New GMOs - Scientific knowledge, what do we know ?
Regulation and risk assessment, where do we come from ?
26 Oct 2023 EU Parliament Brussels

The role of the precautionary principle in dealing with new and emerging gene technologies

Prof Dr. Jeroen P. van der Sluijs
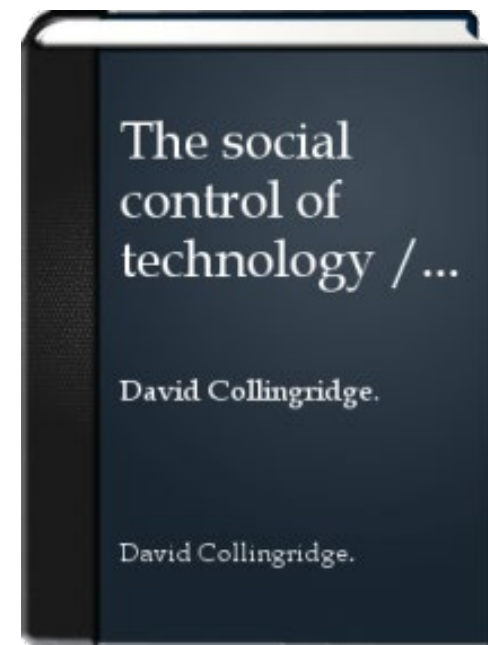
@Jeroen_vdSluijs

Collingridge Dilemma

"The social consequences of a technology **cannot be predicted** early in the life of the technology.

By the time undesirable consequences are discovered, however, the technology is so much part of the whole economics and social fabric that its control is extremely difficult.
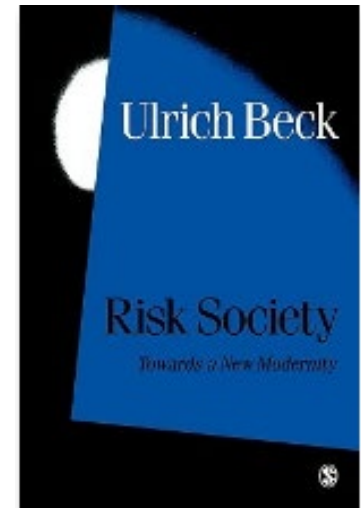
This is the *dilemma of control.*"

1980

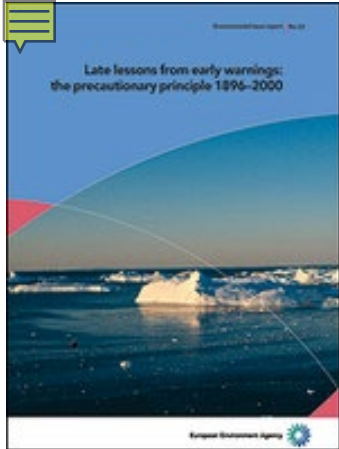# Organised Irresponsibility

Ulrich Beck, 1986, Risk Society

1986/1992

RECIPES **Sector-specific brief on the Precautionary Principle:**
Gene Technology in Agriculture

- **Strengthen** application of the **PP** (**compass** & **safeguard**)
- **Cartagena Protocol**: case by case risk assessment **mandatory**
- **Upstream** societal **engagement** also **pre**-(research)**agenda setting**
- **Promote the PP in research**
- **Post-authorisation review** – mechanisms for **revocation**
- Allow for **alternative** **research pathways** (research funding)
- Promote **safety-by-design**, take environment & health into account
- **Explicit & transparent problem scoping**
- **Broaden the risk assessment** / Pluralise expertise involved
- **Address conflicts** that concern values, knowledge and interests in decision making about applying the PP
- Anticipate **transboundary harm**
- Make **power asymmetry** explicit in participatory processes

EEA: Late Lessons from Early Warnings 2001 & 2013

01. **Acknowledge and respond to ignorance.**

02. *Provide adequate **long-term monitoring (early warnings)***

03. Identify and **reduce blind spots** knowledge gaps

04. *Reduce interdisciplinary obstacles to learning*

05. **Ensure real-world conditions** in regulatory appraisal

06. ***Scrutinize the claimed justifications and benefits***

07. **Promote alternatives** for meeting same needs

08. *Ensure **use of 'lay' and local knowledge***

09. **Take full account** of **values of different social groups**.

10. ***Maintain regulatory independence***

11. **Reduce institutional obstacles** to learning & action.

12. *Avoid 'paralysis by analysis*

CRISPR metaphors are misguiding

- "Editing the genetic code"

- "Cas9 scissor protein"

- "CRISPR may soon become as reliable as a text editor"

- "allows precise and efficient development of improved plant varieties"

Is it responsible to use such metaphors?

- "Describing genetic systems as though they are electrical ones (whereby genes are switched on and off) works to a degree, but unlike switching on a light…the activation of a particular gene depends on numerous parameters." (Pauwels, 2013)

- "**The currently skewed metaphors can silence the negative aspects of technology**." (Blasimme et al. 2015)

- "Metaphors should not go beyond what is scientifically established at the time" (Nordgren 2001)
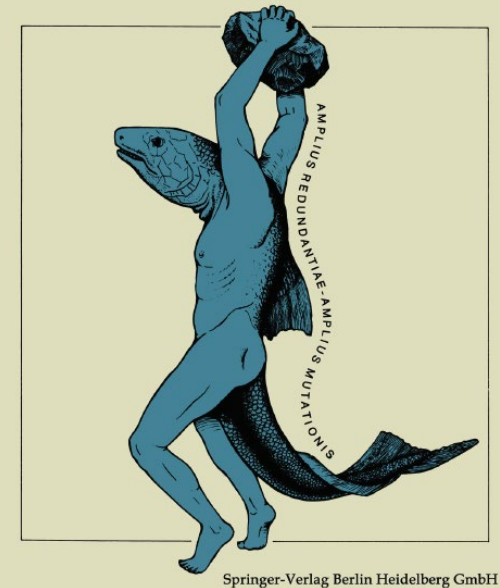
"These enzymes will cut in places other than the places you have designed them to cut, and that has lots of implications"

*"**what other damage might you have done at other sites in the genome**"*

James Haber, Brandeis University in Waltham, Massachusetts.

Source: Safety and Security Risks of CRISPR/Cas9
https://doi.org/10.1007/978-3-319-64731-9_13

S.Ohno Evolution by Gene Duplication

AMPLIUS REDUNDANTIAE AMPLIUS MUTATIONIS

Springer-Verlag Berlin Heidelberg GmbH

Gene duplication:
- redundancy in DNA
- various functions, **largely unknown**

- This insight is relevant for understanding NGT risks

Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements

Michael Kosicki, Kärt Tomberg & Allan Bradley

CRISPR–Cas9 is poised to become the gene editing tool of choice in clinical contexts. Thus far, exploration of Cas9-induced genetic alterations has been limited to the immediate vicinity of the target site and distal off-target sequences, leading to the conclusion that CRISPR–Cas9 was reasonably specific. Here we report significant on-target mutagenesis, such as large deletions and more complex genomic rearrangements at the targeted sites in mouse embryonic stem cells, mouse hematopoietic progenitors and a human differentiated cell line. Using long-read sequencing and long-range PCR genotyping, we show that DNA breaks introduced by single-guide RNA/Cas9 frequently resolved into deletions extending over many kilobases. Furthermore, lesions distal to the cut site and crossover events were identified. The observed genomic damage in mitotically active cells caused by CRISPR–Cas9 editing may have pathogenic consequences.

nature biotechnology

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Huge knowledge gap DNA Damage Repair in plants:

"**knowledge about**, and research into, the **DDR process in plant genomes is still in its early stages**"

"the number of articles published each year about DDR systems in plants **only** represents **10%** of the total number of articles about DDR."

DNA Damage Repair System in Plants: A Worldwide Research Update
https://doi.org/10.3390%2Fgenes8110299

Known Knowns

- Confirmed results
- Reproduced studies
- Protocolls
- guidelines

Unknown Knowns

- Results we do not have access to
- „grey literature"
- Data requests

Known Unknowns

- Questions following from research
- Further research
- Research gaps

Unknown Unknowns

- We don't know what we don't know
- Irregularities
- unexpected phenomena

Why **more** precaution for NGT?

- Lack of a "**history of safe use**" (Court of Justice)
- Hazards involved are not just risks but involve uncertainties and ignorance (**unknown unknowns**)
- Damage control, if things go wrong, may completely fail, **comprehensive risk assessments" insufficient to guarantee damage control**
- **Assumption of precision and predictability is known to be invalid**
- Can also be used to make multiple deletions or **cross-species insertions, also in category 1!**
- **Inconsistent** to say at the same time: "*same as conventional breeding*" AND *patentable*

Responsible Research and Innovation (RRI)

Table 1

Lines of questioning on responsible innovation.

Product questions

How will the risks and benefits be distributed?
What other impacts can we anticipate?

How might these change in the future?
What don't we know about?
What might we never know about?

Process questions

How should standards be drawn up and applied?
How should risks and benefits be defined and measured?

Who is in control?
Who is taking part?
Who will take responsibility if things go wrong?
How do we know we are right?

Purpose questions

Why are researchers doing it?
Are these motivations transparent and in the public interest?
Who will benefit?
What are they going to gain?
What are the alternatives?

Stilgoe, Owen & Macnaghten, 2013
http://dx.doi.org/10.1016/j.respol.2013.05.008

Compare to Mario Giampietro 22 Sept PNS5DJ presentation here:

The three MAGIC checks on the quality of the narratives used in a policy domain

JUSTIFICATION NARRATIVES WHY are we doing it?	NORMATIVE NARRATIVES WHAT should we do?	EXPLANATION NARRATIVES HOW do we know it?
#1 - Checking the quality of pre-analytical choices: whose concerns?	#2 - Checking the quality of the proposed policies	#3 - Checking the quality of the process of epistemic boxing
* What are the problems to be solved? * What is the priority that has been given to existing concerns?	* Are they feasible? (compatible with external limits) * Are they viable? (compatible with internal limits)	* What information is missing for a better informed decision? * Can we organize the available information into a more robust decision support tool?
* Whose concerns are acknowledged? * Whose concerns are ignored? * Whose problems will be solved first?	* What are the gains and losses across the various indicators of performance (impact matrix) * Who are the winners and losers among the various social actors (equity matrix)	* Can we implement procedures based on participatory processes allowing a more robust process of co-production of knowledge and a fairer deliberation?
* Who has chosen the given story-telling? * How has it been chosen? * Why has it been chosen?	* How do the policies look when considering an evolutionary view?	