Current shortcommings and uncertainties in the risk assessment of GMOs

Legal requirements

Assessing long- term effects	EC Reg. 178/2002 Article 14
Assessing effects on subsequent generations	EC Reg. 178/2002 Article 14
Assessing cumulative toxic effects	EC Reg. 178/2002 Article 14
Description of uncertainties e.g.assumptions made in the risk assessment, and of the known limits of mitigation measures	EC Decision 2002/623

None of these legal requirements are addressed in the risk assessment of EFSA

- Maize NK 603 (Monsanto) EFSA Journal 2003, 9:1-14
- Rape GT 73 (Monsanto) EFSA Journal 2004, 29:1-19
- Maize Mon 863 (Monsanto) EFSA Journal 2004, 50:1-25

EFSA methods

Method	Comment
• Comparative chemical analyses of protein, amino acid content, ash content etc.	• No scientific basis of how to translate results into human toxicity assessment
• Sequence Analyses	• Almost identical sequences can show differences in function monkey/human DNA
• 28 days study with the protein	• Short term toxic studies are useless, and must be avoided from terms of animal rights
• Comparative 90 day study with rats (NK603 and Mon863 but not in GT73)	• Subchronic study, not able to extrapolate to chronic effects (cancergogenicity, immuno toxicity)

EFSA vocabulary on observed statistically significant differences between GM and control

phrases	source
1. **Altered level of linolenic acid is considered as not biologically significant, greater differences between GT73 and Westar but without statistical analyses**	**Rape GT 73** (Monsanto) EFSA Journal 2004, 29:1-19
1. **no consistent differences**, 2. **no biological significance**, 3. **artifactual differences** of corbuscular haemoglobin values (90 days feeding study) 4. **No conclusive** differences of chemical constituents	**Maize NK 603** (Monsanto) EFSA Journal 2003, 9:1-14

EFSA vocabulary on observed statistically significant differences between GM and control

phrases	source
1. Minor differences in some plant constituents are **not considered to be biologically significant**	Mon 863 (Monsanto) EFSA Journal 2004, 50:1-25
2. slight increase of lymphocyte counts, slight decrease in kidney weights are **not considered to be meaningful**	
3. Lower incidence of mineralized kidney tubules **are not considered as concern.**	
4. Reported findings are **considered as incidential and not treatment related**	

EFSA

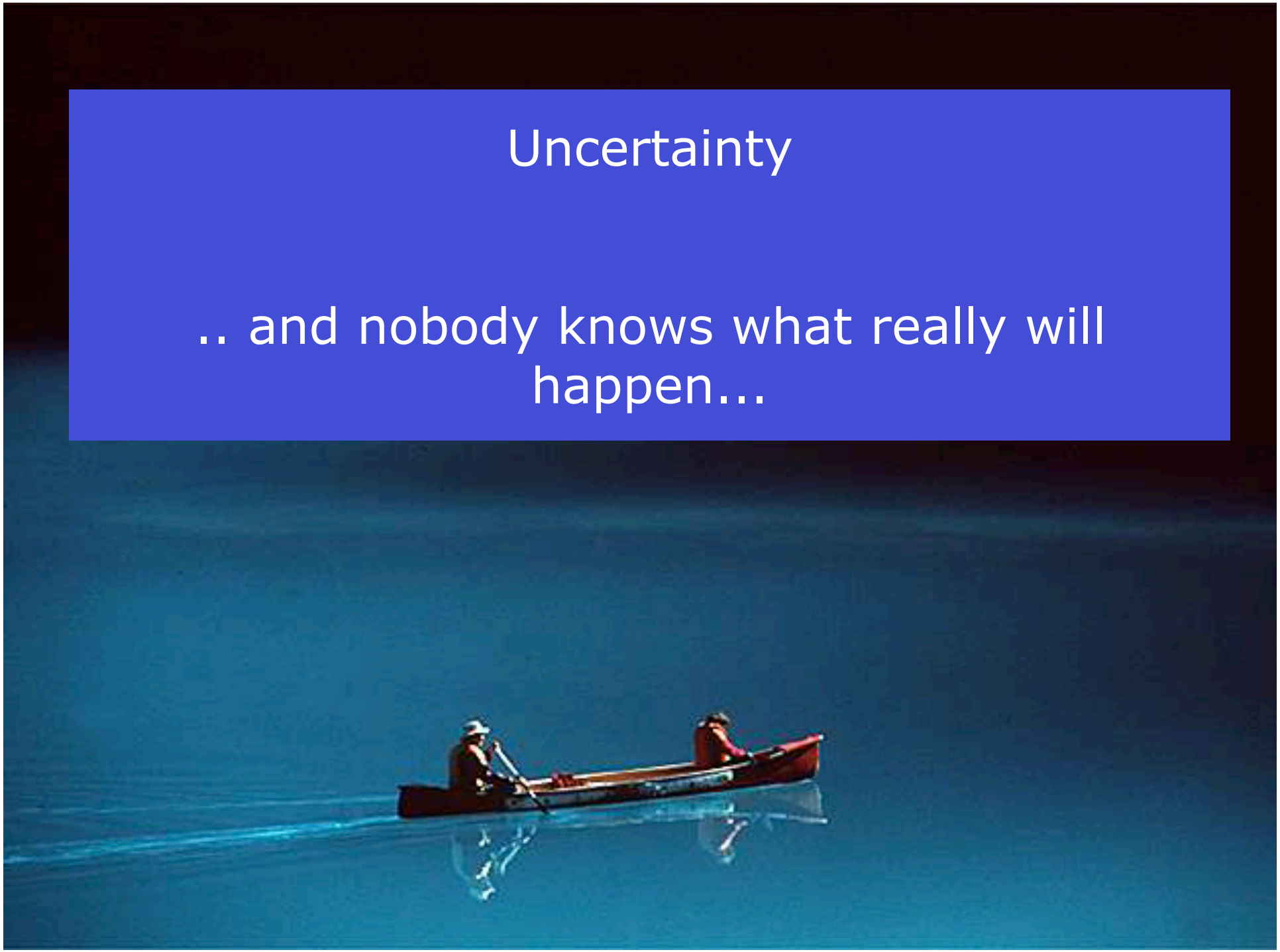
- Up to now **ALL** observed differences between GM and Non-GM variety **had been tolerated** by EFSA.
- No argumentation to what extent observed differences are generally tolerated is provided.
- The question remains why these parameters are tested when statistically significant differences are not of biological relevance.

Wording of Monsanto and EFSA e.g. NK603

Data interpretation of	Judgement by **Monsanto**	Judgement by **EFSA**
observed differences found in the subchronic 90 days toxicity study	**absence of biologically relevant differences**	**"The applicant concludes that these findings are of no biological significance. The panel accepts this as a reasonable interpretation of the data."**
safety claims of CP4 EPSPS-Protein	the **long history** of safe consumption of similar proteins	humans have a **long history** of dietary exposure to the protein. No adverse effects associated with its intake have been identified.

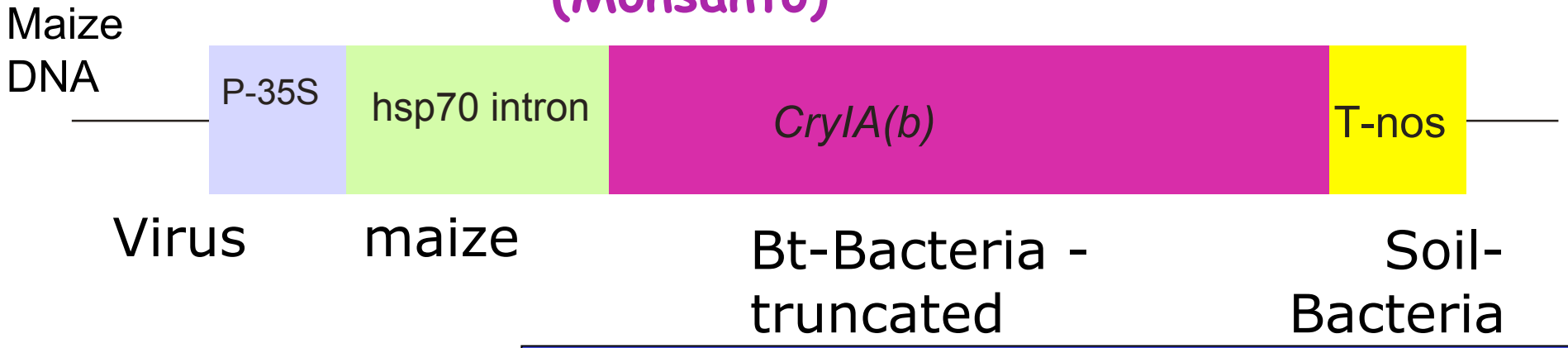
Uncertainty

.. and nobody knows what really will happen...



synthetic gene new for humans

Mon810 maize- *YieldGard™* (Monsanto)



Synthetic genes are man made genes and do not exist in any natural living species on the planet

synthetic genes cause unintended recombinations

CHARACTERISATION OF COMMERCIAL GMO INSERTS: A SOURCE OF USEFUL MATERIAL TO STUDY GENOME FLUIDITY.

INRA

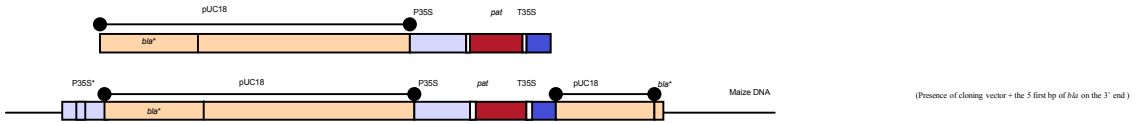
T25 maize - *Libertylink*™ (Bayer)

Tolerance to herbicide glufosinate, Peg-mediated transformation

Construct content : truncated *bla* gene (*bla**), pUC cloning vector (pUC), synthetic *pat* gene (*pat*), CaMV 35S promotor and terminator (P35S, T35S).

Sequence expected (public data)

Sequence observed



(Presence of cloning vector + the 5 first bp of *bla* on the 3' end)

DNA rearrangement: presence of a second truncated and rearranged P35S on the 5' end.

Insertion site: the 5' and 3' ends of the insert show homologies with Huck retrotransposons.

(Collonnier et al. (2003) Eur. Food Res. Tech. (submitted))

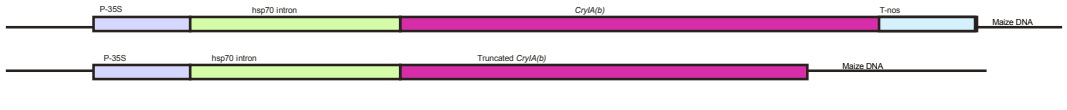
Mon810 maize- *YieldGard*™ (Monsanto)

Resistance to lepidopteran insects (corn borer)

Construct content : CaMV 35S promotor (P35S), *CryIA(b)* toxin synthetic gene (*CryIA(b)*), nos terminator (T-nos).

Sequence expected

Sequence observed



DNA rearrangement: deletion of T-nos in the insert (but Tnos detected in the genome) and deletion of a part of *CryIA(b)*.

(Hernandez et al. (2003) Transgenic Res. 12: 179-189; Holck et al. (2002) Eur. Food Res. Tech. 214: 449-453)

Insertion site: the 5' end of the insert shows homology with LTR sequences of the *Z. mays* alpha Zein gene cluster. No homology between LTR sequences and the 3' end: rearrangement of the integration site.

Tolerance to herbicide glyphosate (Roundup Ready ™), Bombardment
Construct content : CaMV 35S promotor (P35S), N-terminal chloroplast transit peptide (CTP4), modified *epsps* gene (CP4EPSPS), nos terminator (T-nos).

Sequence expected (public data)

Sequence observed

➡ *DNA rearrangement*: on the 3'end of the insert, presence of a 245bp sequence homologous to CP4 EPSPS and a 534 bp unknown sequence.

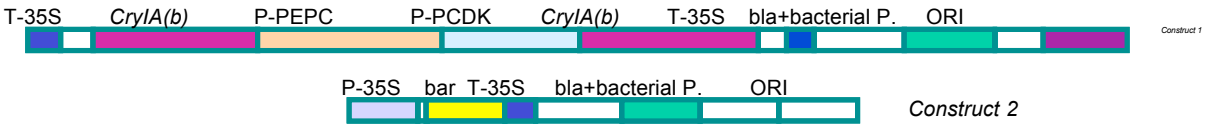
Insertion site: the two junction fragments share no homology; some DNA rearrangements or a large target site deletion on the 5' end of the insert.

(Windels et al. (2001) Eur Food Res Technol 213, 107-112)

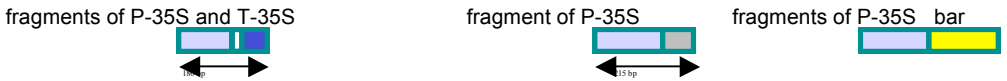
Bt176 maize (Syngenta)

Tolerance to herbicide glufosinate, male sterility, insect resistance – Bombardment.
Construct content : CryIA(b) toxin synthesis gene (*CryIA(b)*), bialaphos resistance gene (*bar*), ampicillin resistance gene (*bla*) + bacterial promoter, PEPC promotor (P-PEPC), PCDK promotor (P-PCDK), CaMV 35S promotor and terminator (P35S, T35S), plasmid replication origin (ORI).

Sequence expected (public data)



Sequences observed when looking for the *bar* cassette of Construct 2



➡ *DNA rearrangement*: 3 rearranged fragments detected. The first of 118 bp is homologous to P35S and T35S. The second contains a fragment of P35S and an unknown sequence of 215 bp, the third contains P35S and the *bla* gene (deletion of T35S).

Insertion site: at least 3 integration sites for construct 2.

(unpublished data Unité MDO-INRA, Versailles, France; TEPRAL, Strasbourg, France)

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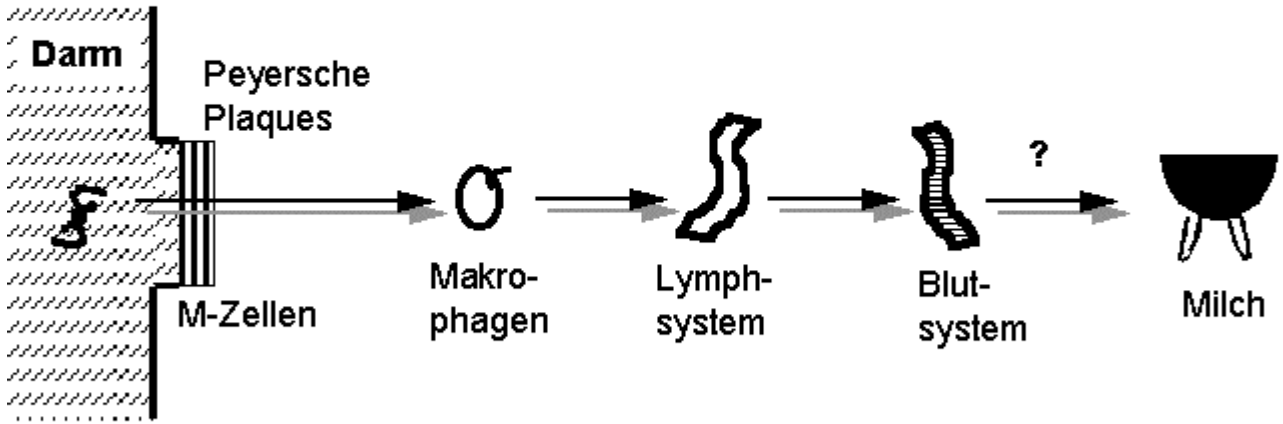
Food-DNA pieces of rubisco gene had been detected in lymphocytes, blood, liver, spleen, kidney, muscles and milk

Potentielle Resorption von Nahrungs-DNA im Darm der Säugetiere



GALT: gut associated lymphoid tissue
(Darm-assoziiertes Lymphsystem)

Food-DNA pieces interact directly with the immune system

- The protective **effects** of probiotics **are mediated by their own DNA** rather than by their metabolites or ability to colonize the colon

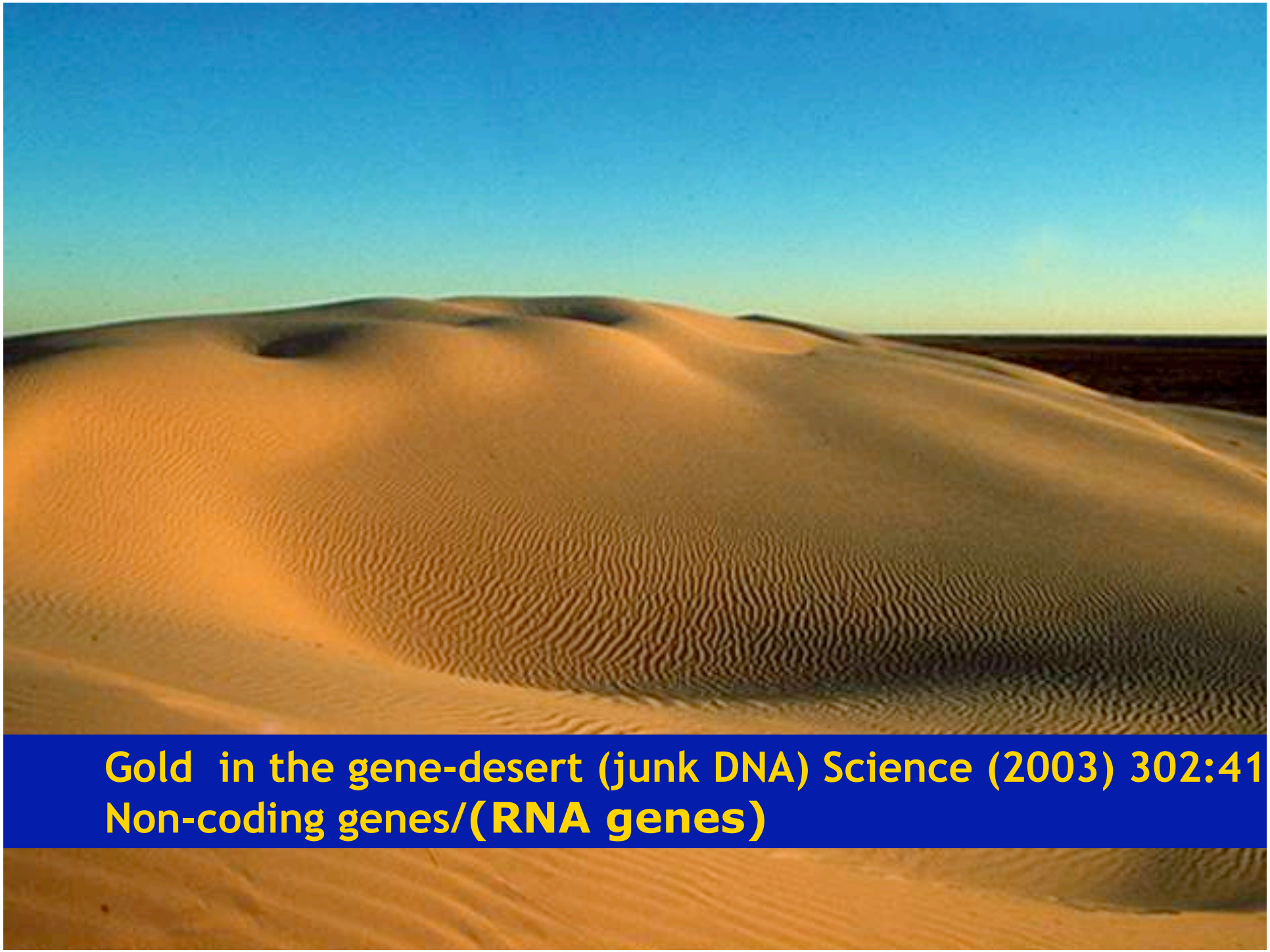
  – Rachmilewitz et al: Gastroenterology 2004 Feb;126(2):520-8

Eric Neumann,
vice president of bioinformatics at Beyond Genomics

” We really have a poor understanding of what a gene actually does and where and when it should do it. You can understand the entire genome and [still] understand less than 1 percent about what is going on in a cell."

DODGE J (2003) *Data glut*. The Boston Globe

http://www.boston.com/


Gold in the gene-desert (junk DNA) Science (2003) 302:41
Non-coding genes/(RNA genes)

Central paradigm (focus on proteins and chemical contents) of risk assessment is tumbling down

If we do not understand what a food-DNA/RNA piece really does
then why would we think that a comprehensive risk assessment of GMO is possible?

"While the duty of preventing damage to the environment is based on a known risk, the notion of precaution is based on lack of certainty."(OECD 2001)

as a consequence of the lack of long-term tests and major uncertainties in the risk assessement of GMOs

the approval of GMOs is not in line with the precautionary principle as outlined in Directive2001/18 and Regulation 1829/2003