THE HUMAN HEALTH EFFECTS OF GM FOOD - GAPS IN RISK ASSESSMENT

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The Basic Tenets of the GM Biotechnology Industry:

- There is no “credible”evidence that GM crops damage the environment
- There is no evidence either that GM food can harm human/animal health
- Accordingly: they are as safe as their “substantially equivalent conventional counterparts” and need no testing

Are these views backed up by data published in peer-reviewed science journals?

- **A recent review concluded that the most pertinent questions on environmental safety of GM crops have not yet been asked let alone studied (Wolfanberger & Phifer, Science, 2000)**
- **A review (Domingo,Science, 2000) found only eight peer-reviewed papers published on the potential health aspects of GM food; this increased to over a dozen by 2003 (Pusztai et al, 2003)**
- **Royal Society Canada report stated that "substantial equivalence" is fatally flawed and regulation based on it exposes Canadians to potential potential health risks of toxic and allergic reactions**

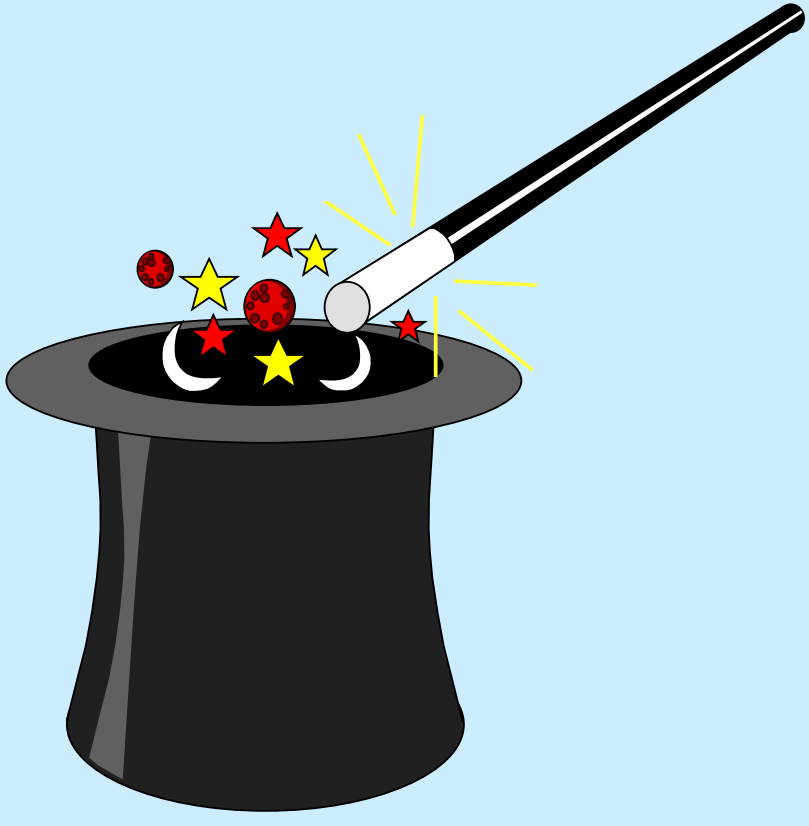
Is it accepted by all that GM crops/foods are safe and no testing is needed?

- **British Medical Association report: (soon to be updated) “Any conclusion upon the safety of introducing GM material into the UK is premature as there is insufficient evidence to inform the decision making process at present”**
- **A majority of British consumers thinks that GM foods are unsafe. As there is no demand for them most UK supermarkets have phased them out**
- **Most consumers in Europe demand, as a minimum, their labelling and rigorous, transparent and independent safety testing**

PRESENT STATE OF GM FOOD SCIENCE

- **MANY OPINIONS BUT FEW DATA!**
- **NO PROPER HUMAN CLINICAL TRIALS AND ONLY A FEW ANIMAL STUDIES HAVE BEEN PUBLISHED TO DATE**
- **THE INDUSTRY'S AND REGULATORS' PREFERRED "SAFETY ASSESSMENT" IS BASED ON THE POORLY DEFINED AND NOT LEGALLY BINDING CONCEPT OF "SUBSTANTIAL EQUIVALENCE"**

How can a plant be novel and ‘the same’?



This is the reason for the use of substantial equivalence:

- **A plant should be novel to be patented (this is why you have to insert the new gene)**
- **The plant should be the same as its parents, so it does not need to be safety tested**

SUBSTANTIAL EQUIVALENCE

- **A BSE-cow is substantially equivalent to a healthy cow**
- **Similarity in composition is no guarantee that GM- is as safe as conventional food**
- **It must be used only as a starting point in risk assessment**
- **It must be established by animal testing that GM food has no harmful, toxic or allergenic effects**

ALIMENTARY TRACT AS THE FIRST TARGET OF GM FOOD RISK ASSESSMENT

A PERSONAL OPINION OF ARPAD PUSZTAI and SUSAN BARDOCZ

THE CASE FOR BIOLOGICAL TESTING

- **To show the presence of new toxins/allergens by chemical methods is, at best, difficult**
- **In contrast, the consumption of unexpected but potent bioagents can have disproportionally large effects on health**
- **Like all foods, gm food will first affect the alimentary tract**

FLAVR-SAVR™ TOMATO

(see Pusztai et al, 2003)

- **A product of ‘antisense’ technology**
- **It has been claimed that the insertion of Flavr-Savr^{tm} and kan^{r} genes caused no changes in gross fruit composition or the contents of potentially toxic glycoalkaloids**

Incidence of Stomach Erosion/Necrosis on GM and Non-GM tomatoes

- **Study 677-004**

- **Non-trg male 0/20**
- **Non-trg female 0/20**
- **Trg male 0/20**
- **Trg female 4/20**
- **re-scored 7/20**

- **Study 677-005 (different tomatoes)**

- **Non-trg male 1/20**
- **Non-trg female 0/19**
- **Trg male 0/20**
- **Trg female 2/15**

EROSION/NECROSIS

- **In humans glandular stomach erosions can lead to life-threatening haemorrhage, particularly in the elderly and patients on non-steroidal anti-inflammatory agents (Pusztai et al, 2003)**
- **Necrosis may also be potentially serious because seven out of forty rats eating GM tomatoes died within two weeks without any explanation**

GM POTATOES EXPRESSING BT-TOXIN (Fares & El-Sayed, 1998)

- **Bt-potatoes and Bt-toxin caused the disruption, multinucleation, swelling, increased degradation of ileal surface cells in rats**
- **These effects demonstrated that Bt-toxin survives in functionally and immunologically active form in the gut**

Cry1Ac binds to surface carbohydrates of the mouse jejunum (Vazquez-Padron et al, 2000a)

- **In vitro indirect immuno-histochemical detection of protoxin binding to fixed jejunal sections**
- **Ligand blotting assay with BBMVs isolated from mouse small intestine showed 6 binding proteins**

Cry1Ac protoxin is a systemic and mucosal immunogen (Vazquez-Padron et al, 1999)

- **Both crystalline and soluble Cry1Ac protoxin given intraperitoneally or intragastrically to mice induced high systemic anti-Cry1Ac antibody response**
- **Only the soluble form produced strong mucosal response intragastrically**
- **High antibody levels were detected in the fluids of both small and large intestines**

Cry1Ac protoxin is a systemic and mucosal adjuvant (Vazquez-Padron et al, 2000b)

- On co-administration with antigens both cholera toxin (CT) and Cry1Ac protoxin increased serum antibody levels to these antigens by both routes of administration
- The enhancement is very strong for serum and intestinal IgG antibody, particularly the large intestine
- Cry1Ac must survive intestinal passage

GM POTATOES EXPRESSING GNA
(Ewen & Pusztai, 1999)

- **Feeding rats GNA-potato-diets induced proliferative growth in their stomach, small- and large intestines and also lymphocyte infiltration that was not shown by controls fed non-GM potatoes with or without GNA supplements**
- **These effects were thus not due to transgene expression but possibly to its genomic insertion**

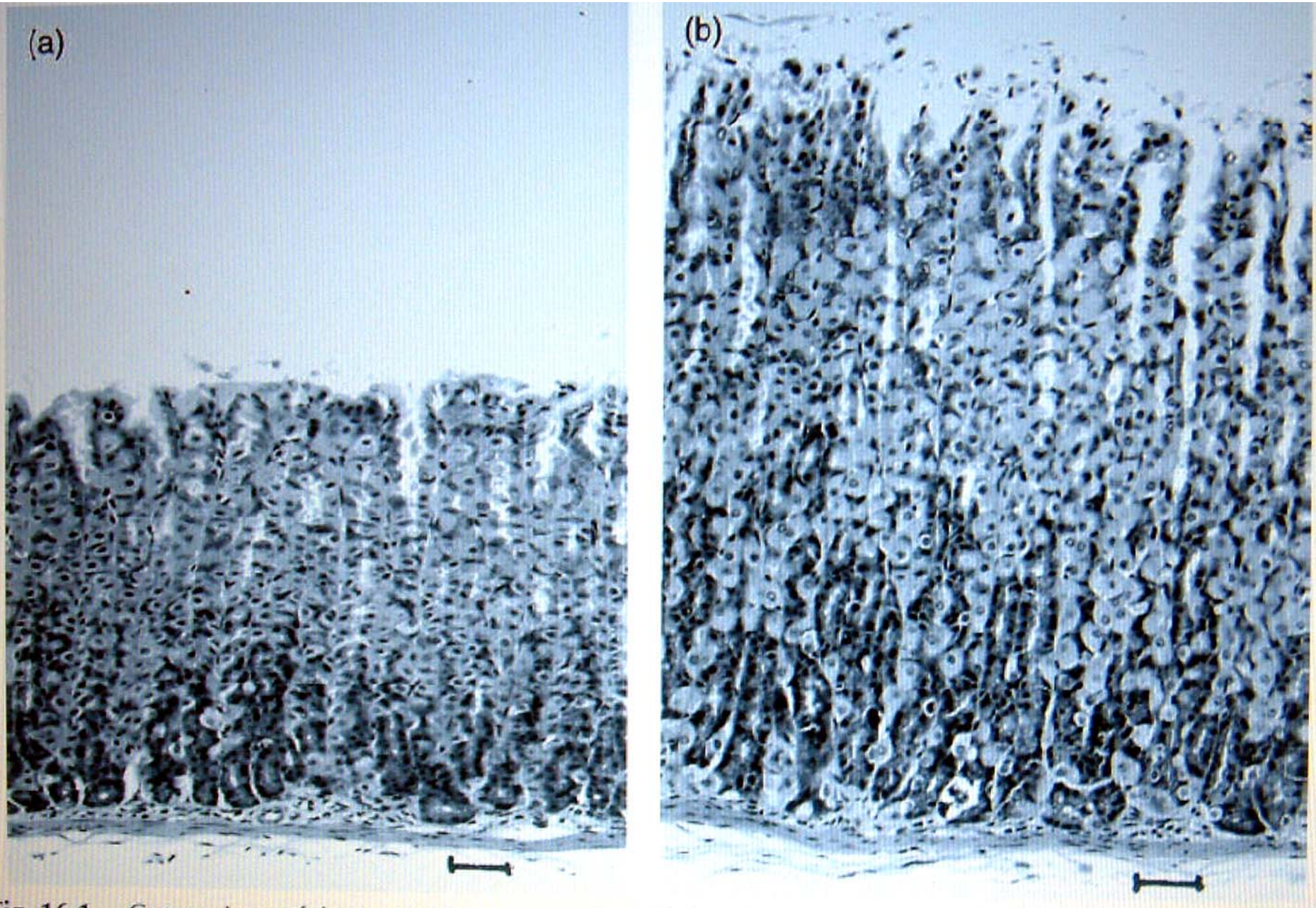
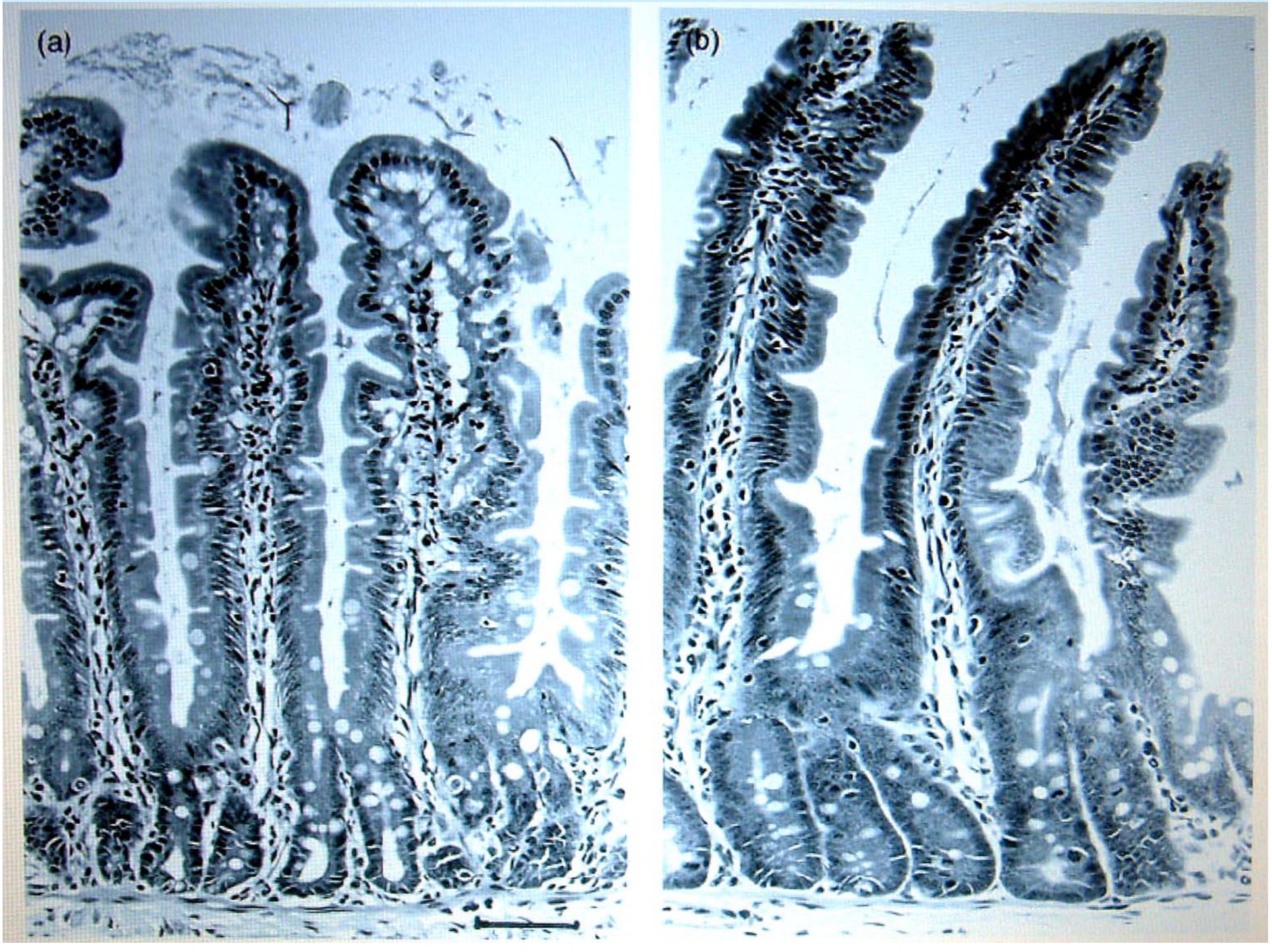


Fig. 16.1. Comparison of the stomach mucosa of rats fed with raw GM potato diet (b) shows marked thickening due to hypertrophy of mucosal cells in comparison with that of rats given the parental line (a) (bar = 100 µm).

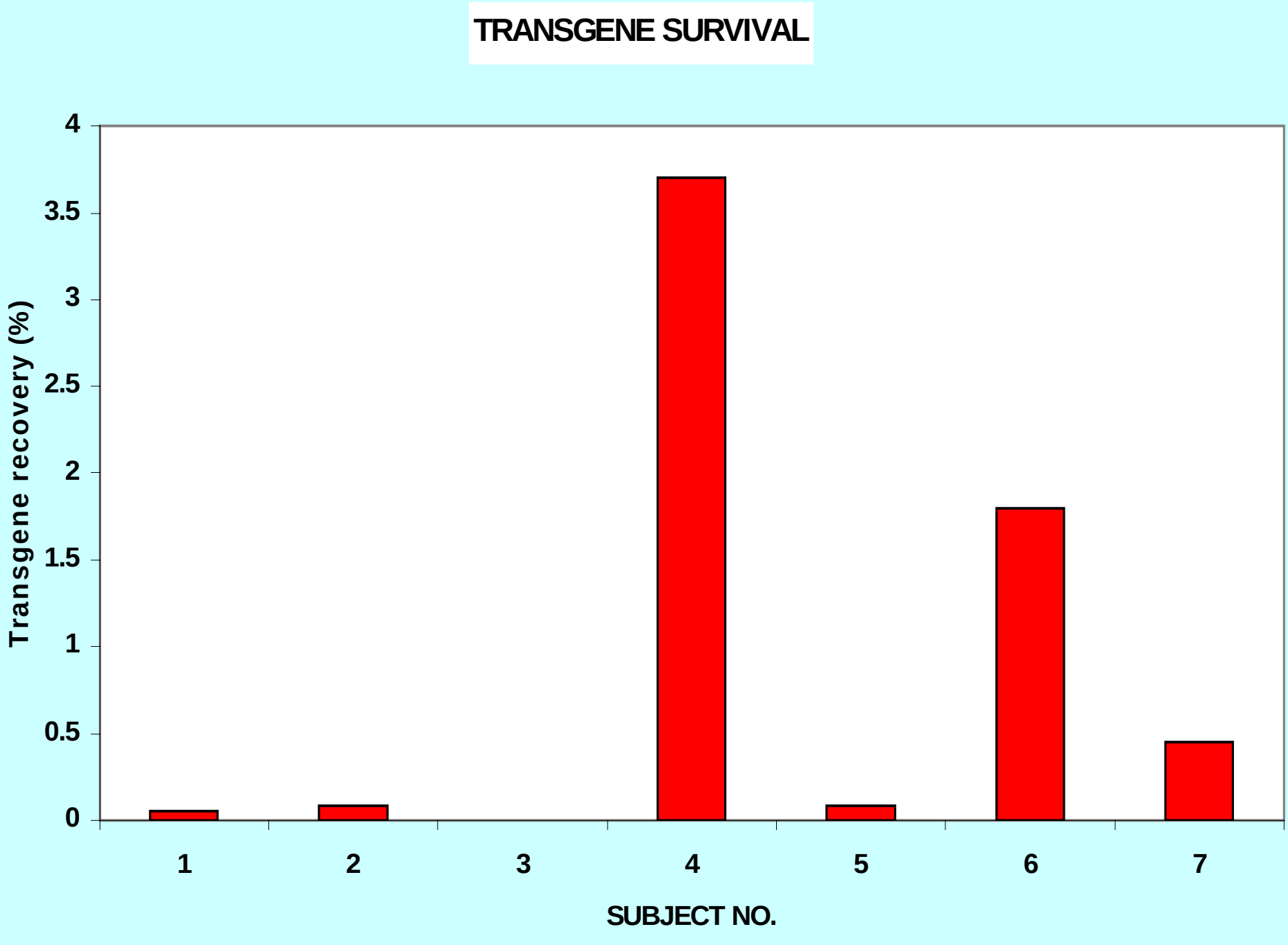

(a)
(b)

THE *IN VITRO* SIMULATION OF PROTEIN DIGESTION IN THE GUT IS BASICALLY FLAWED

- **All lectins (including Cry toxins) resist proteolysis (breakdown) in the gut *in vivo* but are degraded by gut proteases *in vitro* assays**
- ***E. coli* recombinant proteins are quickly degraded both *in vivo* and *in vitro***
- **Transgenic proteins must be isolated from the GM plant and digestibility assays should be done *in vivo*. The use of *E. coli* recombinants in digestibility and toxicity assays is unacceptable**

TRANSGENE SURVIVAL IN HUMANS (1)

- **There has been only one human study with GM food (still unpublished) to see whether the antibiotic resistance marker gene survives in the gut**
- **in six out of the seven ileostomy patients given one meal of GM soya small but measurable amounts of the full length transgene construct was shown to be present**


TRANSGENE SURVIVAL
Transgene recovery (%)
4
3.5
3
2.5
2
1.5
1
0.5
0
1
2
3
4
5
6
7
SUBJECT NO.

TRANSGENE SURVIVAL IN HUMANS (2)

- **The "official" view is that only *small fragments of GM DNA* survived transit while in fact the results showed the presence of *small amounts of full length DNA* in bacteria of the gut pouch**
- **For man all the transgene's important biological effects occur during its gut passage; however its absence from faeces can benefit the environment**

TRANSGENE SURVIVAL IN PIGS (Chowdhury et al, 2003)

- **In a new study fragments of recombinant cry1Ab gene were detected in the GI tract of Bt11 maize-fed pigs**
- **No such fragments were detected in peripheral blood by PCR**
- **More sensitive methods are needed**

CONCLUSIONS ON TRANSGENE EFFECTS AND SURVIVAL IN THE GUT

- **The few studies that have been done demonstrate that the most informative data has come from studies of their biological effects on the alimentary tract**
- **The best way to strengthen the science base of GM food risk assessment is to enlarge this data base by carrying out more work transparently and independent of the industry**

HEPATOCYTE NUCLEAR FUNCTION IS MODIFIED IN GM SOYA-FED MICE (Malatesta et al, 2002)

- **GM soya feeding increases:**
- **the index of metabolic rate in hepatocyte nuclei**
- **the number of nuclear pores indicative of intense molecular trafficking**
- **nucleoplasmic (snRNPs and SC 35) and nucleolar (fibrillarin) splicing factors**
- **mechanism is unknown**

GM DNA SAFETY STUDIES IN THE GASTROINTESTINAL TRACT

- **TASKS:**
- **To trace GM DNA through the intestinal tract**
- **To show whether GM DNA is absorbed into the systemic circulation and body organs**
- **To show whether GM DNA pass into the placenta and foetus?**
- **What are the biological consequences?**

Feeding studies investigating potential risk factors of GM food

Terje Traavik and co-workers

GenOk; University of Tromso

Evaluate potential hazards of GM food consumption

- **Whether parts of the DNA constructs (containing CaMV 35 s) are taken up by the gut and have biological effects?**
- **Is GM DNA from Bt maize taken up by the gut and has biological effects?**
- **Does Bt toxin of GM maize affect the gut, body organs and the immune system?**
- **Can the antibiotic resistance gene transform gut bacteria in vivo?**

GM FOOD SAFETY

- **In the absence of safety studies, the lack of evidence that GM food is unsafe cannot be interpreted as proof that it is safe**
- **The few well-designed studies published to date demonstrate potentially worrisome biological effects of GM food**
- **Regulators have largely ignored these**

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