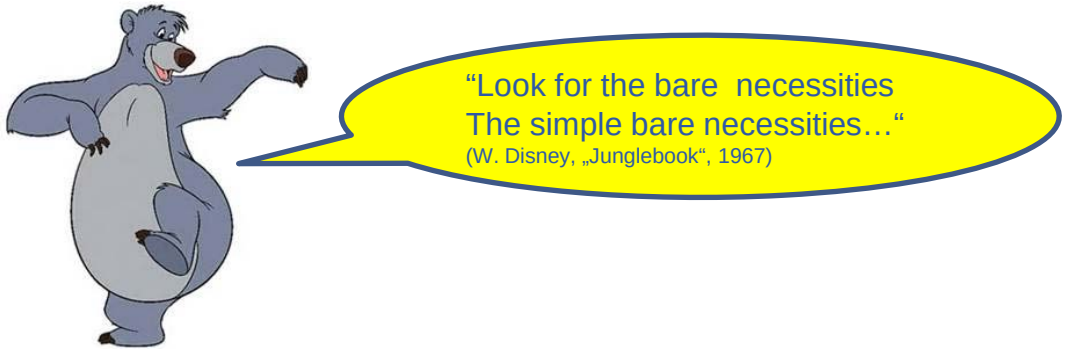

Authorisation:
the bare necessities

Cooperation project between German industry and DE-MSCA to come to a „Standardised Application for Authorisation“

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Bayer HealthCare, BAuA, BASF SE

Science For A Better Life

Bundesanstalt für Arbeitsschutz und Arbeitsmedizin

150 Jahre BASF We create chemistry

Background

- 2011: Several aprotic solvents on Candidate List
  Anxiety at industries for a.o. dichloroethane (EDC)
  (Carc. 1B, no threshold → SEA route mandatory)
  – Process solvent, not in final product.
- Discussions with BAuA: General exemption not possible
  → but in view of use in a closed system a relatively „simple“ AfA may be expected.
- 2014: EDC on Annex XIV (SunsetDate: 22/11/17)
  Despite guidances, AfA is considered by many as cumbersome, time consuming, fuzzy and uncertain in outcome – and failure is no option
- 2014: Supported by the German government, Bayer, BASF, BAUA, VCI looked for cooperation in creating a „standardised example“ to get AfA for an aprotic solvent.
  → aim is to generalise principles and experiences to other cases and use results for wider benefit.

Actions

- During five meetings dichloroethane (EDC) was discussed in detail for two specific uses:
  1. What is needed for an AfA ?
     (Process description, Exposure data, Analysis of Alternatives, SEA Data)
  2. What data are already there that can be used, what needs refinement?
  3. What are the essentials to build the case?
- Industry did the work, BAuA gave advise and made suggestions. VCI (German Chem. Industry Assoc.) as observer
- Very fruitful cooperation to discover the essentials – not all is as difficult as it looks at first sight.

The working example

- EDC as an example for carcinogens without threshold
- Used by Bayer as a process solvent for production of a medical agent (API= Active Pharmaceutical Ingredient).
- Solvent used in a closed system, not part of final product
- Production process very critical – quality of end product depends on purity
- Subtle changes in the product will lead to need of re-qualifications for final marketed product

This example will show what we selected as “bare necessities” for the AfA in this case.

However, these findings can be generalised to other substances.
(e.g. BASF case : extraction solvent for a high purity chemical)

Exposure - Description

- Describe exposure of the substance in a transparent and comprehensible way

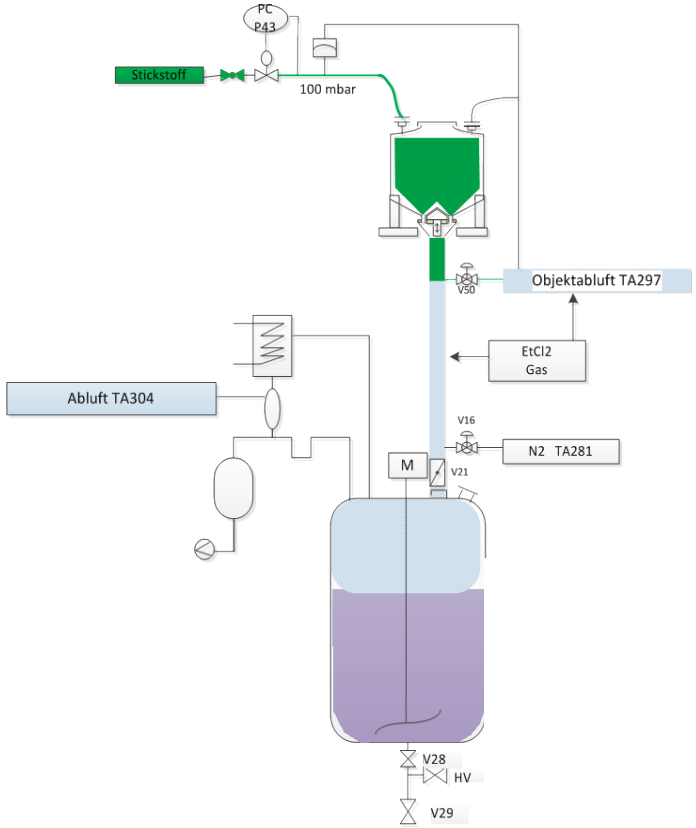
  - Technical process descriptions, pictures, flow charts….
  - Number of exposed individuals in relation to the time of exposure
  - Exposure measurements (including critical areas like sampling, filling, hose connections...)
  - Risk management measures (technical measures, personal protective equipment…)

- Demonstration and documentation of all actions undertaken to achieve the lowest exposure level (acc. to Article 60)

Minimal exposure should be a compelling argument to achieve a long review period.

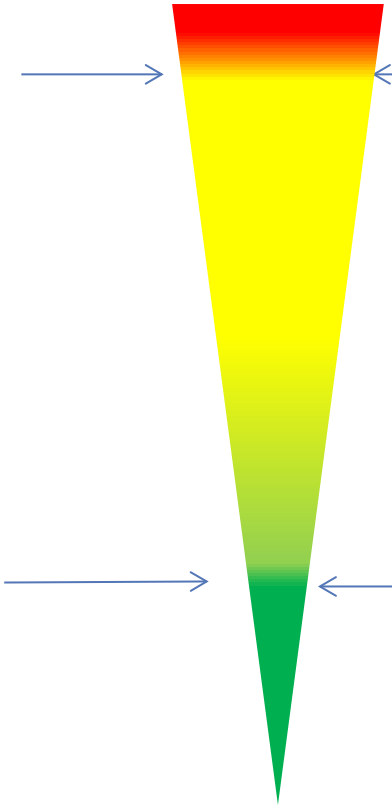
Exposure - Examples

Closed system: Filling



Closed system: Sampling

Exposure and Risk



German Model	Excess cancer risk	Corresponding Exposure mg/m³
Tolerable Risk Threshold	4/1 000	6.6
Acceptable Risk Threshold	4/10 000	0.6 (2013)

Risk assessments: If available, take RAC reference values

Analysis of Alternatives

- Basis of the AoA is a detailed and specific description of the substance function
- Potential alternatives could be:
  - substitution by another substance,
  - process changes
  - implementation of a new technology
- Substance parameters:
  - Function in process
  - Properties and quality criteria
  - Process conditions
  - Regulatory requirements, product registrations
  - Customer requirements…..

Describe the substance function as detailed as possible to discard obviously infeasible substitution candidates.

Analysis of Alternatives

Task	Description
No reaction with substance A + HCl	Inert against very reactive substances like HCl and substance A
Boiling point (xx°C)	Boiling point has to be in a range to separate potential reaction gases without appreciable loss of solvent
Good solubility with intermediate 1	Good solvent properties for intermediate 1 (to avoid sticking and incomplete conversion)
No solubility with substance B + HCL	Low dissolving power for HCl and substance B to eliminate these substances from the reaction equilibrium
No solubility with target intermediate 2	Low dissolving power for intermediate 2 to eliminate it from the reaction mixture (to avoid preterm spontaneous crystallization)
Good solubility with side products	Good solvent properties to eliminate impurities in particular chromophoric impurities
Recycling	Good recyclable solvent, to eliminate all acid by stirring with NaOH

Analysis of Alternatives

Substances	Lower Risk vs. EDC	Technical Feasibility	Economic Feasibility
Substance 1	No	Yes	Yes
Substance 2	Yes	Yes	No
Substance 3	Yes (Potentially)	No	No
Substance 4	Yes	Yes (Potentially)	No

Technology	Availability	Technical Feasibility	Economic Feasibility
Technology 1	No R&D ~ 80% Completed	Unknown	No
Technology 2	No 3rd Party Patents in Place	Yes (Potentially) in Use at Competitor‘s Plant	No

Socio Economic Analysis

Calculation of the “non-use scenario”

- Negative impact on society
  - General supply shortage of this kind of pharmaceuticals
  - Quality of this certain product no longer available
- Loss of profit
- Contract penalties
- Negative effects on suppliers

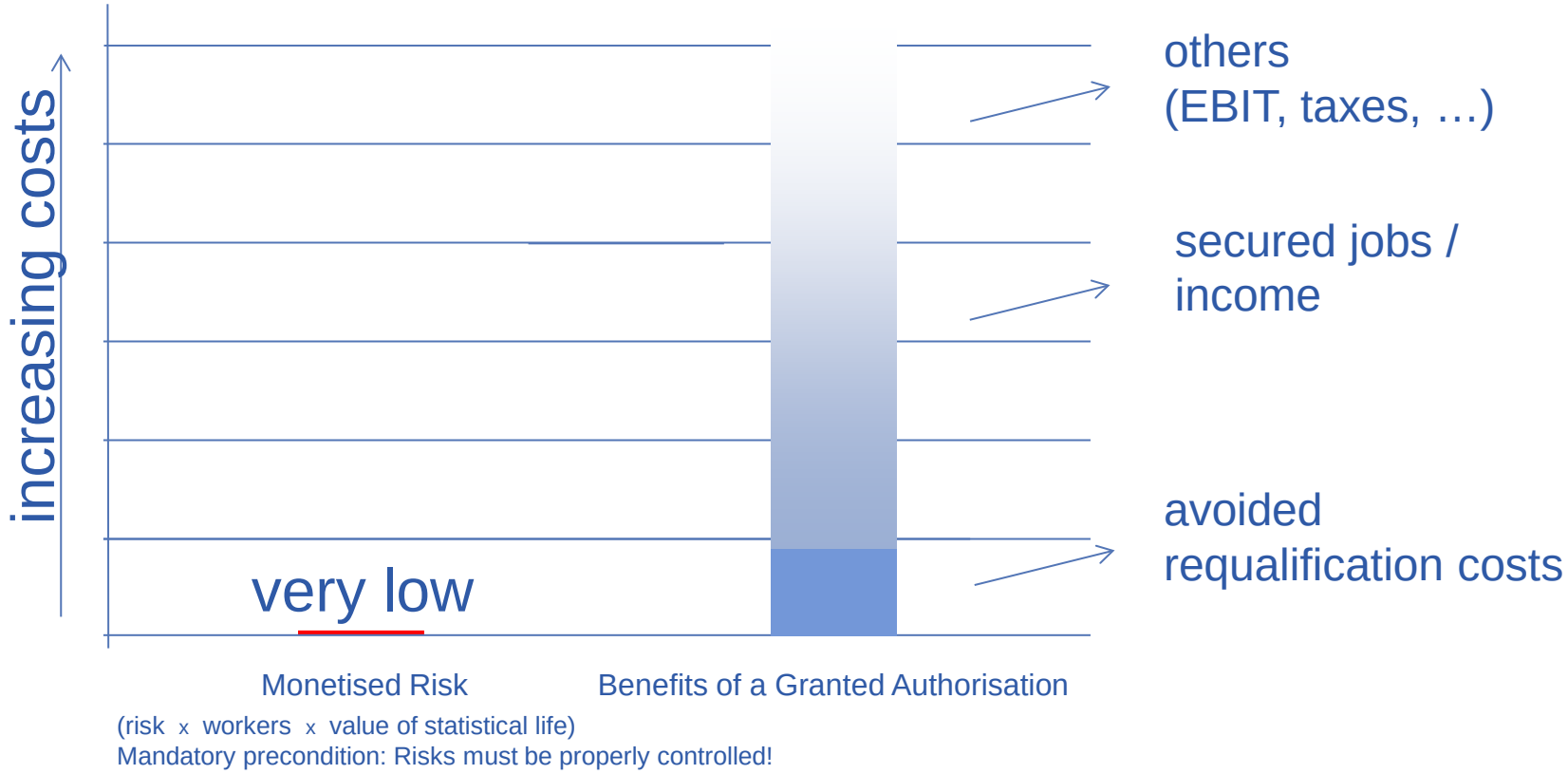
Calculation of the “use scenario”

- **Impacts on human health and environment**

Demonstration of a reliable, transparent "Non Use scenario"

Risks for individual worker must be properly controlled!

Socio Economic Analysis

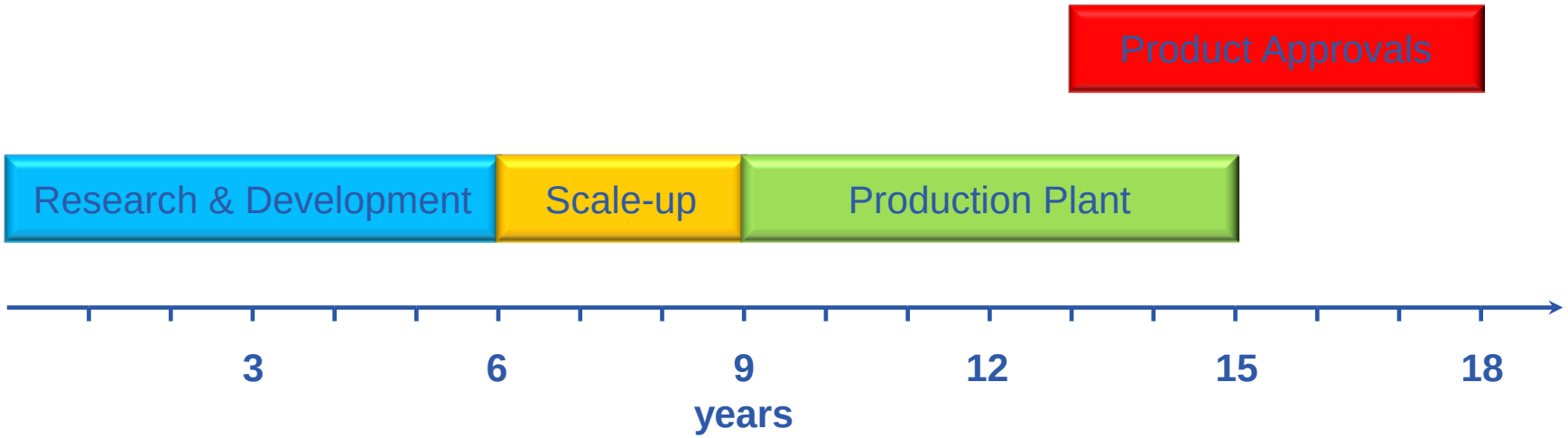


Compelling SEA for continued use! (benefits outweigh costs by orders of magnitude)

Review Period

- **Low risk**
- **High socio-economic benefit**
- **No alternative available**

→ (Hypothetical) Substitution Plan



⇨ Review period needed > 15 years!

Summary

- 2 examples show that standardisation is possible
- Transparent presentation including pictures and tables is necessary
- RAC-Reference-values for risk estimations are needed at an early stage
- Structured approach in compiling AoA
- Focus on main arguments in SEA
- Approach can be transferred to other process solvents in closed systems
- Potential for standardisation available
  – continuation of discussions needed

Thank you for your attention

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