

Paradigms of Risk Assessment and Uncertainty in Policy research

Applying the Tolerability of Risk heuristic
outside the Health and safety field: does it
work ?

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Key question:

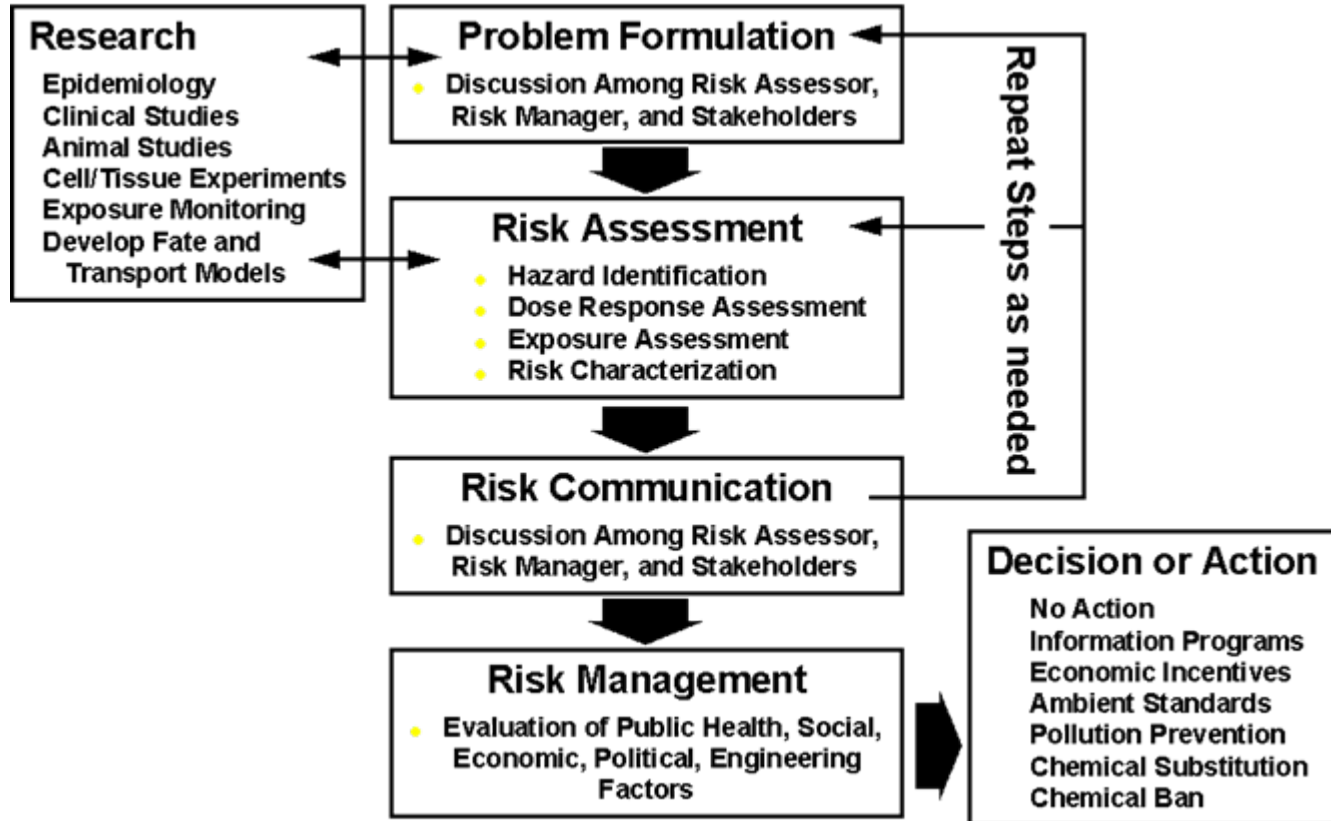
Under what circumstances could we adapt existing risk assessment models to new situations?

My approach

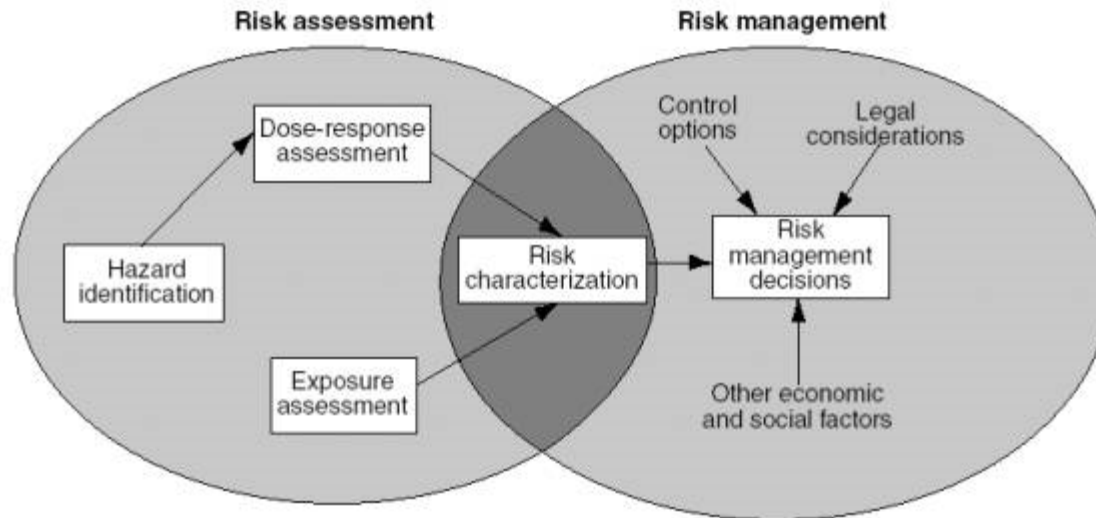
- Multiplicity of risk assessment paradigms
- Pharma risk assessment: heading for change?
- Testing new paradigm on specific cases

Risk assessment paradigms on both sides of the Atlantic

NRC approach

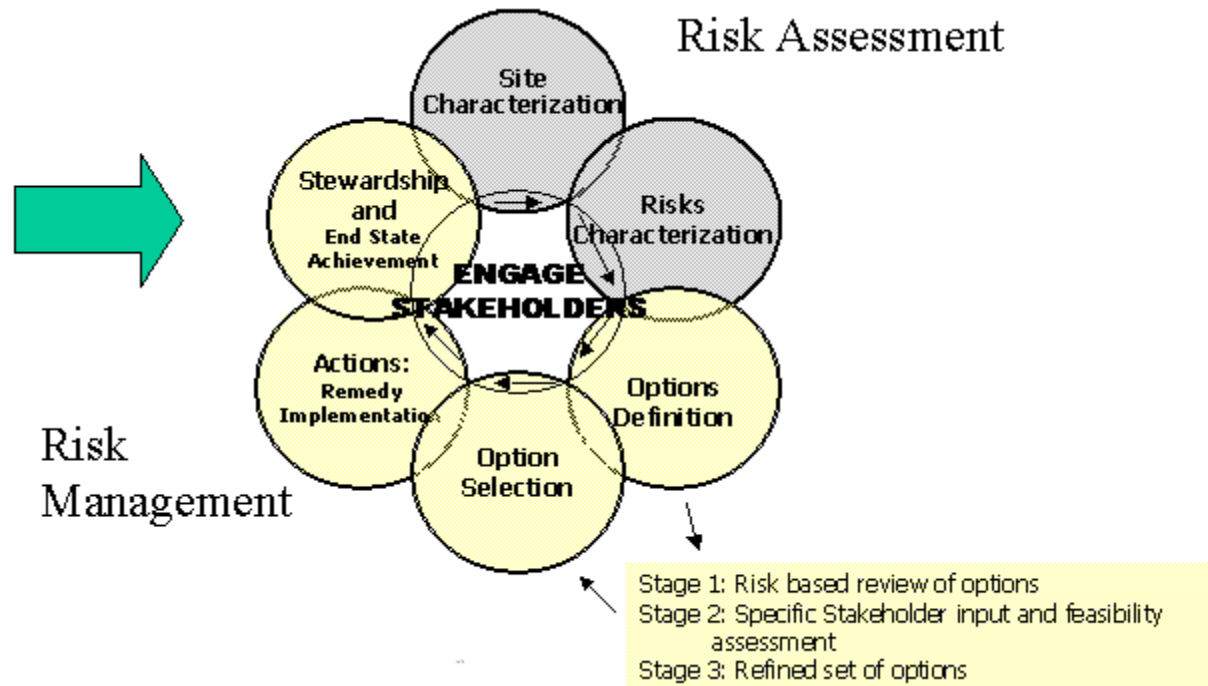


NRC (from EPA)



Source: EPA Office of Research and Development.

PPC 1997



Europe

France

'Risk avoidance principle', i.e. reluctance to accept statistical models to make risk acceptability judgements.

Code of work (1991): Avoid risks (1)
Evaluate the risks that cannot be avoided (2) and (3) combat risks at their source

Germany

Hazard based model (i) basic level of acceptability; (ii) state of art of safety technology; (iii) state of art of science (Okstad and Hoskstad 2001)

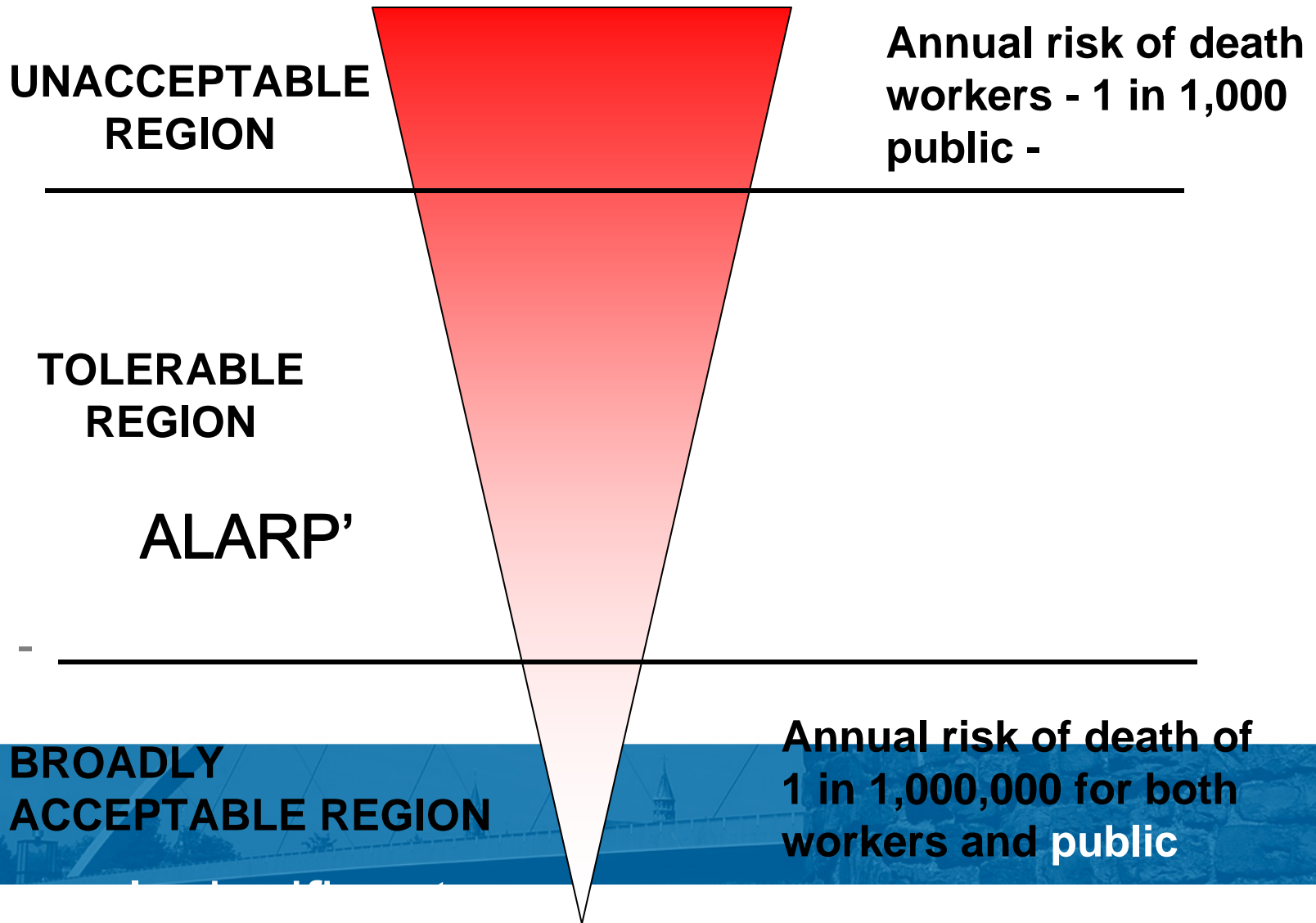
UK

Hazard-based models , e.g. Flooding,
flammables

“Best technology”: environmental field

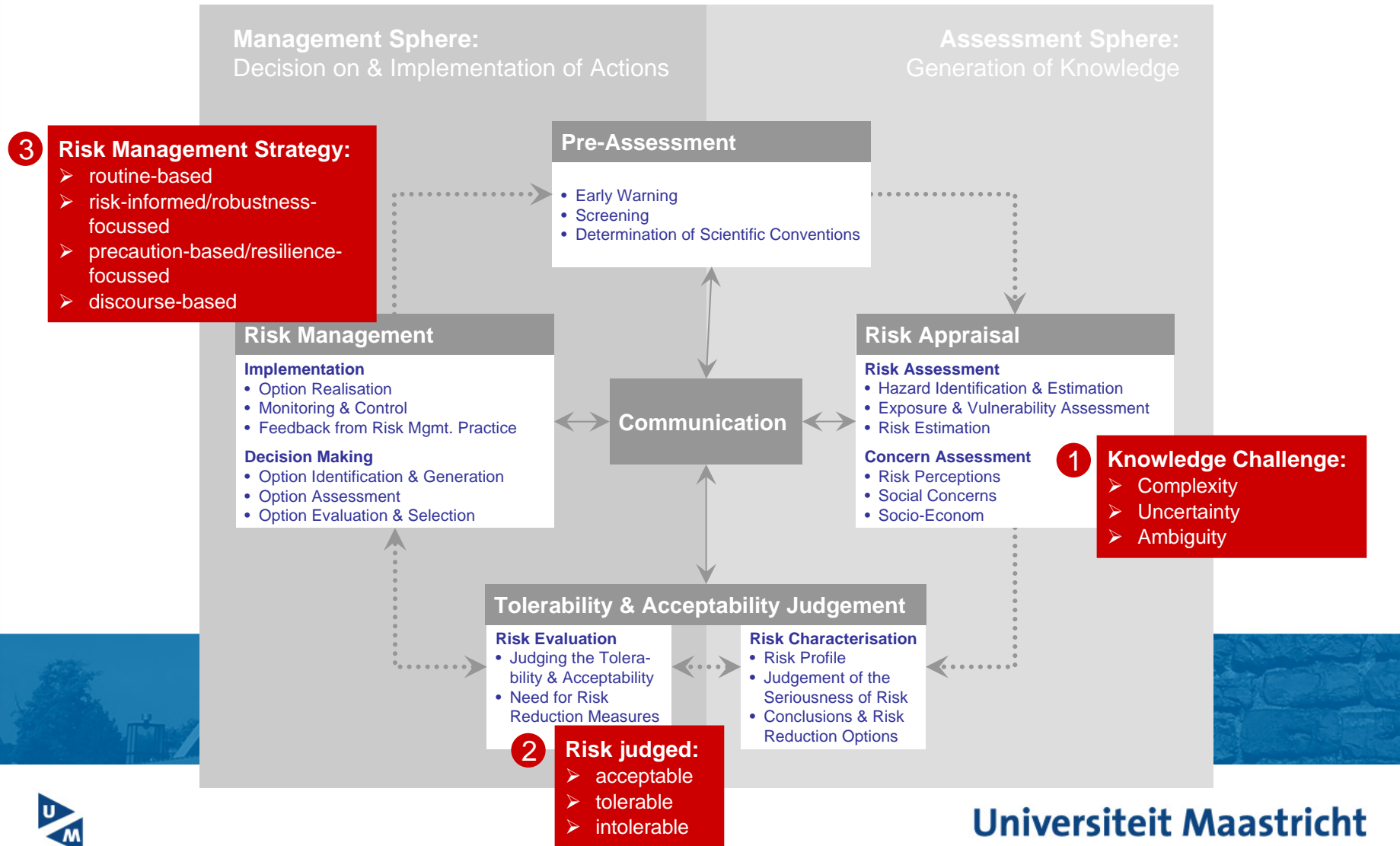
Risk-based model: Health and safety ToR

Tolerability of Risk (ToR)



Assessment Components	Definition	Indicators
1 Risk characterisation	Collecting and summarising all rel-evant evidence	
	a risk profile	<ul style="list-style-type: none"> –Risk estimates –risk perceptions –social and economic implications –Etc.
	b judging the seriousness of risk	<ul style="list-style-type: none"> –compatibility with legal re-quirements –risk-risk trade-offs –effects on equity –public acceptance
	c conclusions and risk reduction options	suggestions for: <ul style="list-style-type: none"> –tolerable risk levels –acceptable risk levels –options for handling risks
2 Risk evaluation	Applying societal values and norms to the judgement	<ul style="list-style-type: none"> –choice of technology –potential for substitution –risk-benefit comparison –political priorities –compensation potential –conflict management –potential for social mo-bilisation
	Adapted from Renn, 2006	

IRGC RISK GOVERNANCE FRAMEWORK



Fiduciary avoidance model

Elected officials and bodies determine the acceptable risks. No official individual risk estimates; weak mechanisms to include public views

**France environmental legisl.
Italy (theory)**

Consensual containment model

Consensual agreement among experts on the “best level”. Individual risk estimates support compliance with best technological solution

German industrial sites

Consensual control and assessment model

Engineering safety approach focussing on reduction. Thresholds supported by individual risk estimates + societal risk criterion
Dutch industrial sites

Risk assessment model

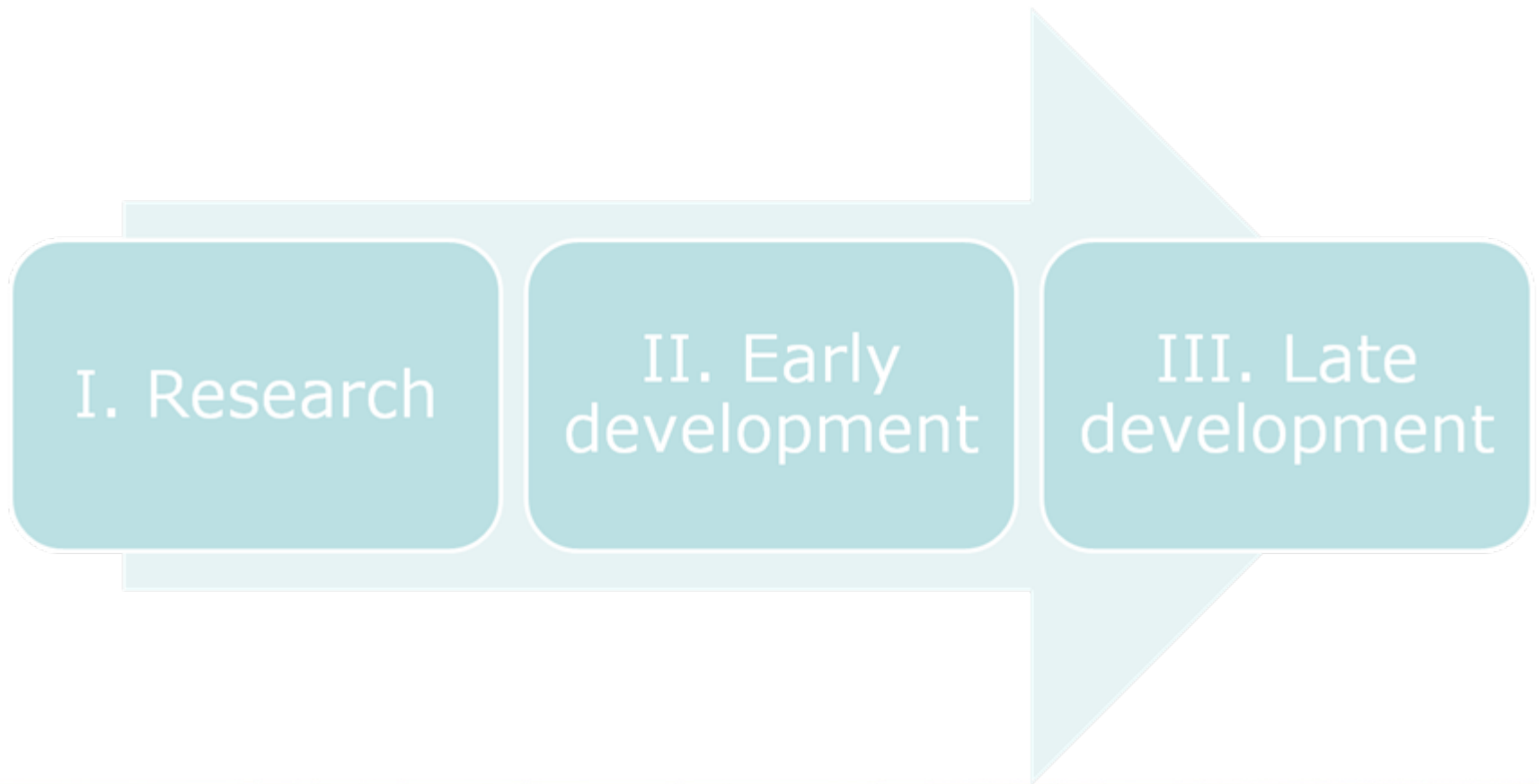
Pluralistic: Individual risk estimates looking at risk, costs and benefits, including through open mechanisms to include public views
NRC, EPA

Consensual: Individual risk estimates looking at risk, costs and benefits (in theory). Weak deliberation mechanisms.
UK ToR

Paradigm shift in the pharmaceutical area?

1960s Thalidomide: towards one of the most formalised regulatory process

Drug Development



Post-marketing

Surveillance and pharmacovigilance

Does the current model work?

- ➡ Early 2000s Cardiovascular risks : Vioxx recall and Cox II inhibitors
- ➡ Late 2000s: mental health
- ➡ Vaccines: MMR in the UK, Hepatitis B in France (Bouder 2006), Gardasil in Spain (Bouder 2010)

Increasing discontent

- ➡ Since the 1990s more major drugs withdrawals than before (Avorn 2004)
- ➡ Risk assessment criticised

Too lax? Abraham, 1995; Abraham and Lewis, 1998 and 2000; Abraham and Reed, 2001; Angel, 2004; Avorn, 2004, 2006; House of Commons, 2005; IOM, 2006.

Too precautionary? Vogel 2002, Sunstein 2003

Hypothesis

Hazard-based:

Quantifying signals rather than risks

“Bipartite” rather than “corporatist”
(Abraham 2002) : weak third parties

Questions

What would protect patients better, more “hazard containment” or more “risk management” ?

Does the bipartite system deliver a higher or lower level of protection?

ToR as heuristic

- ➡ Includes probabilistic assessment
- ➡ Integrates individual and societal views
- ➡ Flexible negotiation process between risks and benefits
- ➡ Consensual/corporatist: Fairman 2007 points out that ToR requires 'tripartite' models of regulation (see Schmitter 1974)

Case studies

MMR/Hepatitis B – Bouder 2006

Cox 2 inhibitors– Lofstedt 2007

Cardiovascular (QT)– Bouder 2007

Genotoxicity– Bouder 2008

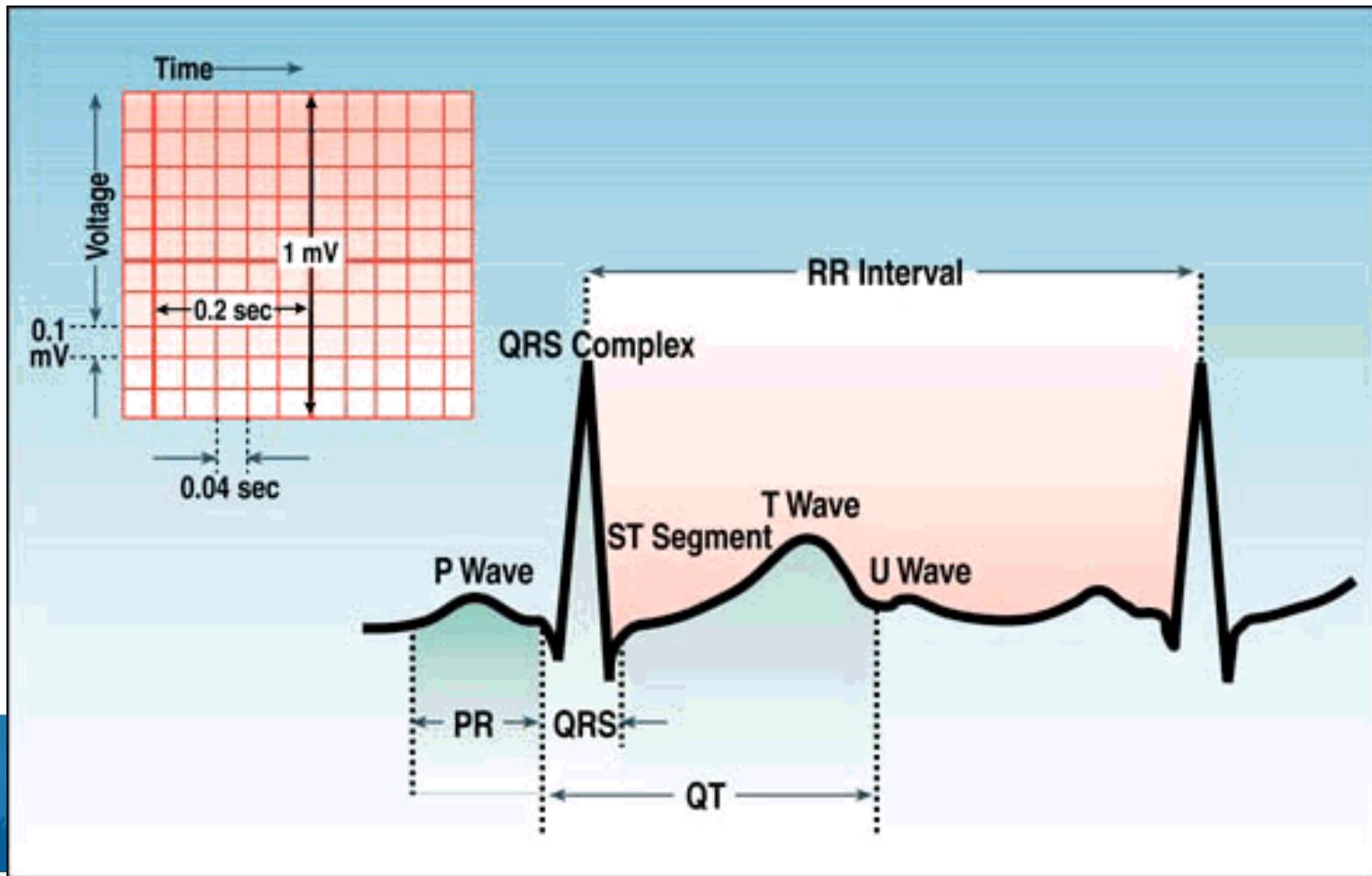
Avandia – Lofstedt 2009

Viracept – Bouder 2010

Gardasil – Bouder 2010

Acomplia- Bouder 2010

QT interval case study



Basic facts about QT prolongation

- ✓ QT prolongation can degenerate into a potentially fatal form of tachyarrhythmia called Torsades de Pointes (TdP).
Dessertenne 1966.
- ✓ QT interval varies naturally (e.g. age and gender variability) *Meyerberg 1999.*
- ✓ A large number of cardiac and noncardiac drugs prolong QT. About 90 noncardiac drugs reported. *Shah 2002.*

Dealing with scientific evidence

“There is no clear correlation between QT prolongation and the risk of death”.

“There is no scientific evidence indicating that a certain QT interval is related to x% increase of death”. *NIH 2004.*

But...

“ QT is the best and only surrogate marker for TdP, especially so because the definition of this arrhythmia requires prolongation of the QT as a preceding event. *Haverkamp and al. 2000; Shah 2002.*

Triggers for action

- 1985. Approval of Terfenadine, a drug prescribed for hay fever and itchy rash. No cardiovascular events. *Botstein, 1993.*
- 1990. Some cases of sudden death observed. First case report (Dec.) Symptomatic TdP occurring with the use of Terfenadine.
- 1991 Similar worries concerning Terodiline (used against incontinence) *Connolly et al. 1991; Stewart et al., 1992*
- FDA calling for more research on subpopulation at risk, announcing warning labels and sending "Dear Doctor" letters

In 1996, similar cases of unexplained death among patients taking Cisapride, meant to cure dysfunctions of the oesophagi. *Wysowski and al. 1996.*

Despite the lack of epidemiological studies (*Darpö 2001*), FDA decided the risk was unacceptable. Terfenadine was withdrawn from the US market in 1998. "Voluntary" withdrawal of Cisapride in 2000 (*WHO annual index*).

The EU : assessment or precaution?

The European regulator (EMA) did not withdraw Terfenadine nor Cisapride

- EMA's convened in 1997 an ad-hoc expert group to "provide reassurance concerning the safe clinical usage of such products"
- Outcome: "Points to consider" document acknowledging potential risks and suggesting general recommendations for future applicants. Human and non-human testing envisaged

From globalisation of concerns to trilateral action

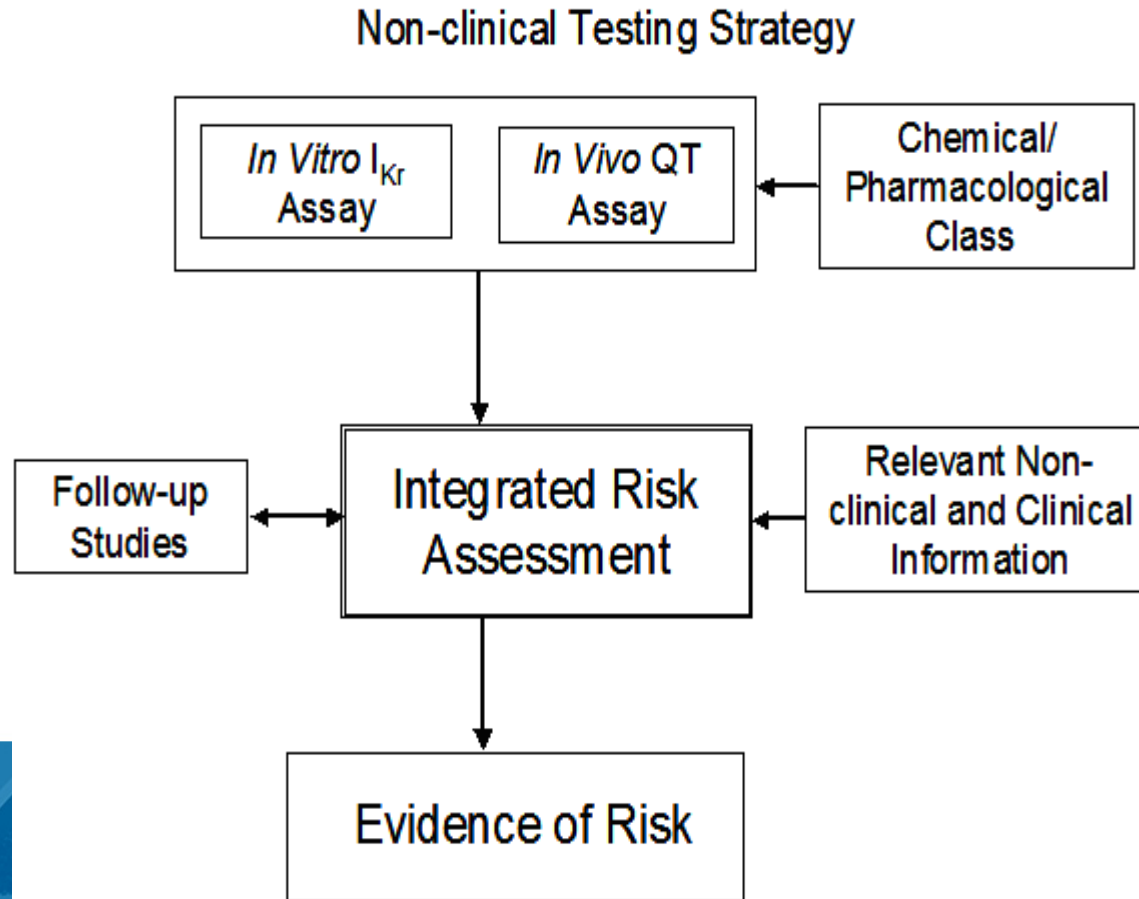
- Consultation Workshop, Washington DC, 01/03 Tripartite (Europe-US-Japan) ICH Expert Working Group (EWG) composed of 6 stakeholders (public + private)
- EWG meetings: Tokyo, Brussels, Osaka, Washington DC (7-10/06/04)
- “Step 2” document signed on 10/06/04 and open for public comments 06-10/04
- Endorsement : “Step 4” final document May 2005
- End of 2005: S7B (non clinical) and E14 (clinical) guidance

Areas of disagreement with major consequences

- ▶ Levels of thresholds
- ▶ Calculation of thresholds
- ▶ Gathering of human (clinical) data

E14 does not rule out the most restrictive options

Risk judgement in principle



How does judgement in practice fit with ToR?

Signal gathering

Weak consensus on science, no acceptability tools, heavy burdens on the Industry (thorough QT/QTc study)

The cost/benefit argument challenged

How much will QT regulation cost? Not clear
Low concerns for stigmatisation effects of drugs that approach the upper limit

QT interval conclusions

- 'Tennis game' more influential than probabilistic estimates on increase of risk resulting from drug intake
- Little attention paid to risk perception and societal acceptance
- Confirmation of consensual model of regulation
- Confirmation of globalisation of regulation

Case 2: Impurities in pharmaceutical products

Unavoidable small risk?

Drug manufacturing generates impurities,
incl. metals.

Question:

Is it genotoxic, i.e. does it cause damage
to DNA leading to tumours?

1.5 $\mu\text{g}/\text{day}$ intake of a genotoxic materials
could give rise to:

Between 1 in a hundred thousand and 1 in a
million risk of cancer (daily lifetime
exposure)

How are these numbers built?

Toxicological assessment– believed to be conservative:

In vitro, in vivo

“Data derived mainly from extrapolation from lifetime exposure in rodents” (FDA)

Hard to prove in the ‘real world’

The regulatory story

International *quality* guidelines on Impurities found in pharmaceutical and food

ICH Q3 guidelines (2002)

“Regulators and Industry were satisfied with the guidelines. Except for one thing: how to deal with ‘unusual toxicity’ In particular how to deal with ‘genotoxicity’, which is considered ‘unusual’?” (Bfarm)

e.g. from metals as well?

Trigger

Disagreements between the regulator and the Industry in a couple of drugs, one among others anti-infectives to cure life-threatening conditions .

EMA felt compelled to “regulate” and prepare guidelines as it is by statute no longer allowed to simply raise issues as “points to consider”

Safety working party (SWP) of Committee for Medicinal Products for Human Use (CHMP) in charge

Consultation procedure, including industry submissions – bipartite dialogue

Towards European guidelines

DIA/ European meeting. London Oct. 2003
PhRMA White paper feb. 2005 (Müller et al. 2006)

TTC concept

'Virtually safe doses':

1.5 $\mu\text{g}/\text{day}$ for lifetime intake

120 $\mu\text{g}/\text{day}$ for ≤ 1 month

1.5 $\mu\text{g}/\text{day}$ seems agreed in regulatory circles as
TTC value . Duration of exposure not
consensual, is TTC value the same for shorter
exposure or when higher benefits expected?

Guidelines EMEA/CHMP/15404/2007

- ➡ Scope unclear. Only for new active substances?
- ➡ What significance does the TTC threshold carry in the eyes of the regulator?
- ➡ Decision tree introduces 'ALARP': process or a value? Should 'ALARP' stop at TTC value?
- ➡ Implementation already controversial (e.g. tough stance from AFSSAPS in France even before implementation date)

Lessons

Case by case assessment (shorter treatment etc.). But...

Regulators: “impurities are a pollution bringing no benefit. It should be avoided as much as possible”.

- ➡ Conservative TTC threshold: lower tolerability than for impurities in food
- ➡ ALARP or “AMAP” (*As Much As Possible*)?
- ➡ Constant reduction: what about the cost of delays and elimination?

Summary of impurity case

Probabilistic estimates on risk of cancer outdated, “imported” (food regulation) and interpreted in a precautionary way

No attention paid to risk perception and societal acceptance

Confirmation of consensual model of regulation

Conclusions on introducing a risk-based paradigm

The globalisation and consensual model of regulation may allow a “three-legged corporatist” model like ToR.

Test: capacity to strengthen third parties

Need for linking decisions to credible risk probabilities

Need for understanding societal risk

Answering the question

A risk-based approach is possible *BUT* would require efforts and investment.

Does the pharmaceutical sector feel the urge to move beyond signal detection and “bipartite” models?