

aggregates in Eprex did not increase after the formulation change, and was certainly not higher than in other erythropoiesis-stimulating agents¹¹.

We agree with Schellekens & Jiskoot that it is important to monitor the incidence of immunogenicity in patients treated with biopharmaceuticals. There is also a need for standardized assays to detect antibodies against these therapeutic proteins. As demonstrated by our research, in addition to known factors that can influence the immunogenicity of therapeutic proteins, factors that are less often considered (e.g., container closures) may also have a significant impact by affecting product integrity.

J&J and independent researchers have made an effort to make the research related to the investigations available to the public through the publication of several articles^{1,2,4,8–11}. In addition, the data were reviewed by regulatory authorities, including the Therapeutic Goods Administration (Australia), Health Canada and the European Medicines Agency, which have approved the reintroduction of s.c. administration of Eprex, thereby independently confirming the validity of the data demonstrating the safety of the currently marketed formulation of Eprex, including a reduction of EPO antibody-mediated PRCA to the baseline level observed with any erythropoiesis-stimulating agent.

Basant Sharma¹, Mary H. Ryan² & Katia Boven³

¹Pharmaceutical Technology, Global Biologics Supply Chain, 1000 Route 202 South, PO Box 300, Raritan, New Jersey 08869-0602, USA.

²Biopharmaceutical Research, Centocor Research and Development, Inc., 145 King of Prussia Rd., Radnor, Pennsylvania 19087, USA. ³Global Clinical Development, Tibotec Inc., 1020 Stony Hill Road, Suite 300, Yardley, Pennsylvania 19067, USA.

e-mail: bsharma@centus.jnj.com

1. Sharma, B. *et al.* *Eur. J. Hosp. Pharm.* **5**, 86–91 (2004).
2. Ryan, M.H. *et al.* *Int. Immunopharmacol.* **6**, 647–655 (2006).
3. Yano, K., Ohno, S., Nakajima, Y., Toyoshima, S. & Nakajin, S. *J. Health Sci.* **49**, 195–204 (2003).
4. Boven, K. *et al.* *Kidney Int.* **67**, 2346–2353 (2005).
5. NKF-K/DOQI. *Am. J. Kidney Dis.* **37** (1 Suppl 1), S182–S238 (2001).
6. Locatelli, F. *et al.* *Nephrol. Dial. Transplant.* **19** Suppl 2, ii1–47 (2004).
7. Rossert, J. *et al.* *Nephrol. Dial. Transplant.* **21** Suppl 4, iv153 (2006).
8. Tredree, R. & Pearce, S. *Eur. J. Hosp. Pharm.* **1**, 11–15 (2003).
9. Wegewijs, H.W. *Eur. J. Hosp. Pharm.* **1**, 15–17 (2003).
10. Crommelin, D.J.A., Bissig, M., Gouveia, W. & Tredree, R. *Eur. J. Hosp. Pharm.* **1**, 17–22 (2003).
11. Boven, K. *et al.* *Nephrol. Dial. Transplant.* **20** Suppl 3, iii33–40 (2005).

Schellekens and Jiskoot respond:

In contrast to the assumption of Sharma *et al.*, we scrutinized all the (highly redundant) publications of J&J concerning their explanation of Eprex-associated PRCA. In all of their papers, the only support for a modest adjuvant effect of leachables is a single experiment in mice immunized with ovalbumin. Because this mouse model is not based on breaking B-cell tolerance, this experiment is irrelevant for the induction of antibodies by Eprex. And as confirmed in many models, immune tolerance to soluble self proteins like erythropoietin cannot be broken by an adjuvant.

Sharma *et al.* refer to results of Yano *et al.*¹ for confirmation of the immune stimulant effect of the alkyl phenols present in the leachates. In the Yano *et al.* paper, however, none of the compounds identified as leachates by Sharma *et al.*² are studied. Yano *et al.* showed only that this class of compounds has no effect on interleukin 4 and interferon γ production *in vitro* in the concentrations present in Eprex with uncoated rubber stoppers. In higher concentrations, alkyl phenols inhibit immune stimulatory cytokine products—exactly the opposite activity that Sharma *et al.* claim.

Sharma *et al.* agree with us that analyses-based spontaneous reporting should be interpreted with caution, the same caution

that the European Medicines Agency has shown by allowing the limited reintroduction of the subcutaneous use of Eprex with chronic renal failure under strict patient surveillance.

Thus, in contrast to the claim of Sharma *et al.*, the European regulatory agencies still need further data to confirm the safety of Eprex. And even if the data were to show the reduction of Eprex-associated PRCA to background levels, this cannot be interpreted as definitive proof that leachates were responsible for the Eprex-associated cases, considering the other changes that have been introduced.

We recently published³ a detailed analysis of all the theories offered to explain the higher incidence of PRCA after the formulation change of Eprex. Our conclusion is that the formulation change resulted in a slightly less stable product with a higher tendency to form aggregates during storage or use. Although the PRCA problem is under control, unbiased explanations of the effect of the formulation change are important now that protein therapeutics are becoming a major part of the new drugs introduced.

1. Yano, K., Ohno, S., Nakajima, Y., Toyoshima, S. & Nakajin, S. *J. Health Sci.* **49**, 195–204 (2003).
2. Sharma, B. *et al.* *Eur. J. Hosp. Pharm.* **5**, 86–91 (2004).
3. Schellekens, H. & Jiskoot, W. Erythropoietin-associated PRCA, an unsolved mystery. *J. Immunotoxicol.* **3**, 123–130 (2006).

Potential impact and cost-effectiveness of Golden Rice

To the editor

A News & Views article by Michael Grusak in last year's April issue (*Nat. Biotechnol.* **23**, 429–430, 2005) highlighted the unresolved debate concerning the efficacy of Golden Rice in addressing the problem of vitamin A deficiency (VAD). He pointed out that an assessment of the potential impact of Golden Rice on this type of malnutrition requires the consideration of multiple variables, including the target individuals' life stages, the average amount of rice consumed daily by these individuals and the percentage of β -carotene that would be absorbed from rice. He further explains how early critics of the original Golden Rice technology had used simple estimates of these variables to suggest that unrealistic amounts of the transgenic rice would need to be consumed to satisfy the recommended dietary intakes of vitamin A equivalents (exclusively) through rice consumption. By replacing the daffodil

phytoene synthase gene with the equivalent gene from maize, researchers have managed to increase the amount of β -carotene that accumulates in rice considerably¹. However, a sound impact analysis of this new Golden Rice 2 variety, based on a solid methodological framework, is still outstanding.

Previous impact studies of Golden Rice either focused solely on effects of the rice on individual β -carotene intakes without considering the outcome on the health of those suffering from VAD² or considered health outcomes but used only highly aggregate intake data without taking into account important nutritional features like dietary heterogeneity³. Using a methodology developed for comprehensive *ex ante* evaluation, we present here a framework that substantially improves on these studies by combining health and nutrition details, as well as socioeconomic and policy factors, thus increasing the reliability of the results.

Table 1 Disease burden of VAD in India and impact and cost effectiveness of Golden Rice 2

Scenario	Measure
<i>Current disease burden of VAD</i>	
Number of DALYs lost annually	2,328,000
Number of lives lost annually	71,600
<i>Potential impact of Golden Rice 2</i>	
Number of DALYs saved annually in low-impact scenario	204,000
Number of DALYs saved annually in high-impact scenario	1,382,000
Annual reduction in the DALYs burden in low-impact scenario	8.8%
Annual reduction in the DALYs burden in high-impact scenario	59.4%
Number of lives saved annually in low-impact scenario	5,500
Number of lives saved annually in high-impact scenario	39,700
<i>Cost-effectiveness of public health interventions</i>	
Cost per DALY saved through Golden Rice 2 in low-impact scenario	\$19.4
Cost per DALY saved through Golden Rice 2 in high-impact scenario	\$3.1
Cost per life saved through Golden Rice 2 in low-impact scenario	\$358
Cost per life saved through Golden Rice 2 in high-impact scenario	\$54
World Bank cost-effectiveness standard for DALYs saved ^a	\$200
World Health Organization standard for valuing DALYs ^b	\$620–1,860
Cost per DALY saved through supplementation ^c	\$134–599

^aThe costs per DALY given in ref. 5 are expressed in 1990 US dollars; the equivalent in current terms rises above \$200.

^bThe WHO suggests that one DALY should be valued at the single-to-triple per capita income^b; for India the gross national income per capita in 2004 was \$620 (ref. 7). ^cDALY-costs for vitamin A supplementation in South Asia^a, converted into 2004 US dollars. For more details, see **Supplementary Discussion** online.

We apply our methodology in an empirical study of Golden Rice 2's impact in India (**Supplementary Discussion** online).

Adverse health outcomes of VAD include increased mortality, night blindness, corneal scars, blindness and measles among children, as well as night blindness among pregnant and lactating women. We calculated the disease burden associated with VAD-attributable fractions of these outcomes, building on a disability-adjusted life years (DALYs) approach. The combined annual mortality and morbidity burden is expressed in terms of the number of DALYs lost⁴. The present burden, calculated based on available health statistics, is the situation without Golden Rice 2.

Next, we derived present individual β -carotene intakes from nationally representative food consumption data and simulated the expected shift in the intake distribution through future consumption of Golden Rice 2. Higher β -carotene intakes will improve the vitamin A status of individuals, thus reducing the incidence of adverse health outcomes. We derived these new incidence rates to recalculate the expected remaining disease burden with Golden Rice 2. The difference in the disease burden with and without Golden Rice 2 is the impact of the technology expressed in terms of the number of DALYs saved. To allow for the uncertainty in *ex ante*

analysis, we used different assumptions and constructed a high and a low impact scenario (**Supplementary Discussion** online).

According to our calculations, the current annual disease burden of VAD in India amounts to a loss of 2.3 million DALYs, of which 2.0 million are lost due to child mortality alone. In terms of incidence numbers, >70,000 Indian children under the age of six die each year due to VAD. In this context, widespread consumption of Golden Rice 2 with a high β -carotene content could reduce the burden of VAD by 59%, whereas under pessimistic assumptions the burden would be reduced by 9% (**Table 1**). In both scenarios, thousands of lives could be saved. As the severity of VAD is negatively correlated with income, the positive effects of Golden Rice 2 are most pronounced in the lowest income groups.

We also assessed Golden Rice 2's potential cost-effectiveness relative to alternative vitamin A interventions and appropriate benchmarks, with a view to informing policy decisions and international comparisons. Following the low-impact/high-impact scenario approach to determine the research, development and dissemination costs of Golden Rice 2 (**Supplementary Discussion** online), we find that even under pessimistic assumptions, the cost of saving one DALY is <\$20. Compared with a cost of \$134–599

of saving one DALY through vitamin A supplementation, which is a commonly practiced intervention, or compared with the World Bank's benchmark of \$200, Golden Rice 2 promises to be very cost effective (**Table 1**). Sensitivity analyses have been carried out to identify critical factors of success and the robustness of the results.

In the future, preliminary results on β -carotene bioavailability will have to be verified, the Golden Rice trait needs to be incorporated into agronomically superior local varieties, biosafety and food safety tests have to be carried out and technology dissemination has to be promoted through public marketing campaigns.

Our findings suggest that related investments are worthwhile. These promising results notwithstanding, Golden Rice is no panacea in the fight against malnutrition. Given the magnitude and complexity of the problem, a multiplicity of approaches is needed.

ACKNOWLEDGMENTS

We are grateful to G. Barry, A. Dubock, J. Mayer, S.R. Rao, A.K. Singh and U. Kapil for providing cost figures and expert inputs for essential assumptions. The financial support of the German Research Foundation (DFG) and the Golden Rice Humanitarian Board is gratefully acknowledged.

Note: Supplementary information is available on the Nature Biotechnology website.

Alexander J. Stein¹, H.P.S. Sachdev² & Matin Qaim¹

¹University of Hohenheim, Department of Agricultural Economics & Social Sciences (490b), 70593 Stuttgart, Germany. ²Sitaram Bhartia Institute of Science & Research, B-16 Qutab Institutional Area, New Delhi 110 016, India. e-mail: astein1@uni-hohenheim.de; qaim@uni-hohenheim.de

- Paine J. *et al.* *Nat. Biotechnol.* **23**, 482–487 (2005).
- Dawe, D., Robertson, R. & Unnevehr, L. *Food Policy* **27**, 541–560 (2002).
- Zimmermann, R. & Qaim, M. *Food Policy* **29**, 147–168 (2004).
- Stein, A.J. *et al.* Analyzing the Health Benefits of Biofortified Staple Crops by Means of the Disability-Adjusted Life Years Approach. HarvestPlus Technical Monograph 4 (International Food Policy Research Institute, Washington, DC, USA, 2005). <http://www.harvestplus.org/pubs.html#tech>
- World Bank. *World Development Report 1993* (World Bank, Washington, DC, USA, 1993). <http://econ.worldbank.org/wdr>
- World Health Organization. *Macroeconomics and Health: Investing in Health for Economic Development* (World Health Organization, Geneva, 2001). <http://www.who.int/cmreport/>
- World Bank. *World Development Indicators Database: India Data Profile* (World Bank, Washington, DC, USA, 2006). <http://www.worldbank.org/data/countrydata/countrydata.html>
- Tan-Torres Edejer, T. *et al.* *Br. Med. J.* **331**, e1177 (2005).