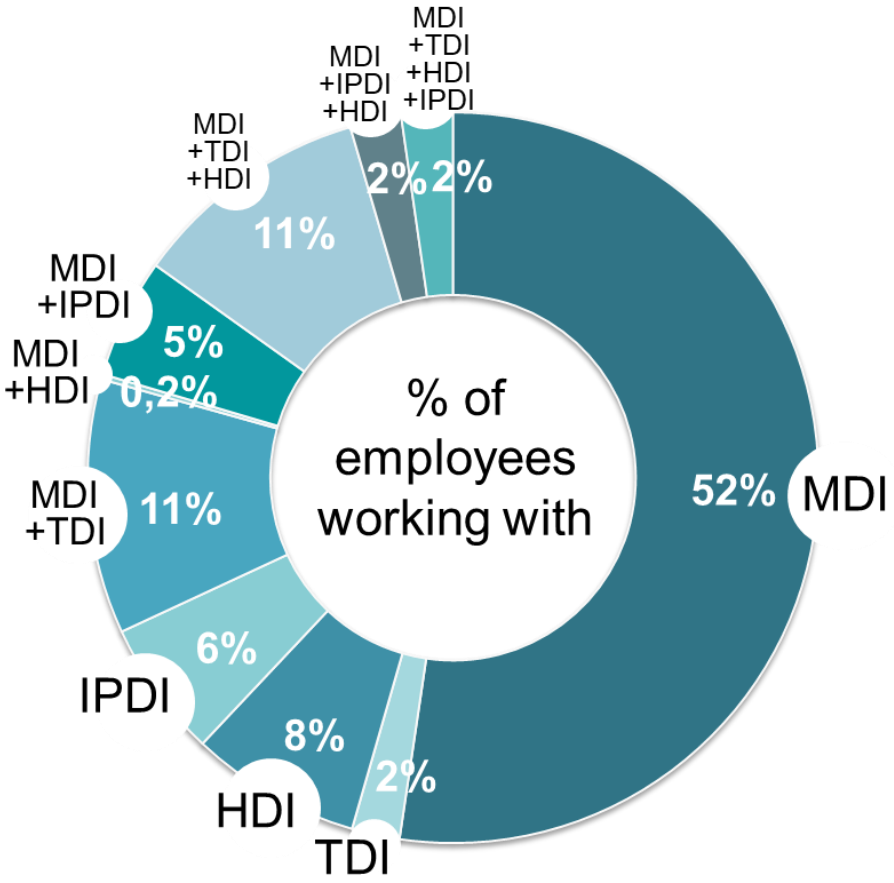
PU Production in Europe

- Total (2019) ~5,43 Mill. tonnes
- Estimated (2024) ~5,50 Mill. tonnes

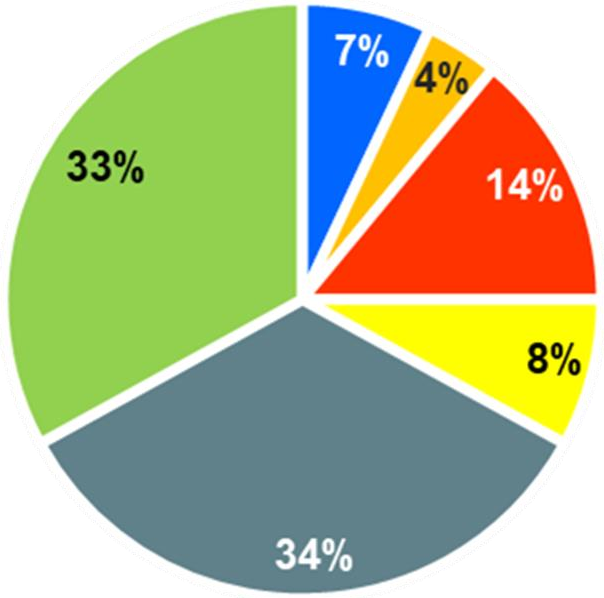


* IAL (**2020**) „*Polyurethane chemicals and products in Europe, middle east & Africa*“, IAL Consultants, London

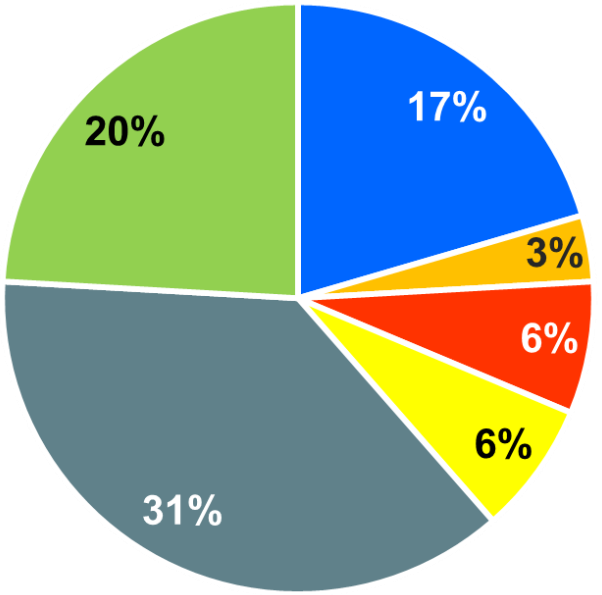
Diisocyanates & Industrial Sectors



„Market Research“



Our current cohort



- Adhesives & Sealants
- Binders
- Coatings
- Elastomers
- Flexible Foam
- Rigid Foam

Study Implementation – A 2-Step Process

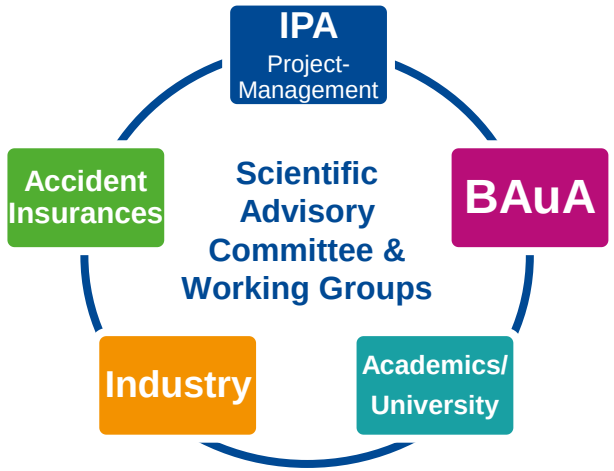
Feasibility Study
2 years, recruiting the cohort

Main Study (Longitudinal Design)
5 years, annual examinations / checkups

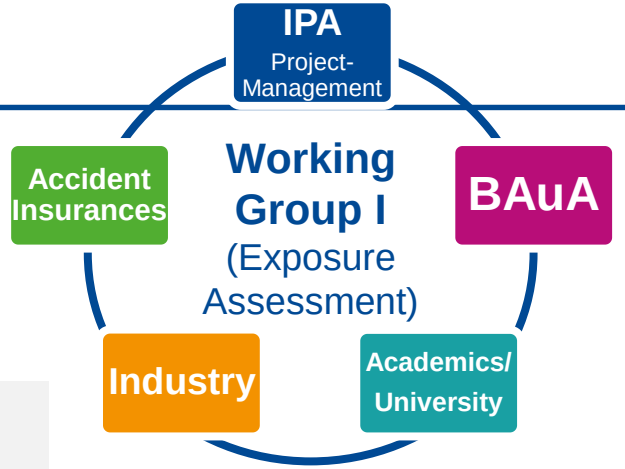
2018 2019 2020 2025

- Recruiting of ~1.500 exposed individuals and 200 controls

- Developing study design and study measures (*i.e.*, assessing exposure and health effects)



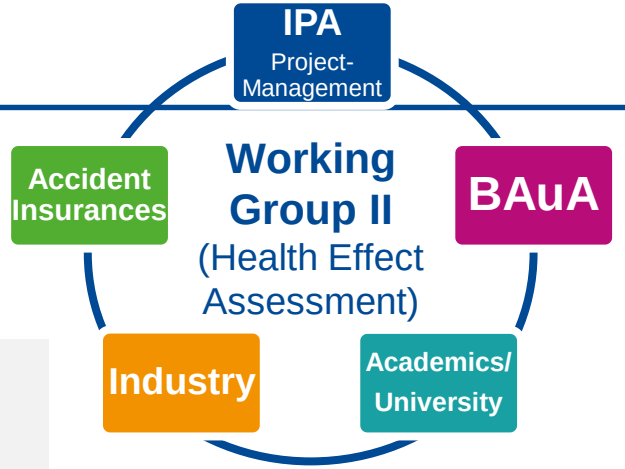
Main Study – Assessing Exposure



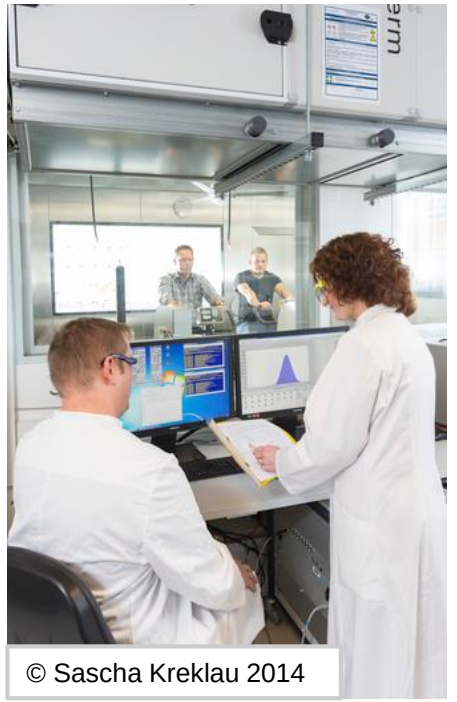
- Ambient exposure (total & specific DII)
- Biological Monitoring
  - Specific (DII-derived) hemoglobin adducts in blood (MDI, TDI)
  - Aromatic / aliphatic aromatic amines in urine (MDI, TDI, NDI & HDI, IPDI)
- Skin exposure / Skin contact (Harari *et al.* **2016**, *Ann. Occup. Hyg.* 60: 1092)
- Questionnaires (potential confounders, workplace hygiene)
- Photo documentation of workplaces & working tasks

© Sascha Kreklau 2014

Main Study – Assessing Health Effects



- Lung function & Nitric oxide in exhaled air (FeNO)
- Atopy-Screen (sx1), total IgE, DII-specific IgE/IgG
- Serum chemistry & Blood Counts
- Skin documentation of the employees´ hands
- Methacholin challenge
- Questionnaires & phone interviews (work-related health complaints, drop-outs)
- Prevalence / incidence of DII-induced respiratory diseases
- Biobanking (for possible follow-up measurements)



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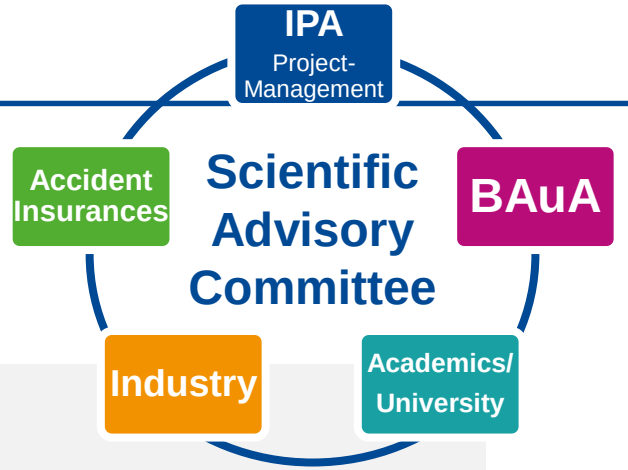

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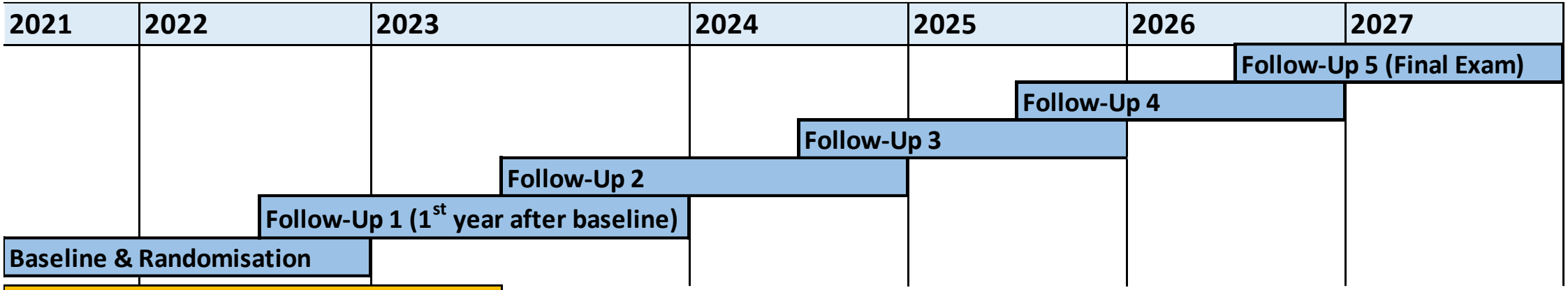
REACH Restriction – Evaluation

- If possible: randomization



Feasible endpoint: exposure reduction (before / after teaching)

On-Going & Up-Coming Aspects

- Verify Possibility for Randomisation
- Open Cohort (On-going recrution)
- Data Protection (Companies, Employees)
- Ethical Approval
- Cost estimations of the main study

„*Balance between what is scientifically interesting, scientifically necessary, practically feasible at all, and financially feasible*“

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Thank you for your interest

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