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Ingo Potrykus

Biofortification, a cost-effective intervention for micro-nutrient deficiency

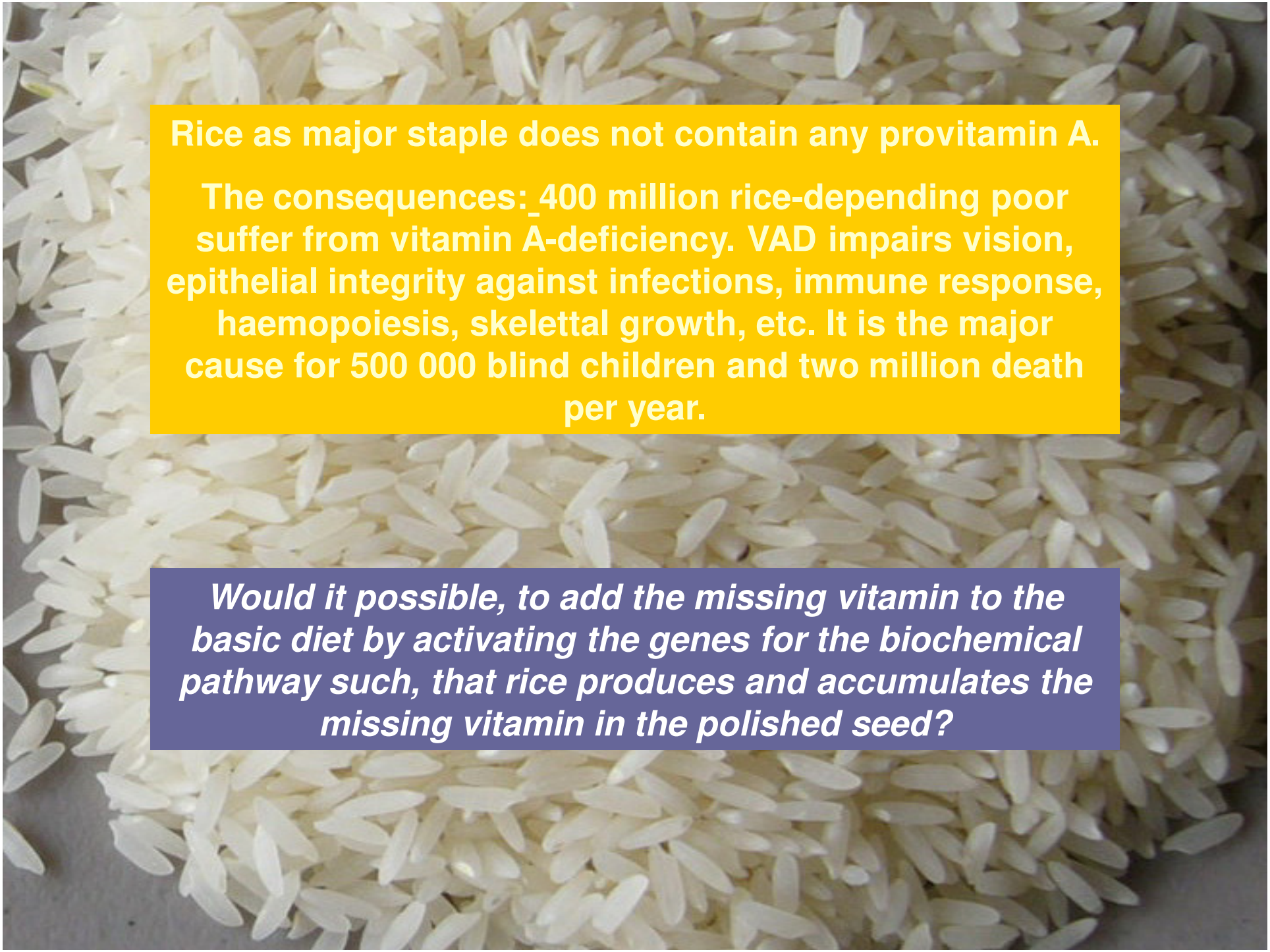
1. Micro-nutrient deficiencies: „Hidden Hunger“:
2. Normal rice causes widespread vitamin A-deficiency.
3. Golden Rice provides the missing vitamin.
4. The expected impact on vitamin A-deficiency is substantial.
5. Golden Rice enables cost-effective, sustained interventions.
6. Golden Rice is the first GMO case of „biofortification“.
7. Iron, zinc, essential amino acids, other vitamin are following.
8. GMO-regulation virtually prevents use of GMO-technology.
9. There is no scientific justification for GMO-regulation.
10. Golden Rice will - with ten years of delay - grow in the farmers fields from 2012 onwards.

1) „Hidden Hunger“: Deficiency in micro nutrients.

24 000 die every day from micro nutrient deficiency. The major cause is poverty-based lack of sufficient nutritious food. The key missing micro nutrients include vitamins, minerals, and essential amino acids. Numerous public and philanthropic institutions are engaged in traditional interventions such as supplementation, fortification, plant breeding, diet diversification, and disease control, to reduce this heavy health burden.

These traditional interventions are effective, but they are not effective enough. Despite enormous investments in traditional interventions such as free distribution of vitamin A capsules for ca. US$ 100 million per year, we are still faced with e.g. 500‘000 blind children caused by vitamin A-deficiency. And there are even larger malnutrition problems for e.g. iron affecting 3 billion, zinc affecting 1.5 billion.

2) Vitamin A-deficiency and rice.

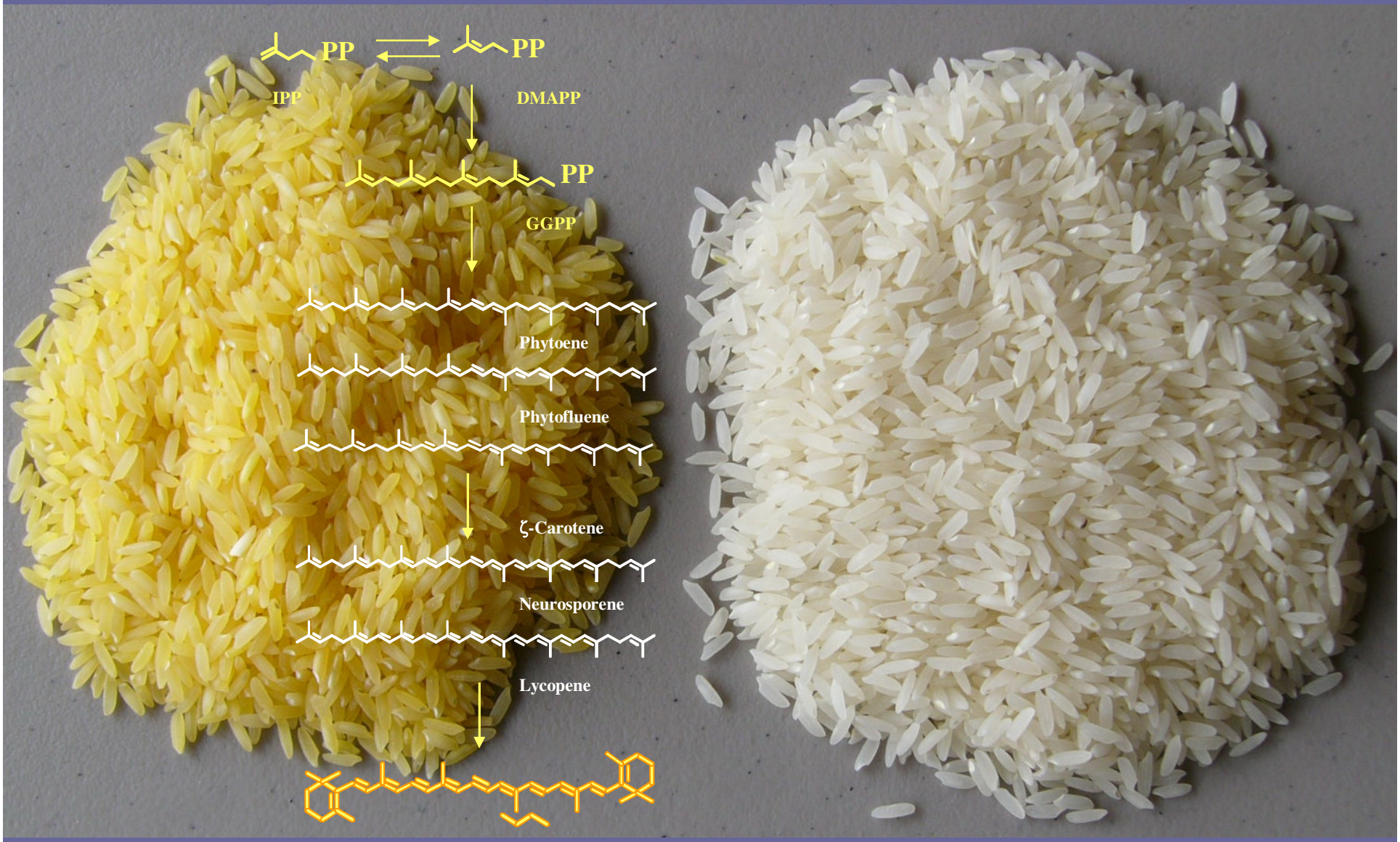


Rice as major staple does not contain any provitamin A.

The consequences:_400 million rice-depending poor suffer from vitamin A-deficiency. VAD impairs vision, epithelial integrity against infections, immune response, haemopoiesis, skelettal growth, etc. It is the major cause for 500 000 blind children and two million death per year.

Would it possible, to add the missing vitamin to the basic diet by activating the genes for the biochemical pathway such, that rice produces and accumulates the missing vitamin in the polished seed?

Yes, it was possible to engineer the biochemical pathway into rice such that provitamin A is synthesized and accumulates in the endosperm.

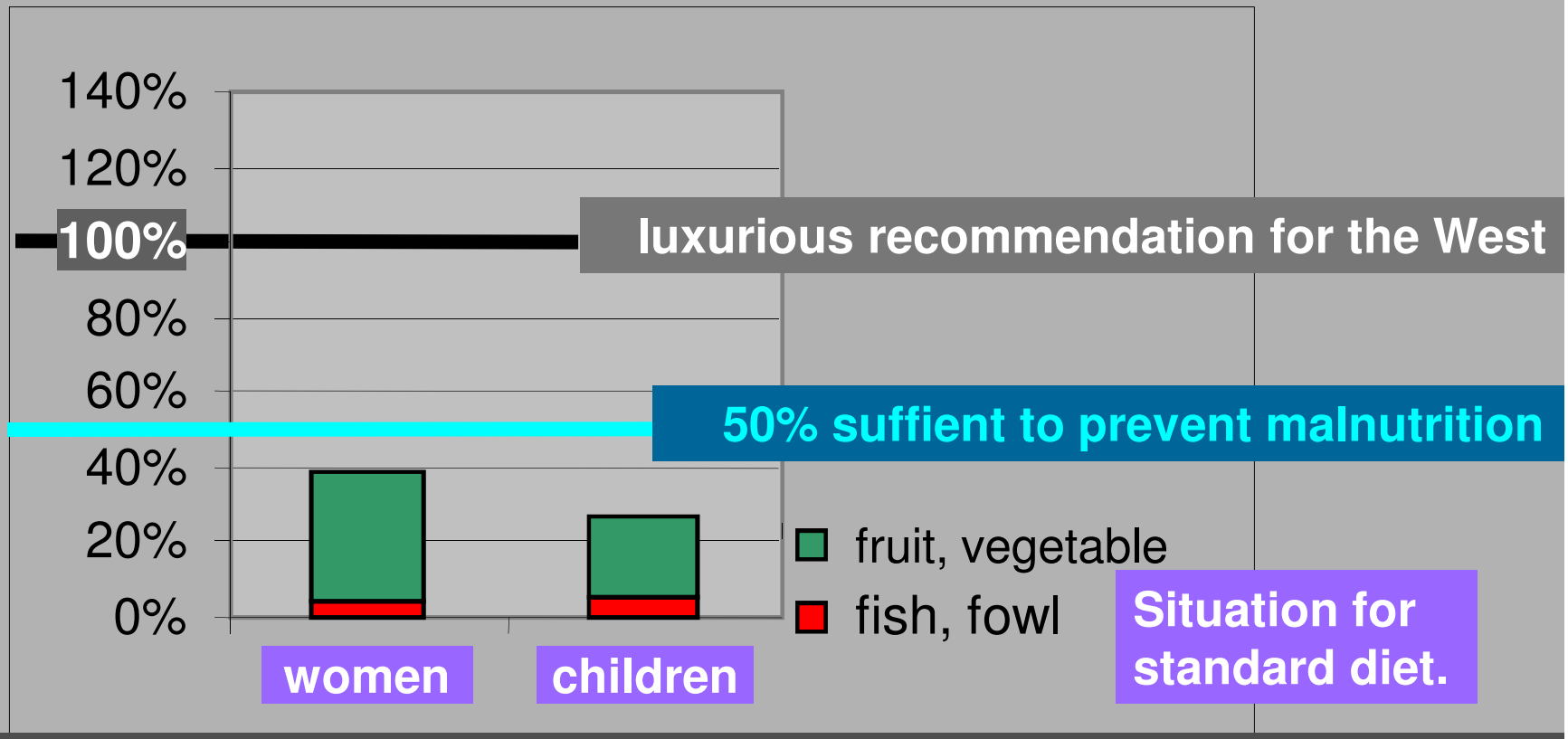


The „golden“ colour is a reflection of the presence of provitamin A. The intensity of the colour is a measure of the concentration.

3) Golden Rice can substantially reduce vitamin A-deficiency.

Why do rice-depending poor societies suffer from vitamin A-malnutrition?

Recommended daily nutrient intake (WHO) in%



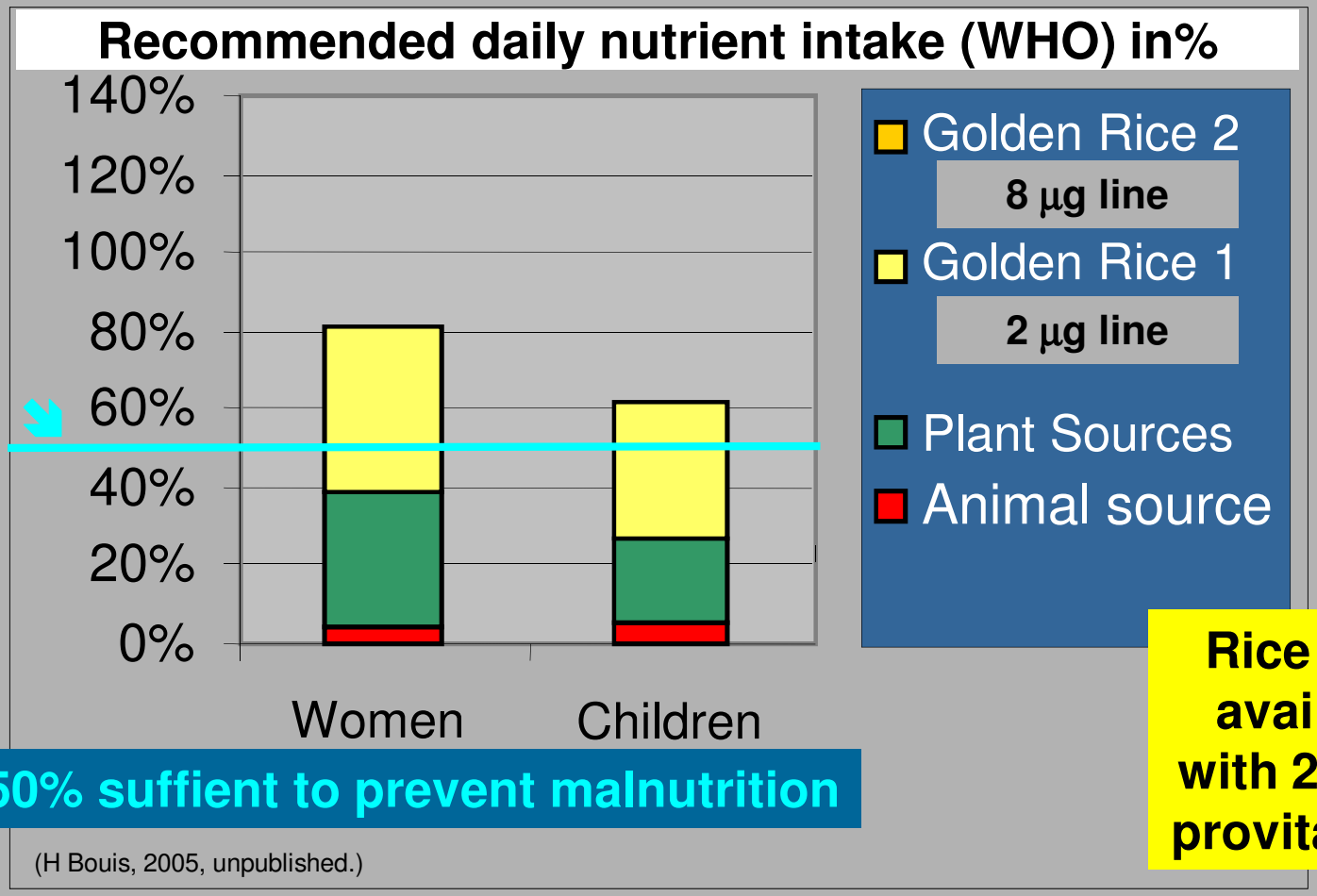
Sources and amount of provitamin A for poor and rice-dependent populations in Southeast Asia. Excample Bangladesh.

Contribution to food energy:

fish, fowl (5%), vegetable, fruit (10%), rice (85%).

How much provitamin A does Golden Rice contain and how much rice have people to eat per day?

Consequences when changing the diet to Golden Rice.



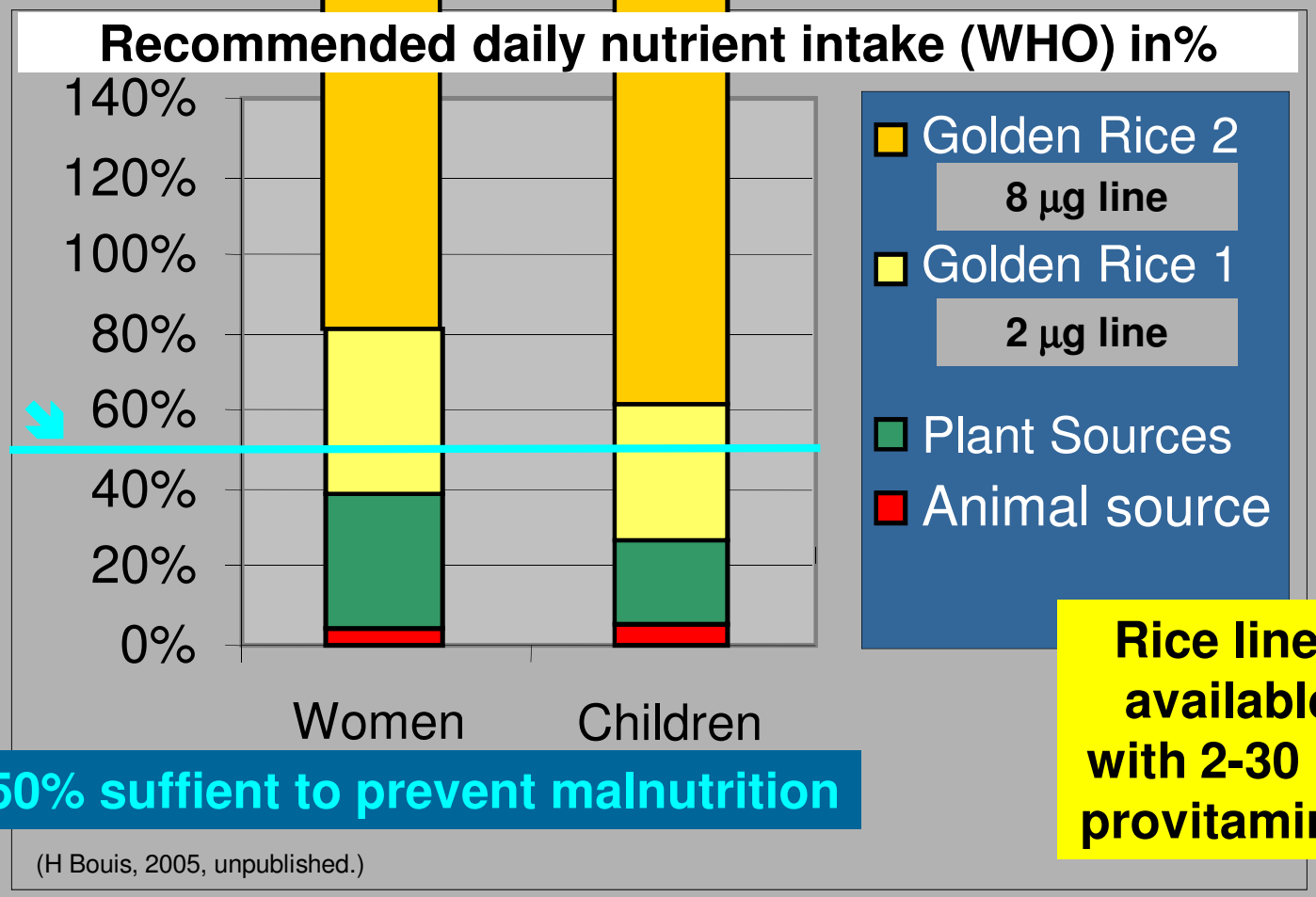
(H Bouis, 2005, unpublished.)

Rice lines available with 2-30 µg provitamin A

Even rice lines with a relatively low provitamin A content would have a substantial health benefit.

How much provitamin A does Golden Rice contain and how much rice have people to eat per day?

Consequences when changing the diet to Golden Rice.



Rice lines available with 2-30 µg provitamin A

50% suffient to prevent malnutrition

(H Bouis, 2005, unpublished.)

Golden Rice would have the potential to cure vitamin A-deficiency as soon as the normal diet would be changed to Golden Rice.

4) What is the expected impact ?

Which impact do we expect e.g. for India?

Potential Impact and Cost-effectiveness of Golden Rice in India.

A.J. Stein, H.P.S.Sachdev, M.Qaim, Nature Biotechnology 24 (10), 2006

Annual burden of vitamin A-deficiency in India:

Lives lost: 71 600

DALYs lost: 2 328 000

Potenial annual impact of Golden Rice:

Lives saved: 5 500 to 39 700

DALYs gained: 204 000 to 1 382 000

Cost-effectiveness per DALY's saved

WHO standard: $ 620 - 1'860

World Bank benchmark: $ 200

Supplementation costs: $ 134 - 599

Golden Rice: $ 3 – 19

5) Golden Rice is a sustained intervention against micro-nutrient malnutrition.

Golden Rice will complement, not replace traditional interventions. It is, however, more cost-effective and therefore more sustainable. The trait is in the seed. Once a variety has been developed, there are no further recurrent costs as with industrial fortification and distribution.

Seeds of agronomically optimized, locally adapted Golden Rice varieties will be provided to the farmer free of charge and limitations, within the framework of a humanitarian project. The farmer will use part of the harvest for the next sowing and does not require any additional input.

6) Golden Rice is the first GMO-case of „biofortification“.

Biofortification describes the concept of using genetics to improve the micronutrient contents of crop plants.

Biofortification is a method of breeding crops to increase their nutritional value. This can be done either through conventional selective breeding, or through genetic engineering. Biofortification differs from ordinary fortification because it focuses on making plant foods more nutritious as the plants are growing, rather than having nutrients added to the foods when they are being processed.This is an improvement on ordinary fortification when it comes to providing nutrients for the rural poor, who rarely have access to commercially fortified foods. As such, biofortification is seen as an upcoming strategy for dealing with deficiencies of micronutrients in the developing world.

This concpet is applied to vitamins, minerals, amino acids, and fatty acids not present in sufficient amounts in major crops serving poor populations in developing countries.

7) Iron, zinc, essential aminoacids, and further vitamins are in the R&D pipeline.

Iron Deficiency Aneamia

The problems :

Rice contains very little iron (1), an inhibitor of iron resorption (2), and does not support iron uptake from a vegetative diet (3).

The consequences:

Rice-eating poor suffer from iron deficiency. Iron deficiency affects nearly 3 billion people. It impairs body growth, mental & motor development, activity, intellect & emotion; it favours infectious diseases. It is the major cause for maternal and child death in pregancy.

The transgenic concept:

Decrease the inhibitor (1), increase iron content (2), add uptake-promoting substances (3).

Increase possible, but not yet efficient enough. Further basic research required.

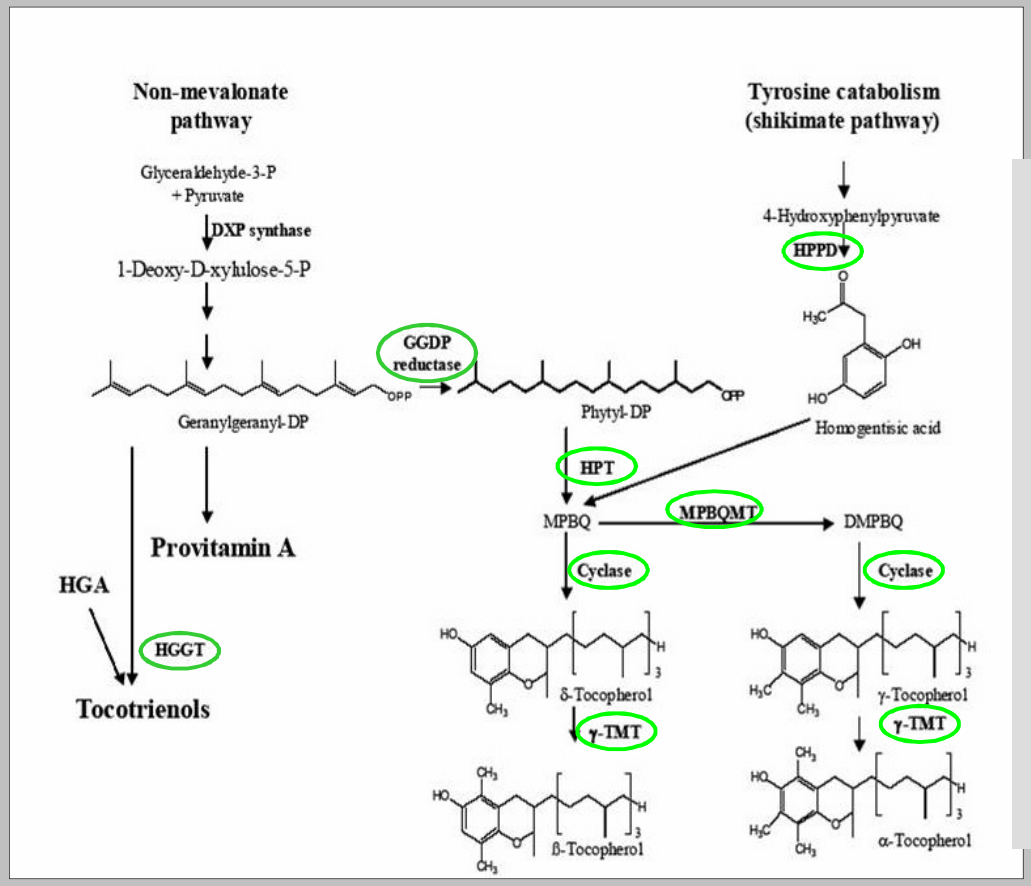
„High-Iron“ Rice has 2-fold iron, 7-fold uptake-promoting cystein, and high inhibitor-degrading activity. However, the inhibitor-degrading enzyme (phytase) does not retain its heat stability when in the apoplast; and when active in the phytate vesicles, is provoking replacement of degraded phytate.

Experiments are, therefore, in progress for

- **expressing the phytase in a different compartment,**
- **enhancing iron uptake via excretion from the roots of mucogenic acid, and**
- **supporting phloem transport of iron via an iron transporter.**

Vitamin E

Rate-limiting steps unknown in rice endosperm

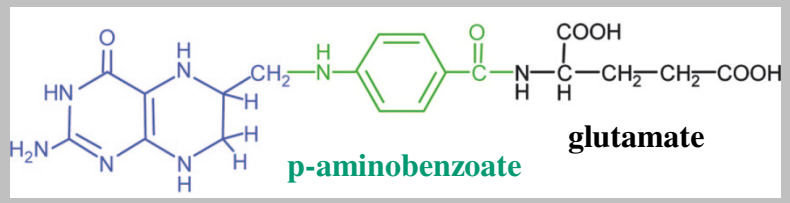


genes	expected outcome
At-HPPD	increased tocotrienols
Os-GGDPR	increased tocopherols
At-HPT	increased tocopherols
hv-HGGT	increased tocotrienols
At-MPBQ-MT	increased γ/α proportions
At-Toc-Cyc	increased tocotrienols
At-gTMT	increased α/β proportions

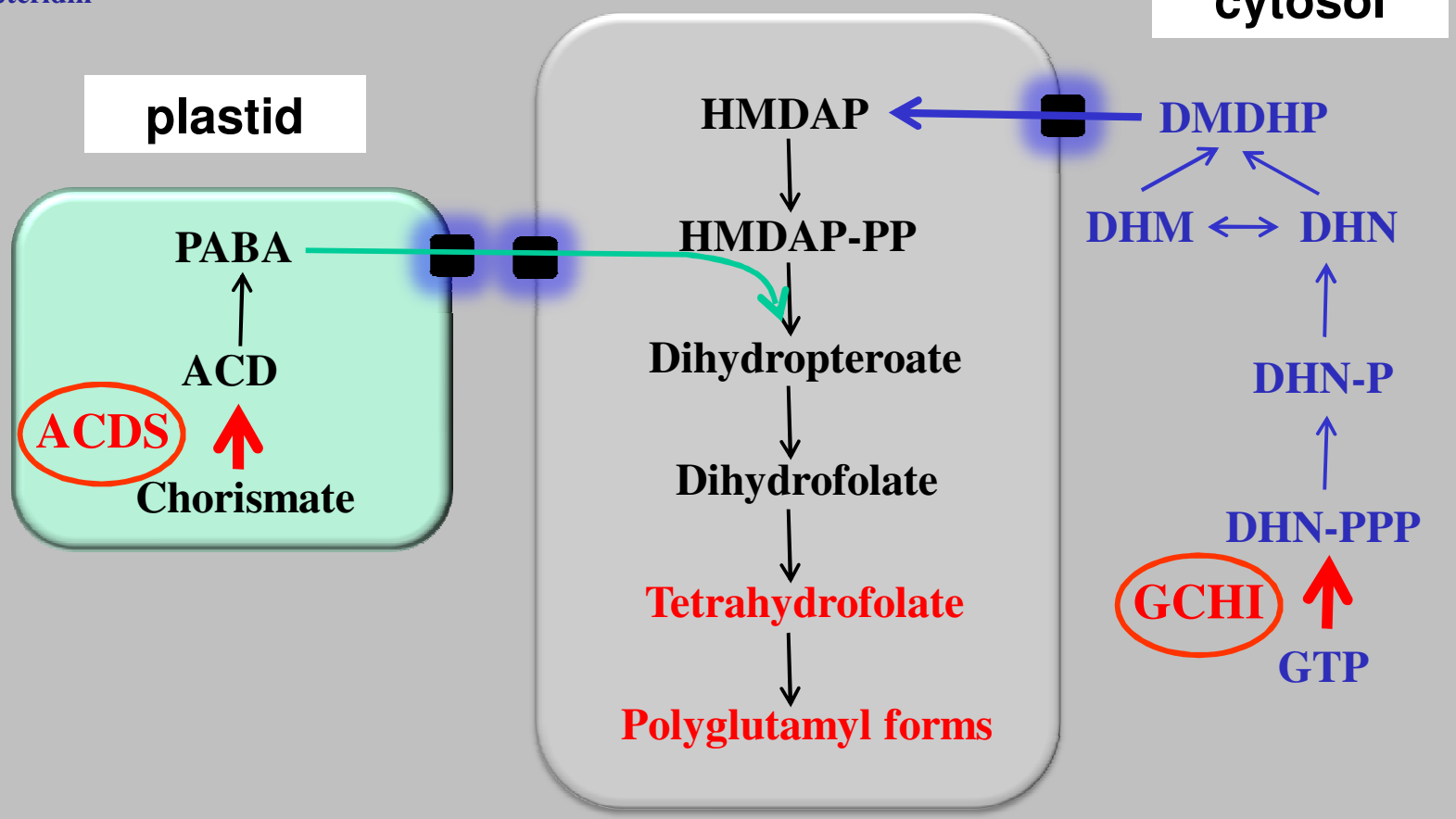
Status: All genes transformed, T1 seeds being harvested.

Folate deficiency

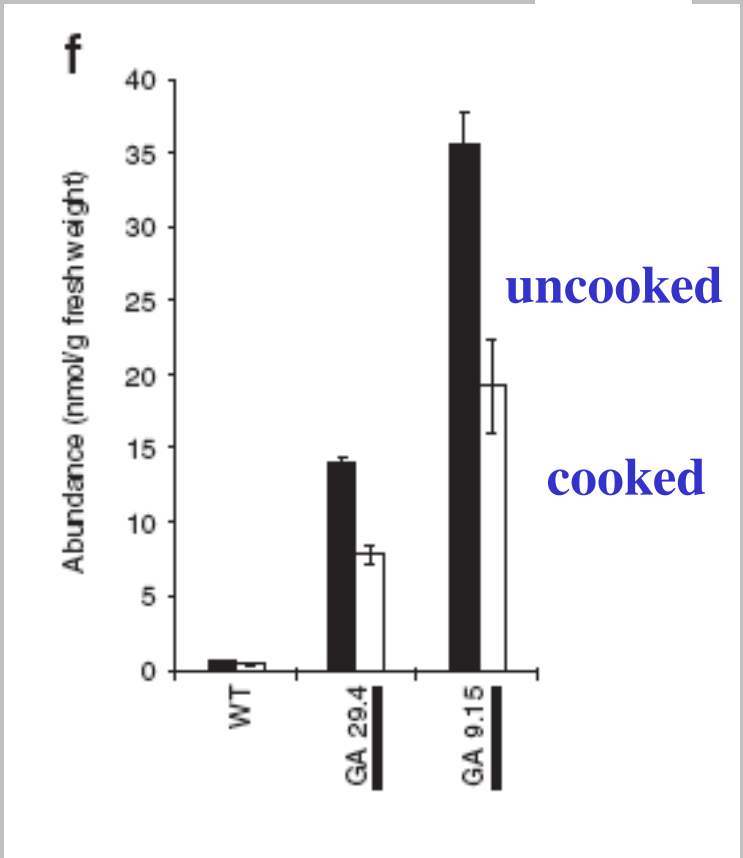
Folate deficiency: Megaloblastic anemia, birth defects
Folate fortification mandatory in the US since 1998



Monoglutamyl-THF



High Folate Rice.



- Genes from Arabidopsis
- Rice glutelin promoter
- 17 µg/g in milled Nipponbare rice (RDA for adults 400 µg)
- Ca. 25g (50 g cooked) needed
- In highly bioavailable form

High folate rice: Storozhenko et al., *Nature Biotech. 2007*
High folate tomato: De la Garza et al., *PNAS* 2007

A Lysine-rich Storage Protein in Winged Bean

Regularily consumed by 300 million in Southeast Asian countries.

Pod

Seed

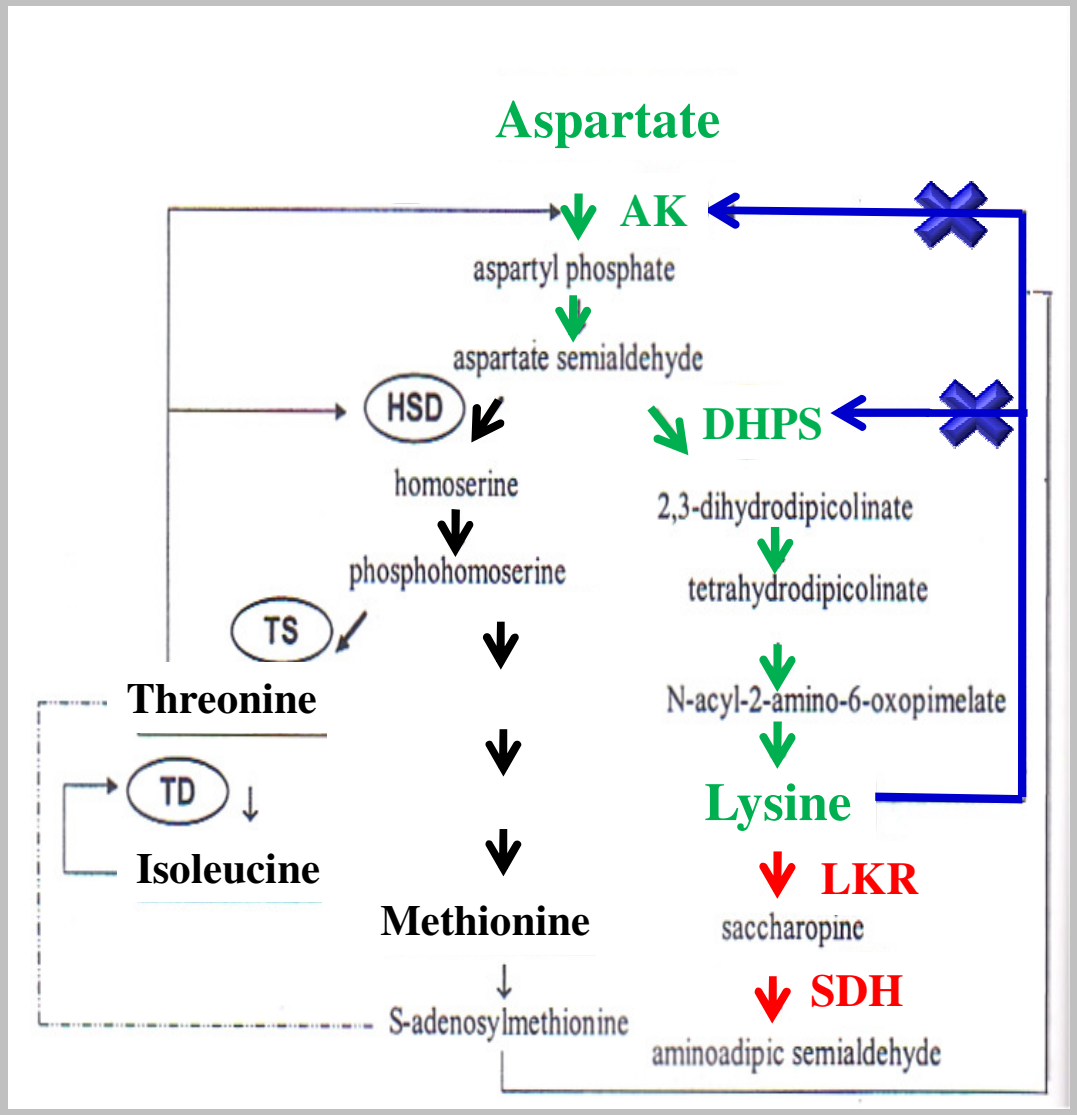
MGVFTYEDETTSPVAPAILYKAIVKDADNIFPKAVDSFKSVE
IVEGNGGPGTIKKISFVEDGESKFVLHKIESIDEANLGYSYSI
VGGAALPDTVEKITFESKLSAGPSGGSVGKLTVKYQTKGDA
EPNEELKVGKAKGDALFKAVEAYLLAHPEYN

Amino acid composition:

Ala (A)	15	9.6%
Arg (R)	0	0.0%
Asn (N)	5	3.2%
Asp (D)	9	5.7%
Cys (C)	0	0.0%
Gln (Q)	1	0.6%
Glu (E)	16	10.2%
Gly (G)	16	10.2%
His (H)	2	1.3%
Ile (I)	10	6.4%
Leu (L)	10	6.4%
Lys (K)	17	10.8%
Met (M)	0	0.0%
Phe (F)	7	4.5%
Pro (P)	8	5.1%
Ser (S)	12	7.6%
Thr (T)	8	5.1%
Trp (W)	0	0.0%
Tyr (Y)	7	4.5%
Val (V)	14	8.9%
Asx (B)	0	0.0%
Glx (Z)	0	0.0%
Xaa (X)	0	0.0%

A cDNA encoding 18kD-LRP cloned, transformed into Rice; stable, high-level expression achieved. Stopped because of hypothetical allergenicity.

Metaboling engineering to increase lysine accumulation



Aspartate Family Amino Acids Pathway

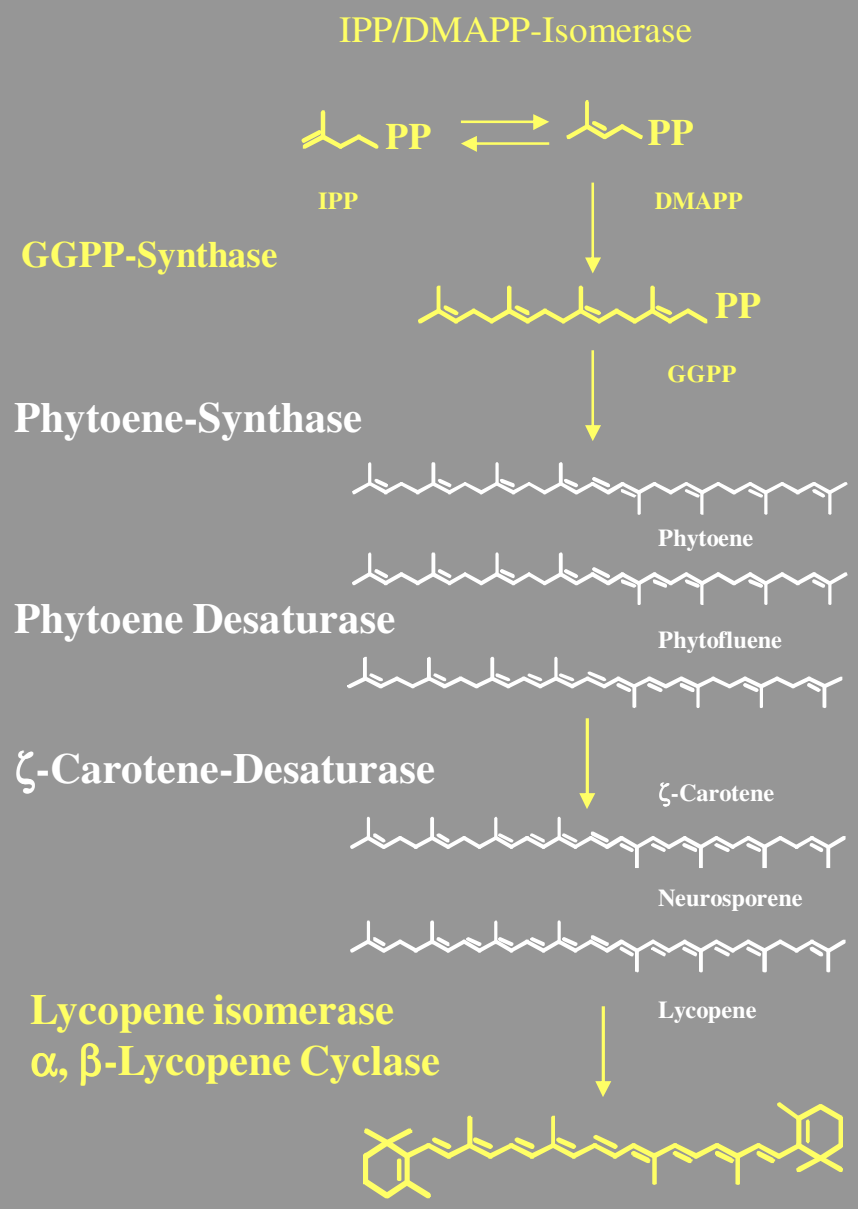
Negative feedback

Lysine Biosynthesis upregulated

S. Sun, CUHK, China – Grand Challenges of Global Health, BMGF

Lysine Catabolism downregulated

Two field trails yielded 40% increased lysine.



Following provitamin A there are several further important micro nutrients in the R&D pipeline for biofortification of crop plants important for food security in developing countries.

- Carotenoids
- High Iron
- High Zinc
- Vitamin E
- Folate
- Vitamin B6
- Essential amino acids
- Healthy fatty acids

Two international programs, using traditional and molecular techniques, are engaging in the concept of „biofortification“.

With major funding from the M&B Gates Foundation science can now seriously challenge the concept of biofortification.

„Grand Challenges in Global Health“, Gates Foundation using GMO approaches.

- Rice
- Sorghum
- Cassava
- Banana

- Provitamin A
- Iron content & bio-availability
- Zinc content & bio-availability
- High-quality protein
- Vitamin E

„HarvestPlus“, CGIAR using predominantly breeding approaches

- Rice
- Maize
- Wheat
- Cassava
- Sweet Potato
- Beans

- Provitamin A
- Iron content & bio-availability
- Zinc content & bio-availability
- High-quality protein

8) GMO-regulation prevents effective use of GM-technology.

GMO-Regulation delays use of ‚Golden Rice‘for many years.

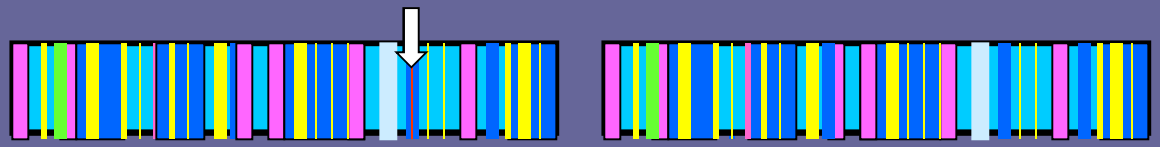
Deletion of selectable marker: unjustified	2 years
Screening for streamlined integration: unjustified	2 years
Screening for regulatory clean events: unjustified	2 years
Protection against liability problems: justified	1 year
Transboundary movement of seeds: unjustified	2 years
Obligatory sequence greenhouse-field: unjustified	1 year
Permission for working in the field: unjustified	2 years
Requirement for one-event selection: unjustified	2 years
Experiments for the regulatory dosier: only partly justified	4 years
Deregulation procedure: only partly justified	1 year

Delay of Golden Rice for 1 year costs a minimum of 40‘ 000 lives!

9) There is no scientific justification for GMO-regulation.

The ‚genetic modifications' resulting from genetic engineering are, in comparison to those resulting from traditional breeding, minor, precise, predictable, and extremely well studied!

GMO



traditional

Therefore, there is no scientific justification for specific GMO-regulation.

And this is confirmed by <u>all</u> biosafety research, <u>all</u> results of regulatory review, a wealth of publications of independent scientific institutions – and all data from 25 years of biosafety research.

It is unjustified to maintain ‚GMO regulation' - even if it would not cost lives.

Present regulatory regimes ignore benefits, are obsessed with hypothetical risks, are an opportunistic response to anti GMO activists. They prevent use of GMO- technology in public goods research and development.

It is time to shift to *regulation* of *traits* instead of *technology!*

„GMO plants are at least as safe as traditionally bred ones.“

European Commission‘s Scientific Advisory Panel 2008

International Union of Food Science and Technology. 2005

Royal Society London, US Natl. Acad. Sciences, Barzilian Acad.Sci., Chinese Acad.Sci., Indian Acad.Sci., Mexican Acad.Sci., Third World Acad.Sci. 2004.

GM Science Review Panel UK, 2003.

Pontifical Academy of Sciences, 2002.

New Zealand Royal Commission, 2001.

Food and Agriculture Organization of the UN, 2000.

American Medical Association Council, 2000.

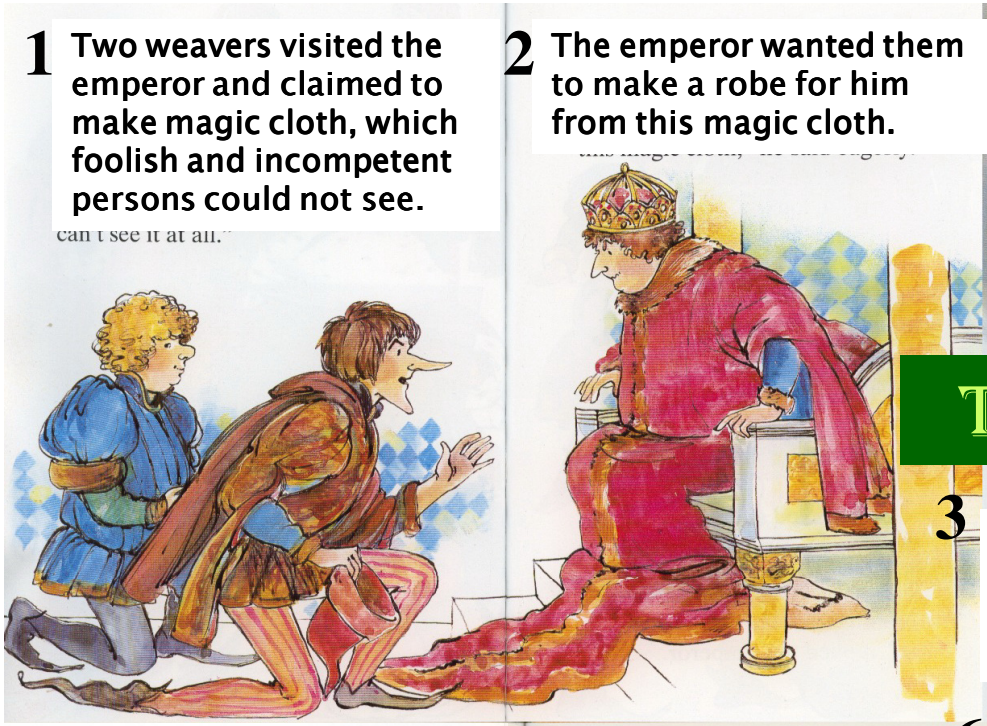
American Council of Science and Health, 2000.

etc.etc.etc.

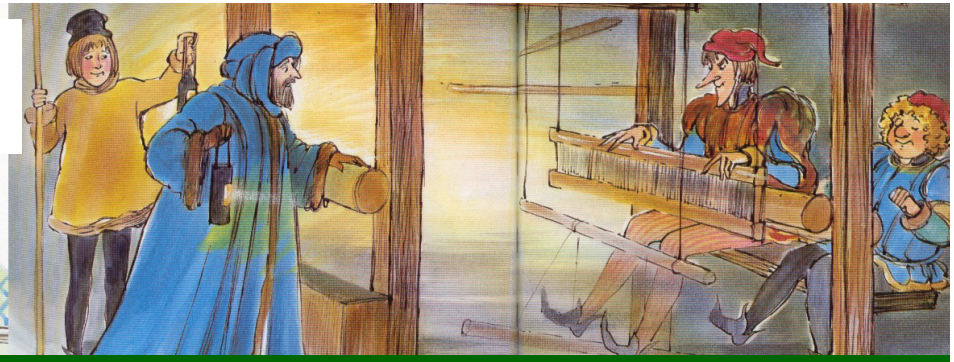
10) The „Emperor is naked!

THE EMPRORS NEW CLOTHS.

1 Two weavers visited the emperor and claimed to make magic cloth, which foolish and incompetent persons could not see.



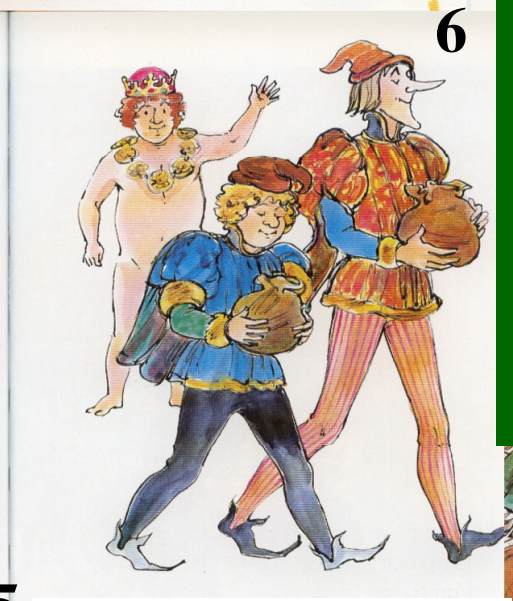
2 The emperor wanted them to make a robe for him from this magic cloth.



3 The prime minister was sent, to look at the progress, but could not see anything. As he had to prevent to be considered incompetent, he pretended to never have seen such beautiful cloth.

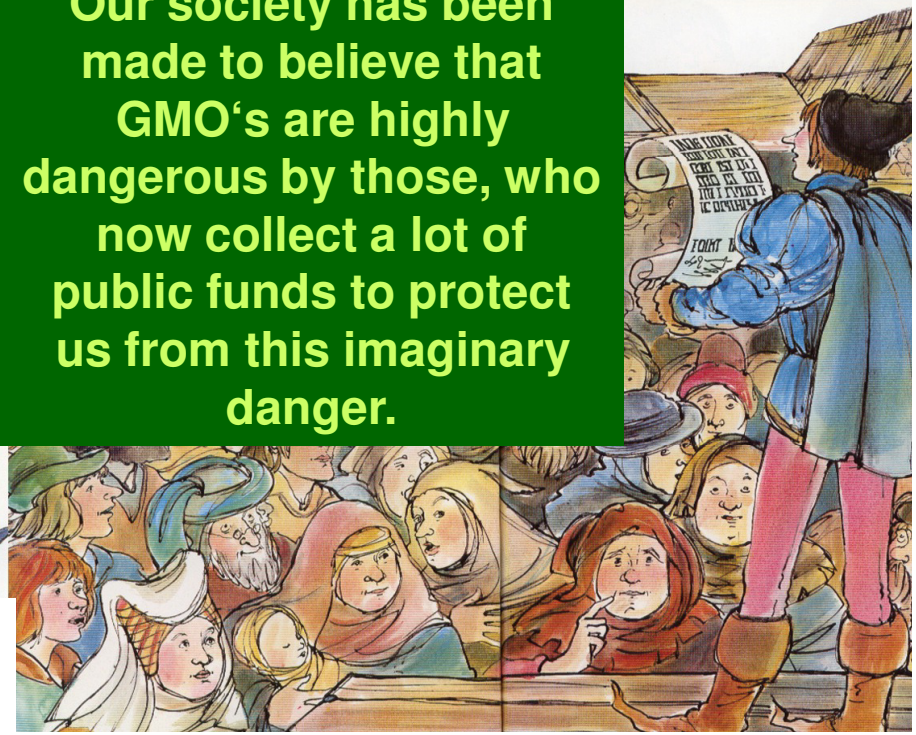
4 Also the emperor had no choice but to prentend the same.

5 The weavers were rewarded very generously – and were never seen again.



6

Our society has been made to believe that GMO's are highly dangerous by those, who now collect a lot of public funds to protect us from this imaginary danger.



How does this „Emperors-New-Cloths“ trick work in our times?

- Create and use anti-GMO sentiment to acquire political power.
- Use this power to lobby EU- & National Governments.
- Channel financial support to NGOs to support anti GMO politics.
- Use these NGOs to lobby the media and the public.
- Use European NGOs to finance NGOs in Developing countries.
- Establish a world-wide anti GMO network.
- Use this network to acquire more anti GMO campaign funds.
- Hide these funds to maintain your „Robin Hood“ image.

European and national governments pour impressive funds into this re-inforcing feed-back circle. NGOs („Non-Governmental Organisations“). may recieve up to 80% of their total income via this mechanism.

This guarantees that the world continues to believe that GMOs are highly dangerous, and in the interest of multinationals only, …… and that anti GMO campaign money is continuing to flow readily.

www.gmobelus.com/news.php?viewStory=145

11) Golden Rice will grow in the farmers fields from 2012 onwards.

The following tasks remain to be solved:

- Selection of the lead event: 2008.
- Completion of variety development: 2009.
- Multi-location trials 2009.
- Variety registration: 2010.
- Regulatory dossier and deregulation: 2010/11.
- Seed multiplication and distribution: 2011.
- Social marketing: already ongoing.
- Epidemiological evaluation.

Despite many hurdles (and no support from Europe, WHO, or FAO), Golden Rice will grow in the farmers fields from 2012 onwards, and will substantially reduce vitamin A-malnutrition in rice-depending societies.

www.goldenrice.org

Acknowledgements:

ETH Zürich and Rockefeller Foundation for support of ‚proof-of-concept‘ work.

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Humanitarian Golden Rice Network for product development and deregulation.

AgBiotech companies for free licenses.

Syngenta for contributions in product development, deregulation, advice and donations.

Rockefeller Foundation, USAid, Syngenta Foundation, HarvestPlus, NIH, IRRI, DBT India, Gates Foundation, for financial support.

A final message to our politicians, the media, NGOs, and our societies:

Micro nutrient deficiency takes a daily toll of 24‘ 000 lives. Biofortification could save many of those lives, at minimal costs. GMO-plants have the safest track record possible. It is time to de-demonise them and free them from exessive regulation. GMO-regulation has, so far, not prevented any harm; instead it has been costing numerous lives. European attitudes have a devastating effect on the live of the poor in developing countries.