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TECHNICAL MONOGRAPH SERIES 4

Analyzing the Health Benefits of Biofortified Staple Crops by Means of the Disability-Adjusted Life Years Approach: a Handbook Focusing on Iron, Zinc and Vitamin A

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Alexander J. Stein, J.V. Meenakshi, Matin Qaim, Penelope Nestel, H.P.S. Sachdev and **Zulfiqar A. Bhutta**, 2005.
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HarvestPlus Technical Monograph 4.

Washington, DC and Cali: International Food Policy Research Institute (IFPRI) and International Center for Tropical Agriculture (CIAT).

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Abstract

Biofortified staple crops – food crops bred for higher micronutrient content – are expected to reduce micronutrient deficiency and its accompanying adverse health outcomes. Health benefits can be measured and expressed in terms of the number of "disability-adjusted life years" (DALYs) saved due to the intervention. This quantification of health benefits can be used in cost-effectiveness and in cost-benefit analyses, by attributing a monetary value to DALYs and juxtaposing this benefit and the research and development costs of the biofortified crop. This handbook describes how to conduct these impact analyses for staple crops biofortified with iron, zinc or beta-carotene. It outlines the underlying method, explains the individual steps of the analysis, and details information and data requirements. The results of analyses of the type described here should prove useful for demonstrating the economic feasibility of biofortification, estimating its impact, creating awareness of this new intervention, directing research priorities, and identifying constraints early on.

Keywords: biofortification, micronutrients, iron, zinc, beta-carotene, vitamin A, deficiency, staple crops, DALYs, health impact, cost-effectiveness, cost-benefit analysis

Acknowledgements: Thanks are due to the three referees who provided valuable input to this report. Also, financial support of the German Research Foundation (DFG) is gratefully acknowledged. We welcome comments, criticisms and questions; please contact Alexander Stein at astein1@uni-hohenheim.de who will relay these to the group as necessary.

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Abbreviations and acronyms

CGIAR	- Consultative Group on International Agricultural Research
CIAT	- Centro Internacional de Agricultura Tropical (International Center for Tropical Agriculture)
CIMMYT	- Centro Internacional de Mejoramiento de Maíz y Trigo (International Maize and Wheat Improvement Center)
DA	- disability
DALY	- disability-adjusted life year
DHS	- Demographic and Health Survey
GBD	- Global Burden of Disease
IDA	- iron deficiency anemia
IFPRI	- International Food Policy Research Institute
IRR	- internal rate of return
MICS	- Multiple Indicator Cluster Survey
NFHS	- National Family and Health Survey (India)
NIN	- National Institute of Nutrition (India)
PTO1	- first person trade-off question
PTO2	- second person trade-off question
R&D	- research and development
RDA	- recommended dietary allowance
SD	- standard deviation
VA	- vitamin A
VAD	- vitamin A deficiency
WHO	- World Health Organization
WTP	- willingness-to-pay
YLD	- years lived with disability
YLL	- years of life lost
ZEF	- Zentrum für Entwicklungsforschung (Center for Development Research, Germany)
µg/dL	- micrograms per deciliter

1 | Introduction

HarvestPlus is a Challenge Program of the Consultative Group on International Agricultural Research (CGIAR) under the leadership of the International Center for Tropical Agriculture (CIAT) and the International Food Policy Research Institute (IFPRI).[1] It is a global program that seeks to improve the nutrition and health status of undernourished people in developing countries by breeding staple crops to enhance the content of essential micronutrients such as iron, zinc and provitamins A.[2] This process is known as *biofortification*.

Among its many activities, HarvestPlus is conducting cost-benefit and cost-effectiveness analyses for the various staple crops and micronutrients concerned. The method for measuring the economic effectiveness of biofortification, which is ultimately measured as the improvement in human health and well-being, was developed through a series of workshops that included participants from the CGIAR centers and cooperating research institutions.[3] The method is based on a paper by Zimmermann and Qaim (2004), in which the concept of "disability-adjusted life years" (DALYs) was first used to measure the potential health benefits of a biofortified staple crop. As biofortified staple crops are not yet available to agricultural producers and hence to consumers, such analyses necessarily take an *ex ante* approach.

This handbook describes the method. In particular, it provides checklists of the data and information required in the analyses, makes transparent the assumptions that need to be made, and points to possible sources of information. Thus, this handbook can help economists wishing to conduct impact analyses related to the micronutrient content of crops. After explaining how to analyze the health benefits of biofortification with iron and zinc in detail, we provide a shorter overview of the information requirements and assumptions related to vitamin A (VA) because the approach is essentially the same as for zinc.

[1] See http://www.harvestplus.org/about.html.

[2] The human body can convert provitamin A carotenoids, such as beta-carotene, alpha-carotene, and beta-cryptoxanthin into vitamin A, or retinol.

[3] Workshops were held at IFPRI, Washington, D.C., Sep. 2–3, 2003, & Oct. 19-21, 2004, the Center for Development Research (ZEF), University of Bonn, Dec. 16–17, 2003, and the CIMMYT regional office in Kathmandu, Mar. 13–15, 2004.

2 | Method

The purpose of biofortifying staple crops is to improve human health and well-being by reducing the burden of disease caused by micronutrient deficiency. When analyzing the impact of biofortification, it is necessary to quantify and value "health". Once this is done, it becomes possible, for instance, to compare the public health improvements that can be achieved through biofortification with those that can be achieved through other interventions such as food fortification or pharmaceutical supplementation. Moreover, quantification of "health" is necessary to contrast potential health benefits of biofortified staple crops with the related research and development (R&D) costs incurred.

The major conceptual issue is how to measure health. In recent years, through the Global Burden of Disease (GBD) project along with a seminal book by Murray and Lopez (1996) that was written with the support of the World Health Organization (WHO) and the World Bank, it has become increasingly popular to measure health – or rather its inverse, the burden of disease – using "disability-adjusted life years" (DALYs).

The DALY method is not without its detractors, and there are valid criticisms of some of its components (Anand and Hanson 1998, Lyttkens 2003, Groce et al. 1999, Allotey et al. 2003, Arnesen and Nord 1999, Richardson 1999, Olsen et al. 2002). Nonetheless, taking a pragmatic approach, we consider it to be the best method available. Building on Zimmerman and Qaim (2004), we have modified the original methodology to counter some of its limitations. In the following, we highlight and explain deviations from the method developed by Murray (1996).

2.1 The DALY formula used

The DALY method provides a single index with which to measure the morbidity and mortality related to a particular disease, and thus the burden of the disease. DALYs lost are, therefore, related to the sum of the "years of life lost" (YLL) due to cause-specific mortality and the sum of the "years lived with disability" (YLD). To be able to add up disability and death, years of life lived with a disability are weighted with "severity" or "disability" weights. These weights range from 0 to 1, with 0 representing perfect health and 1 representing death. Then, the DALYs that are lost due to disease are:

$$DALYs_{lost} = YLL + YLD$$

where the sum of the DALYs lost for each disability gives the total burden of disease. Taking account of different levels of severity and of the varying extent of a disease among groups within a population, following Zimmerman and Qaim (2004), the complete formula can be represented more formally as:

$$DALYs_{lost} = \sum_j T_j M_j \left(\frac{1 - e^{-rL_j}}{r} \right) + \sum_i \sum_j T_j I_{ij} D_{ij} \left(\frac{1 - e^{-rd_{ij}}}{r} \right)$$

T_j = total number of people in target group j
M_j = mortality rate associated with the deficiency in target group j
L_j = average remaining life expectancy for target group j
I_{ij} = incidence rate of disease i in target group j
D_{ij} = disability weight for disease i in target group j
d_{ij} = duration of disease i in target group j (for permanent diseases d_{ij} equals the average remaining life expectancy L_j)
r = discount rate for future life years

2.2 Discounting DALYs

The discount rate is a contentious issue discussed in the literature, the main reproach being that discounting benefits the present generation at the expense of future generations: with discounting, saving one life today is considered to be of greater value than saving one life next year. However, as Musgrove (2000, p. 112) points out, discounting avoids the "time paradox": "In a world where resources can be invested at a positive interest rate, if one does not discount future benefits, it will never pay to undertake an intervention because each year's delay means the benefit can be increased, for example by reaching more beneficiaries." In the GBD, Murray (1996) gives a much more detailed and comprehensive

justification of the necessity to discount future DALYs, yet in the sensitivity analysis of the GBD calculations Murray and Lopez (1996a) look at a zero discount rate scenario. However, it seems reasonable to use a rate above zero and, given the widespread use of a discount rate of 3 percent for social discounting, as was done in the recent World Health Report (WHO 2002), we suggest using this value. Nevertheless, the discount rate certainly merits deliberation, as this choice has a tremendous impact on the absolute results: using a discount rate of zero will increase future health costs (i.e., DALYs lost). One way to diminish the impact of the discount rate, through focusing on relative results, is discussed in Section 4.4.

2.3 Modifications to the DALY formula

Murray's (1996) formula included an age-weighting term; thus, the lives of young, productive adults are given a bigger weight than the lives of infants and the elderly. Murray justifies this approach by referring to studies on the social and individual willingness to pay for health care; to cost-of-illness studies in which, implicitly, life is weighted by income; and to the contribution of young adults to social welfare and to their role as "care-givers" (they are likely to have to look after children and perhaps also their parents). This is a contentious issue because it implies a considerable ethical value judgment. Moreover, it raises the question of where to stop: if information constraints do not exist, one would have to value the life of, say, a physician higher than that of an unskilled day laborer. This is what Lyttkens (2003) describes as "opening Pandora's box". Murray and Lopez (1996a) concede this difficulty by changing the age-weighting assumptions in their sensitivity analysis. We suggest dispensing with age-weighting altogether (which corresponds to using age weights of unity).

Another modification we made to Murray's formula pertains to the value used for the remaining life expectancy. The GBD measures the burden of *all* diseases at once. To calculate the remaining life expectancy then requires making an assumption about a standard life expectancy in the absence of *all* diseases and fatal accidents, i.e., the maximum biological life expectancy. Murray (1996) chose to use a standard life table based on the national life expectancy of Japanese females (82.5 years), the highest life expectancy observed. For men he assumed a slightly lower standard life expectancy (80 years) because of a "biological" difference in survival potential. In our case we are only interested in the remaining life expectancy in the absence of *one* particular condition (micronutrient malnutrition). Because this single condition is not expected to change average life expectancy in a country significantly, national life tables that represent actual life expectancies can be used, thus avoiding further ethical and theoretical issues.

2.4 Calculating the impact of biofortification

To measure the economic impact of biofortified staple crops on public health, both the number of DALYs lost under the *status quo* and the number of DALYs lost under a hypothetical scenario, in which people consume biofortified crops, need to be calculated.

In addition to the information needed to calculate DALYs under the *status quo*, developing a hypothetical scenario where people consume biofortified crops requires further information; specifically, the contribution of biofortified crops to a reduction in micronutrient malnutrition, and hence to an improvement in public health, needs to be specified. This depends primarily on three factors:

1) The number of people who will consume biofortified crops, i.e., the coverage rate. This depends on producers' and consumers' access to and their acceptance of the new technology.
2) The amount of the additional micronutrient that consumers of a biofortified crop will consume and the fraction of the consumed micronutrient that they actually absorb, i.e., the "bioefficacy". This depends on the quantity of the crop consumed, on the additional amount of the micronutrient in the crop, and on its bioavailability to the human body.
3) The size of the effect of the additionally absorbed micronutrient on functional or health outcomes, i.e., the dose-response. This depends on the body's efficiency in using the absorbed micronutrient.

Presumably, less DALYs are lost in the scenario with biofortified crops; the difference between the with and without scenarios corresponds to the impact of biofortification. Thus, the benefit to public health is given as the number of DALYs gained through introduction of the technology.

2.5 Conducting a cost-benefit analysis of biofortification

If a monetary value is attached to a DALY, it is straightforward to carry out a cost-benefit analysis. By juxtaposing cost and benefit streams, and taking into account the research lag, internal rates of return (IRRs) and other measures can be calculated.

There are several approaches to valuing a DALY: (i) use a standardized international value such as US$1,000, (ii) use country-specific annual per capita incomes, or (iii) use an approach based on value of life estimates. The issues associated with choosing among these approaches are discussed in Section 4.5.

The costs to be considered comprise:

- The R&D costs incurred when adding one more trait – in this case higher micronutrient density, reduced levels of iron absorption inhibitors, or enhanced levels of absorption promoters – to the regular breeding efforts for the staple crop in question.
- Country-specific adaptive breeding and dissemination costs.

The specification and attribution of these costs is laid out in Section 3.6.

3 | Information requirements

This section specifies the components of the calculations. Annex 1 provides a "checklist" of all data requirements.

3.1 Functional outcomes, attribution and target groups

As mentioned in Section 2.1, DALYs are calculated separately for different diseases and target groups and then summed to obtain the total burden of disease. However, micronutrient deficiencies are not diseases as such, but can result in adverse functional outcomes. In this case, looking at an outcome, irrespective of its cause, makes little sense as it is the cause that is of interest. To quantify the effect of micronutrient malnutrition on human health, it is first necessary to establish a list of diseases and sequelae that can be caused by a lack of the micronutrient in question (e.g., iron, zinc, VA). If it is established that a lack of a micronutrient changes the probability of getting a disease, a proportion of the disease incidence needs to be attributed to the deficiency of that micronutrient – DALYs lost should only be calculated for the part of the specified disease that is attributable to micronutrient malnutrition.[4]

In a workshop in Kathmandu in March 2004,[5] it was agreed that sufficient scientific evidence exists to relate the functional outcomes specified in the following sections to iron, zinc and vitamin A deficiencies. The experts also determined the appropriate target groups to be considered for the different functional outcomes in the analysis.

The focus of this workshop, however, was on the Indian subcontinent and, where possible, we indicate the India-specificity of the assumptions made.

[4] The assumption here is that the diseases and susceptibilities are independent and additive.

[5] The workshop was held at the CIMMYT regional office in Kathmandu on March 13–15, 2004. The participants included the authors of this monograph and Dr. Erika Meng (agricultural economist, CIMMYT, Mexico).

3.1.1 Functional outcomes and target groups for iron deficiency

Iron deficiency results from an inadequate intake of bioavailable dietary iron and its determination is based on measurements of body iron stores and hemoglobin concentrations (Nestel and Davidsson 2002). Severe iron deficiency results in iron deficiency anemia (IDA). Other factors such as malaria and hookworm can also cause anemia; thus it is important to stress that IDA is a subgroup of anemia. Anemia in turn is classified as mild, moderate, and severe.

At the Kathmandu workshop, three adverse functional outcomes were attributed to IDA:[6]

1) impaired physical activity (Hallberg and Scrimshaw 1981),
2) impaired mental development (Nokes and Bundy 1997),
3) maternal mortality, which leads to further negative outcomes such as increased numbers of stillbirths and child deaths due to the absence of breastfeeding and care caused by death of the mother (Rush 2000).

In specifying these functional outcomes related to iron deficiency, our approach goes beyond the GBD, in which DALYs are calculated for IDA only. In other words, the GBD treats anemia as a "disease" without considering its multiple health consequences.

As in the GBD, we assume that iron deficiency does not have a quantifiable impact on functional outcomes provided it does not result in anemia. Further, because the scientific evidence that mild IDA is linked with adverse functional outcomes is inconclusive (Rush 2000, Stoltzfus 2001), we have excluded this type of IDA from the model. Thus we consider that a significant adverse consequence exists only for moderate and severe IDA. For moderate IDA a link exists with impaired physical activity and mental development. For severe IDA, links exist with maternal mortality as well as with more severe expressions of impaired physical activity and mental development. In all cases, except for maternal mortality, it is assumed that each moderately or severely anemic individual is at risk of the adverse functional outcomes stated. For maternal mortality it is assumed that 5 percent of total maternal mortality is due to IDA.[7]

Having established the adverse functional outcomes related to iron deficiency, the next step is to identify the target groups based on average age of onset of a disease, the prevalence rates of that disease, and its level of severity for different groups within a population. The target groups chosen are:

- for impaired physical activity, children ≤ 5 years, children 6–14 years, women 15+ years and men 15+ years,[8]
- for impaired mental development, children ≤ 5 years (Nokes and Bundy 1997),
- for maternal mortality, women of reproductive age (15–49 years); for stillbirth and child death, pregnant women who died during childbirth due to IDA.

3.1.2 Functional outcomes and target groups for zinc deficiency

Adverse functional outcomes that can be attributed to zinc deficiency are:

1) diarrhea (Bahl et al. 2001 and Bhutta et al. 2000),
2) pneumonia (i.e., severe acute respiratory infection) (Bhutta et al. 1999) and
3) stunting (Brown et al. 2002).

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[6] Although certain studies suggest that stunting might also be a functional outcome of iron deficiency, a recent meta-analysis could not establish a significant cause-effect relationship (Ramakrishnan et al. 2004); similarly, a relationship between iron deficiency anemia and perinatal mortality has been suggested but was not considered in the present analysis.

[7] This value of 5 percent is an assumption made at the Kathmandu workshop. Observational data exist for maternal mortality associated with severe anemia but not with iron deficiency.

[8] A linear association has been reported between iron deficiency and work capacity for agricultural workers and work capacity returned rapidly to normal with iron supplementation (Spurr et al. 1978, Viteri and Torun 1974, Husaini et al. 1984, Davies et al. 1973, Davies and van Haaren 1973, Edgerton et al. 1981, Edgerton et al. 1982, Gardner et al. 1977). Iron supplementation increased work output among road workers and rubber tappers (Basta et al. 1979, Husaini et al. 1981, Husaini et al. 1984, Edgerton et al. 1981, Edgerton et al. 1982, Gardner et al. 1977), agricultural workers (Vijayalakshmi et al. 1987) and industrial workers (Wolgemuth et al. 1982, Li 1993). Non-anemic iron-deficient adolescent female runners significantly improved their levels of endurance and physical performance after supplementation with iron, as compared with those of a placebo control group (Rowland et al. 1988).

All three functional outcomes are specific to the target groups "infants" (aged 0–12 months) and "children" (aged 1–6 years); for stunting the target group is infants only.

Diarrhea and pneumonia are considered to have a certain risk of lethal outcome. Because mortality rates are usually given for children under 5 years old, in this case the target group is defined as "children under 5 years" (aged 0–4 years).

3.1.3 Functional outcomes and target groups for vitamin A deficiency

Adverse functional outcomes that can be attributed to vitamin A deficiency (VAD) are:[9]

1) nightblindness,
2) corneal scarring,
3) blindness,
4) measles, and
5) increased mortality.

All five functional outcomes affect children ≤ 5 years; nightblindness also affects pregnant and lactating women.

3.2 Data requirements for iron

(see Annex 2 for a summary)

3.2.1 Size of target groups

Information on the size of the target groups is available in population and demographic statistics of international organizations, national census bureaus, etc. For India, we use the 2001 national census data. If an analysis focuses on sub-national levels, then the sizes of the target groups have to be chosen accordingly (by region, rural vs. urban, etc.)

3.2.2 Mortality rates

Information on mortality rates is only necessary for the "disease" maternal mortality,[10] stillbirth, and child death because the other functional outcomes of iron deficiency are not considered fatal. For maternal mortality in India, the experts at the Kathmandu meeting agreed that it is reasonable to attribute 5 percent of all maternal deaths to iron deficiency.[11] For other countries it will be necessary to check the applicability of this percentage with reproductive health experts.

To determine the maternal mortality rate for Indian women, we use the ratio obtained in the National Family and Health Survey (NFHS). This does not provide a direct mortality rate for our target group, but rather the number of maternal deaths per 100,000 live births. The calculation of the required mortality rate is set out in Box 1 (p. 12). The method for calculating the number of stillbirths and child deaths associated with this maternal mortality is described in Box 2 (p. 12).

3.2.3 Remaining life expectancy

Information on the average remaining life expectancy for different gender and age groups is available from standard life tables (e.g. WHO 2001). The average remaining life expectancy can be calculated given the average age of death from each cause for a particular target group.

For maternal mortality, the average age of death is assumed to be the average age of women at childbirth, which in most cases needs to be calculated from health and population data. For stillbirths the average age of death for the child is 0 years. For child death, the average age at death can be assumed to be less than 1 year because most child deaths occur among infants.[12]

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[9] Individual studies suggest that diarrhea, acute respiratory infection, stunting, and maternal mortality are associated with VAD, but causality has not been shown (e.g., Vijayaraghavan 1999, Sachdev 1999, Ronsmans et al. 1999, West, Jr, et al. 1999, Caulfield et al. 2004). Therefore, we do not include them as functional outcomes. A standard reference for VAD and diseases is Sommer and West (1996).

[10] For more information about maternal mortality rates and their calculation please consult AbouZahr and Wardlaw (2003) and Stanton et al. (2001).

[11] Cf. footnote 7.

[12] In the 1999 data of the Sample Registration System (Registrar General 2001), on an all India basis 75.2 percent of under five deaths occurred below 1 year of age, and 64.3 percent of all infant (≤12 months) deaths occurred before 28 days of age.

BOX 1

Calculating maternal mortality attributable to IDA

The maternal mortality ratio, according to the International Institute for Population Sciences (IIPS 2000), is defined as the number of deaths among women aged 15–49 years per 100,000 live births. As noted in the text above, "live births" are not defined as a target group in the analysis described here. Therefore, to obtain a mortality rate that can be used within the DALY formula, we use the following approach:

In India the crude birth rate is 27.2 per 1,000 and 91.9 percent of all pregnancies result in a live birth. The average maternal mortality ratio is 540 deaths per 100,000 live births (IIPS 2000). Therefore, based on the total population size, the maternal mortality rate equals (27.2/1,000) * 0.919 * (540/100,000) * 0.05, where the first term in parentheses gives the proportion of births (for the total population), the next term gives the proportion of live births, the second term in parentheses gives the proportion of maternal deaths as a proportion of live births, and the last term gives the fraction of these deaths attributable to IDA. For this calculation, the entire population represents the target group because the crude birth rate refers to the whole population (and, thus, the maternal mortality rate refers to the number of live births that result from applying the crude birth rate to the whole population size).

BOX 2

Number of stillbirths and child deaths associated with maternal mortality

For India, the stillbirth rate is assumed to be 30 percent of the pregnancies of women who died during childbirth due to iron deficiency, i.e., if the mother dies during childbirth only 70 percent of the newborns are born alive. In this case the reference group (denominator) is the result of the calculation of maternal mortality in Box 1, i.e., the number of women who do not survive pregnancy because of iron deficiency, and not the actual target group of infants.*

Additionally, the 70 percent of infants who survive also have a greater mortality risk during infancy because they are not breastfed. The Bellagio Child Survival Study Group (Jones et al. 2003) found that universal coverage with breastfeeding can prevent 13 percent of under-five deaths. The under-five mortality rate for India is 94.9 per 1,000. Given that 55.2 percent of the children under the age of 4 months are exclusively breastfed (IIPS 2000), we can assume that 55 percent of live newborns whose mothers died during childbirth would have been breastfed if their mothers had survived. Putting this information together, the number of these child deaths is given by: number of maternal deaths * (0.7 * 0.13 * 0.0949 * 0.55).

* The death of a mother is likely to be followed by the death of about 50 percent of her children under the age of 5 years (Measham and Gillespie 1998). Forty percent of all maternal perinatal deaths are linked to anemia. Favorable pregnancy outcomes occur 30–45 percent less often in anemic mothers, and their infants have less than one-half of normal iron reserves (Bothwell and Charlton 1981).

3.2.4 Incidence rates

Obtaining information on incidence rates for the functional outcomes needed in the analyses may prove to be a challenge. If prevalence rates are available – keeping in mind that the incidence rate refers to a "flow" while the prevalence rate refers to a "stock" – they can be used to approximate incidence rates by using the simplified formula:

incidence = prevalence / duration.

Functional outcomes related to iron deficiency are considered permanent, unless iron deficiency is treated. For permanent and long-term diseases, the formula to the left is less suitable because it neglects the effect of population growth. To obtain the incidence rate for the target group as a whole, one solution is to apply the prevalence rate to the first age cohort of a target group and to divide the size of the target group by this number. Getting the incidence rate right is crucial, as Brown (1996, p.13) underlines in the summary to the GBD:

> "Ultimately, however, the accuracy of the underlying basic epidemiological data from which disease burden is calculated will influence the final results much more than the discount rate, the age weight, or the disability weighting method. If, for example, estimates of the incidence of blindness are off by a factor of two, then it follows that this will be reflected in the results. The GBD researchers conclude that researchers' efforts should be invested in improving the basic data rather than in spending excessive energy on analyzing the effects of small adjustments to the measure itself."

For iron deficiency, all diseases are defined in relation to either moderate or severe IDA. Therefore, it suffices to use information on the incidence or prevalence of IDA to derive incidence rates for the functional outcomes of interest: everybody who suffers from moderate or severe IDA is considered to be at risk of both impaired physical activity and impaired mental development, i.e., the corresponding prevalence rate for IDA can be applied 1:1 to these functional outcomes.[13] Possible sources of, and ways to extrapolate, prevalence data from existing data are given in Box 3.

3.2.5 Disability weights

One of the more crucial and difficult issues is to establish disability weights for different functional outcomes, as these weights put different health states in relation to each other and to full health and death – the feature that allows combining morbidity and mortality in a single index. Weighting, however, implies a valuation of this health state and is subject to criticism (Groce et al. 1999, Arnesen and Nord 1999, Anand and Hanson 1998, Musgrove 2000). However, any decision in the field of health policy implies a valuation; with the DALY method this valuation simply becomes transparent. Moreover, the disability weights used in the GBD were the result of a special meeting convened at the WHO and sponsored by the World Bank, in which a rigorous, consultative protocol was followed. The weights arrived at by this process also matched closely with the pooled results of previous exercises (Murray 1996).

BOX 3

PREVALENCE RATES

With our approach, prevalence rates are needed for both moderate and severe (but not mild) IDA for the target groups (children ≤ 5 years, children 6–14 years, women 15+ years, and men 15+ years). The most likely source of these data are the Demographic and Health Surveys (DHS) and the UNICEF Multiple Indicator Cluster Surveys (MICS), where available.* In India, as in nearly all countries, data are available for anemia rather than IDA. Because anemia has several causes, the experts at the Kathmandu workshop specified that it is reasonable to attribute 50 percent of anemia to iron deficiency; for infants this figure increases to 60 percent (INACG 2003). In areas where other factors contributing to anemia play a greater role (e.g., incidence of hookworm, AIDS, etc.), this range of 50–60 percent may need to be modified after consulting with local experts.

Where national health and nutrition surveys are not available, other data sources might have to be used. Even when DHS are available, the data may not contain complete information. For example, for India, the National Family and Health Survey (NFHS) only collected data for children < 3 years and their mothers; thus these data had to be combined with data from the National Institute of Nutrition (NIN) to obtain prevalence data for all the target groups outlined above. The evidence from nutrition surveys in each country will be a need to collated, even though these are typically based on sample sizes that are much smaller than those in the DHS. IDA prevalence data for adult men are rarely available for any country. The experts at the Kathmandu workshop judged that, in situations where more accurate figures are lacking, prevalence rates for men can be approximated by taking 50 percent of the corresponding prevalence rate for women.

* DHS data at www.measureprogram.org and MICS data at www.unicef.org/nutrition/index_statistics.html.
The Micronutrient Initiative summarizes country-specific data at www.mn-net.org/idastat.

[13] It should be mentioned, however, that this 1:1 relationship only applies because we use average functional outcomes that are caused by IDA, not extreme cases.

The disability weights given in the GBD served as benchmarks for the deliberations at the Kathmandu workshop, which resulted in the following disability weights for the functional outcomes and target groups considered in this handbook:

- for impaired physical activity occurring at moderate levels of IDA, the disability weight is 0.011 for all target groups,
- for impaired physical activity occurring at severe levels of IDA, the disability weights are 0.087 and 0.09 for children in both age groups and adults, respectively,
- for impaired mental development occurring at moderate levels of IDA, the disability weight is 0.006 for children ≤ 5 years old only, and
- for impaired mental development occurring at severe levels of IDA, the disability weight is 0.024 for children ≤ 5 years old only.

Note that these weights are deemed universally applicable; that is, they are not country-specific. Further information on the procedure followed to arrive at these disability weights is given in Annex 5.

3.2.6 Duration of disease

This component of the DALY formula corresponds to the "remaining life expectancy" used in the calculation of the YLL. For permanent disabilities this duration can be calculated the same way: subtracting the average age of onset of the disability from the average remaining life expectancy.[14] Impaired mental development resulting from iron deficiency is considered to be a permanent disability.

Impaired physical activity resulting from iron deficiency can be reversed by iron treatment, but if left untreated, the condition will persist. In the framework of the DALY approach, the crucial question when determining whether a disability is temporary or permanent is not only whether the disease in question is treatable, but also whether it is actually treated. In the Kathmandu workshop it was agreed that, for India, impaired physical activity can be considered to be quasi-permanent (at least within the age bracket) because iron intervention programs exist only for pregnant women, and even for this group there is no evidence that iron intake is increasing. For the first target age group, the average age of onset was set at 6 months, which is the age at which an infant's iron requirements can no longer be met by breast milk alone. Given the quasi-permanent character of the condition, the duration of "impaired physical activity" is 5.5 years, i.e., the remaining time spent in the target age group. The duration for the second target age group (children aged 6–14 years) is set at 8 years, which is the total time spent in the target group by any individual. For the "adult" target group, the age of onset is set at 15 years and, given the permanent character of the condition, the duration equals the remaining life expectancy at this age. Clearly this is a simplification: a certain percentage of children aged ≤ 5 years suffers from, say, impaired physical activity that is caused by IDA. In India the prevalence rate of impaired physical activity is lower for the next target group, children aged 6–14 years. However, it is obvious that affected children will not immediately recover on their sixth birthday. It might well be that the incidence rate of impaired physical activity is higher while the duration of the condition is shorter (which results in the same prevalence rate). Nevertheless, the experts at the Kathmandu workshop were more at ease with the simplification we present here than with making assumptions about the "true" incidence rates and the corresponding duration of the condition.

3.3 Data requirements for zinc[15]

(see Annex 3 for a summary)

3.3.1 Size of target groups

Information on the size of the target groups is available in population and demographic statistics of international organizations, national census bureaus, etc. For India, we use the 2001 national census data.

[14] Cf. section 3.2.3 Remaining life expectancy.

[15] Some of the information given here duplicates information given earlier in this paper for iron.

3.3.2 Mortality rates

The rates of mortality that can be attributed to zinc deficiency – deaths due to, amongst other conditions, diarrhea and pneumonia – are given as a proportion of overall mortality for specific age groups. It is therefore (only) necessary to obtain these general, age-specific mortality rates for the country or region to be analyzed. Mortality rates can be taken from national census data, from health statistics, or from data generated by international organizations and agencies.[16] As a rule, infant and under-five mortality rates are given per 1,000 live births, i.e., in this case the rate should not be applied to the size of the actual target group but to the number of live births. Moreover, the under-five mortality rate already includes the infant mortality rate; hence the latter has to be calculated out of the former if the mortality among 1–5 year olds is not reported separately.

According to Jones et al. (2003), 4 percent of under-five deaths (i.e. of both infant and child mortality – c.f. 3.1.2) can be prevented if all children have sufficient intakes of zinc. Therefore 4 percent is the rate that has to be applied to the general mortality rates to derive the zinc-specific mortality rates that can be used in the DALY calculations.[17] This 4 percent covers all deaths that can be attributed to zinc deficiency, regardless of whether these deaths are induced by diarrhea or pneumonia.

3.3.3 Remaining life expectancy

Information on the average remaining life expectancy for different gender and age groups is available from standard life tables (e.g. WHO 2001). The average remaining life expectancy can be calculated given the average age of death from each cause for a particular target group.

The average ages of death are assumed to be 8 months for infants and 2 years for children aged 1–5 years. (The life table we use gives life expectancies for larger age brackets only, so the exact age of death does not matter provided it can be assumed to fall within the given brackets.)

3.3.4 Incidence rates

To derive incidence rates for functional outcomes related to iron deficiency, we looked at the incidence (or prevalence) rates of IDA. For zinc deficiency, however, representative prevalence data are rarely available and hence a different approach is taken, namely we look at the general incidence rates of the functional outcomes and attribute part of them to zinc deficiency (Box 4, p. 16).

Based on Kosek et al. (2003), the average incidence rate for diarrhea is assumed to be 2.6 episodes per infant and 1.3 episodes per child per year.[18] Of all cases of diarrhea, 18 percent can be attributed to zinc deficiency (Bhutta et al. 1999). Hence the incidence rate for diarrhea related to zinc deficiency is 2.6 * 0.18 = 0.47 for infants and 1.3 * 0.18 = 0.23 for children.

According to Rudan et al. (in press), the median incidence of acute lower respiratory infections in developing countries is 0.29 episodes per child per year. Of all cases of pneumonia or acute respiratory infection, 41 percent can be attributed to zinc deficiency (Bhutta et al. 1999).[19] Therefore the incidence rate for pneumonia related to zinc deficiency can be calculated as 0.29 * 0.41 = 0.12.

Based on Brown et al. (2002), two different approaches can be considered in determining the incidence of stunting due to zinc deficiency: (a) assume that all infants with zinc deficiency (defined as having less than 60 µg/dL serum zinc) are at risk of being stunted.[20] In this case the incidence rate of zinc deficiency among infants corresponds to the assumed incidence rate of zinc-related stunting; i.e., only the incidence rate of zinc deficiency needs to be determined.

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[16] See for example http://www.unicef.org/sowc04/, http://www.who.int/health_topics/mortality/, http://hdr.undp.org/statistics/data/, http://www.worldbank.org/data/, http://www.usaid.gov/ ("country locator"), or http://www.cia.gov/cia/publications/factbook/.

[17] Four percent is the more conservative value given.

[18] "Child" here always relates to the 1-5 year old target group, in contrast to the target group "infants".

[19] Also see Brooks et al. (2004) for the effect of zinc on pneumonia outcomes.

[20] Hotz and Brown (2004) give zinc deficiency rates based on alternative measures, using "pre-existing suggesting information".

(b) Use the incidence of stunting (height-for-age below –2 SD) in a country and assume that with adequate zinc intake the stunted children would be on average 1 cm taller.

3.3.5 Disability weights

As with iron deficiency, the disability weights given in the GBD also serve as benchmarks for those used for the functional outcomes and target groups related to zinc deficiency:

- for diarrhea, the disability weight is 0.2 for infants and 0.15 for children,
- for pneumonia, the disability weight is 0.3 for infants and 0.2 for children,
- for stunting, the disability weight is (a) 0.001 if stunting is derived from zinc deficiency and if it is assumed that with adequate zinc intake this stunting could be eradicated completely, and (b) 0.0001 if it is assumed that adequate zinc intake would reduce all stunting by 1 cm. These weights apply to infants only (as stunting is assumed to be a permanent condition).

Again, these weights are deemed universally applicable; that is, they are not country-specific. Further information on the procedure followed to arrive at these disability weights is given in Annex 5.

BOX 4

DERIVING INCIDENCE RATES – AN EXAMPLE

The incidence rates for functional outcomes of a micronutrient deficiency can be derived in one of two ways: Either start with the incidence of the deficiency and attribute fractions of it to the functional outcomes, or start from the general incidence of a functional outcome and attribute fractions of it to the deficiency. If, for example, we assume:
a) The incidence of a micronutrient deficiency amongst "children" is 20 percent, and 50 percent of all children with the deficiency become stunted, i.e., in a target population of 100 million children, 20 million children are deficient, and 10 million deficient children are expected to become stunted because of being micronutrient deficient. Without the deficiency, 10 million fewer children would be stunted, and an unspecified number of children would be stunted from other causes.
b) The incidence of stunting amongst "children" is 30 percent, and 30 percent of all stunted children are that way because they are deficient, i.e., in a target population of 100 million children, 30 million children are stunted, and 9 million stunted children are expected to have become stunted because of the deficiency. Without the deficiency, 9 million fewer children would be stunted, while 21 million children would be stunted from other causes.

3.3.6 Duration of disease

As explained in Section 3.2.6, this component of the DALY formula corresponds to the "remaining life expectancy" used for calculating the YLL. Contrary to the functional outcomes related to iron deficiency, which were all considered permanent, the functional outcomes related to zinc deficiency are mostly temporary.

Based on Kosek et al. (2003) and Bhandari et al. (1994), the duration of each case of diarrhea is assumed to be 3 days for infants and 4 days for children 1-5 years (i.e., 3/365 and 4/365 on a yearly basis, respectively). For pneumonia, the average duration of each case is assumed to be 4 days for both infants and children (i.e., 4/365 on a yearly basis), based on the expert opinion of the participants of the Kathmandu workshop and on Qazi, S. (WHO, personal communication 2004).

Stunting is considered to be permanent; the age of onset is assumed to be 6 months (Shrimpton et al. 2001). Accordingly, the duration of stunting corresponds to the remaining life expectancy at the age of onset.

3.4 Data requirements for vitamin A

(see Annex 4 for a summary)

3.4.1 Size of target groups

Please see Section 3.2.1.

3.4.2 Mortality rates

The mortality rate for children that can be attributed to VAD is given as a proportion of overall mortality. It is therefore necessary to obtain the overall, age-specific mortality rate for the country or region to be analyzed (c.f. 3.3.2, although in 3.3.2 mortality rates for infants and children under 5 years old are differentiated).

According to Jones et al. (2003), the mortality rate of under-fives would be reduced by two percent if all children had sufficient intake of VA and an additional one percent of all under-five deaths could be avoided if all children receive therapeutic doses of VA for pertinent infections. Hence, a combined figure of three percent has to be used to determine the burden of VAD in the *status quo*. However, when calculating the potential impact of biofortification the picture becomes somewhat different. Biofortification can provide additional amounts of vitamin A precursors, among which beta-carotene is the most important. These provitamins A prevent VA deficiency because the human body converts them into VA. However, crops biofortified with beta-carotene cannot cure or treat deficiency. In other words, the potential impact of biofortification is limited to a reduction of the 2 percent of under-five deaths that occur due to insufficient VA body stores (Figure 1).

3.4.3 Remaining life expectancy

The average age of death for VAD-related under-five mortality is assumed to be 1 year. The remaining life expectancy can be calculated from standard life tables (see Section 3.2.3).

3.4.4 Incidence rates

For VAD, prevalence rates of nightblindness, corneal scarring, and measles are needed. For information on transforming prevalence rates into incidence rates or calculating incidence rates, please see Sections 3.2.4 and 3.3.4, respectively.

It is assumed that all nightblindness among pregnant and lactating women and all children is due to VAD. For corneal scarring, 20 percent of all cases amongst children are assumed to be due to VAD, of which 50 percent of the children are blind. This means that half of the children with corneal scarring will have a permanent but nondebilitating condition (visual impairment), whereas the other half will be blind.

For measles, it is assumed that 20 percent of all cases are due to VAD and complications can be expected in 50 percent of these cases. (When obtaining measles morbidity data, it is important to check with local health experts regarding the percentage of measles cases that are considered to be reported. In India for example, it is thought that perhaps as few as 30 percent of all cases of measles are actually reported; in such cases the morbidity data needs to be adapted accordingly.[21])

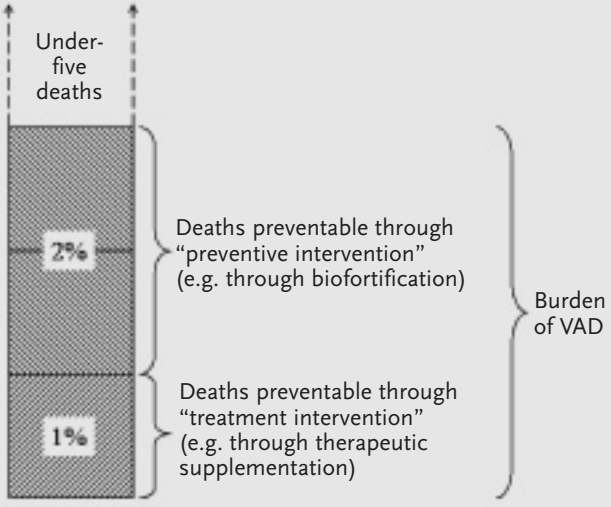
3.4.5 Disability weights

The disability weights for functional outcomes of VAD are:

- for nightblindness 0.1 for women and 0.05 children,
- for corneal scarring 0.2 for children only,
- for blindness 0.5 for children only,
- for measles and for measles with complications 0.35 and 0.7, respectively, for children only.

FIGURE 1

UNDER-FIVE MORTALITY AND VAD



Source: Own illustration, based on Jones et al. (2003).

[21] The WHO may release country-specific estimates of the burden of measles shortly.

Again, these weights are deemed universally applicable (c.f. 3.2.5).

3.4.6 Duration of disease

Nightblindness during pregnancy is expected to continue through the first months of lactation; its duration is assumed to be 5 months for pregnant and 6 months for lactating women. For children, night-blindness is assumed to appear 1 year after birth and then last for 1 year – by which time the child will be on the family diet and be at less risk of succumbing to the debilitating effects of infection compared with the earlier period.

Children are assumed to acquire corneal scars at the age of 1 year. The 50 percent of children who go blind due to corneal scarring are assumed to become blind at the same age. Both corneal scars and blindness are permanent conditions, i.e., the duration of these two functional outcomes corresponds to the remaining life expectancy (c.f. 3.2.6).

Measles is a temporary disease and its duration is assumed to be 10 days. When complications set in, the duration is assumed to be 20 days.

3.5 Food intake data

With the information obtained so far it is possible to calculate the DALYs currently lost due to iron and zinc deficiency or to VAD, i.e., it is possible to establish the *status quo*. To quantify the impact of biofortification of staple crops on health outcomes, it is necessary to frame a counterfactual situation in which people eat biofortified food. In this case, the contribution of a biofortified food to the improvement in the dietary intake of the micronutrient in question (i.e., of iron, zinc or VA) requires knowledge of the difference in intake of the micronutrient between the situation where the biofortified crop is consumed and the situation under the *status quo*. This requires making a number of assumptions, which are outlined below.

Calculating micronutrient intakes requires detailed meal-based individual-level food intake data and appropriate food composition tables, from which the total micronutrient intake for each individual can be computed. In this context the biggest challenge is access to food intake data.

Collecting data on dietary intake – certainly of the principal staples – for each target group and income level is critical. Ideally, we want to characterize the diet in its entirety because the bioavailability of a micro-nutrient depends on the mix of foods consumed at the same time. For iron, the consumption of iron absorption enhancers (i.e., meat and vitamin C-rich foods) and iron absorption inhibitors (i.e., tannins in tea, and phytate in high extraction cereal flours and legumes) is especially important; for zinc, absorption inhibitors (i.e., phytate in high extraction cereal flours and in legumes) are important; and for VA, the amount of fat in the meal is important.[22] Dietary intake surveys are likely to be carried out in the future as part of the evaluation of the use of HarvestPlus crops; thus it may be adequate to use existing data from appropriate surveys in the *ex ante* impact studies. The ideal would be individual-level surveys for each of the target groups mentioned above. However, such surveys are rare and data on household-level food intakes, rather than individual intakes, are more likely to be available. Irrespective of the level of the survey, a cross-tabulation by income level or socio-economic group and place of residence (rural or urban) is useful. In India, we are using the National Sample Survey Organization's household-level survey on food consumption (120,000 households and about 150 foodstuffs) to determine dietary patterns and micronutrient intakes.[23] Because this information pertains to the household level, we use either demographic compositional details to elicit per-equivalent consumption, or other, more limited in coverage, individual-level surveys to apportion consumption to the target groups being considered here.

[22] Only 5-10 g of fat is needed (Olsen 1987, IUNS Committee II/6 1992).

[23] There is a difference between food expenditure and food intake data. The latter include 24-hour-recall or data from 3-day food-weighing and are much more reliable (Gibson 1990). However, food intake data are difficult to obtain, and are often not available because such surveys are costly and not carried out on a routine basis.

With respect to the food composition tables, ideally national tables should be used but, where they do not exist, tables specific to the region should be used as food composition values vary depending on the ecological environment, the variety, and the cooking method, among other things. The food composition information contained in the WorldFood Dietary Assessment System can also be used to extrapolate values for different foodstuffs in different countries. These data, which come from six countries (Egypt, India, Indonesia, Kenya, Mexico, and Senegal), have been carefully reviewed for methodological quality and are generally accepted as being among the best. They are available at:
http://www.fao.org/infoods/software_worldfood_en.stm

Where detailed food intake data are not available, a less precise approach is to use average consumption data, as Zimmerman and Qaim (2004) have done. In this case the issue of "dose-response" becomes relevant (see Section 4.3).

3.6 Cost of breeding biofortified staple crops

As mentioned in Section 2.5, the costs to be included in a cost-benefit analysis comprise R&D costs associated with adding the additional trait to regular breeding efforts at the international level, as well as country-specific costs for adaptive breeding and dissemination.

The inclusion of country-specific costs is clear. However, in many cases the basic breeding efforts take place at CGIAR centers and/or collaborating institutes outside the target countries. How much of these costs to include in cost-benefit analyses depends on the scope of the study. In a cross-country study, the full cost would need to be considered. For individual countries, it may be justified to use a marginal approach and, in the case of less populous countries, to consider only the country-specific costs. In bigger countries, inclusion of only marginal costs would inflate the benefit-cost ratios. In this case, a reasonable share of the basic breeding costs should be included. This share can be attributed according to the country's share of crop production in the developing country total or according to the country's share of deficient individuals – keeping in mind that all countries and all societies that consume the crop are potential beneficiaries of basic R&D.

4 | Quantifying the potential impact of biofortification

4.1 Taking account of the micronutrient content and coverage rate

Once the micronutrient intake for the regular diet has been ascertained, five issues must be clarified before the micronutrient intake of the diet containing the biofortified crop can be calculated:

1) How much additional micronutrient is in the biofortified plant, and where is it located?
2) What post-harvest losses of the micronutrient can be expected during transport and storage?
3) What is the health benefit of the increased micronutrient intake?
4) What is the production share of biofortified varieties or, as this information is unlikely to be available, what is the coverage rate for the cultivation of the biofortified crop?
5) Who are the consumers and how much of the biofortified crop do they eat?

The first question can (and probably has to) be answered by the plant breeders developing the micronutrient-rich varieties. Knowing how much additional micronutrient is in the biofortified crop, and where it occurs in the grain/bean, is important for determining the nutrient composition values for food products made from the crop in question. If all the additional micronutrient is in the grain husk, for example, the iron or zinc content will change only for those food items where the husk is consumed (i.e., probably not for many). If, however, the iron content in the endosperm of wheat is increased by 0.5 mg per 100 grams for example, then the bioconversion factor of all wheat-based products will be increased by 0.5 mg per 100 grams. In the case of VA, biofortified crops are bred for increased levels of beta-carotene, the most important source of provitamin A. The bioconversion factor of beta-carotene to VA in the HarvestPlus crops can be considered to be 12:1.[24]

Post-harvest losses of micronutrients will occur with beta-carotene, especially where the crops are exposed to air and light. Cooking too will result in additional losses. For minerals, washing rice or beans and/or cooking in excess water that is thrown away may result in the minerals being leached into the water and thus lost. For milled grain, the extraction rate of the flour determines how much of minerals are lost. Some food tables specify the food composition after processing and/or cooking while others simply refer to the composition of the unprocessed food. It is important to note how the food was described in the food composition table used.

The third question is covered in Sections 4.2 and 4.3. Information on the likely coverage rate of the biofortified crop needs to be obtained separately for each region, perhaps from national extension agencies and agricultural experts or from the center where the plant was bred.

Given that biofortified varieties will not make up 100 percent of a particular staple crop, it is necessary to determine who consumes how much of the biofortified crop when calculating the "new" micronutrient intake. Two basic assumptions are possible, in accordance with the coverage rate of the crop in cultivation:[25] (i) a certain percentage of consumers switch completely to the biofortified crop, while the remainder continue to consume only the unfortified crop, and (ii) all consumers replace a certain percentage of their consumption with the biofortified crop and continue to consume some unfortified crop in parallel. We suggest following the second assumption, at least for iron-rich and zinc-rich crops, because such crops have no

[24] Where beta-carotene does not play a role in photosynthesis (e.g., sweetpotato and cassava roots or maize kernels), it is located in the cell chromoplasts (Czygan, 1980), where it is found in lipid droplets or bound to a protein that is released during cooking. The amount of beta-carotene from foods that is converted to vitamin A depends on a number of factors (West and Castenmiller 1998) that have been characterized as bioaccessibility, bioavailability, bioconversion, and bioefficacy (Tanumihardjo 2002). Bioaccessibility is the fraction of total dietary carotenoid made available for absorption in the gut. Bioavailability is the fraction of dietary carotenoid absorbed from food. Bioconversion is the ratio of retinol formed to total provitamin A carotenoid absorbed. Bioefficacy is the ratio of retinol formed to the total provitamin A carotenoid in the diet.

[25] Here the RDA is not seen as the point where there is no risk at all, but – following the definition of RDA levels – as point where the greatest majority of the population is not at risk.

visible signs showing that the crop is biofortified; hence, provided there are no separate marketing channels, consumers who purchase the crop will consume both varieties in parallel. Moreover, producer-consumers will likely not switch all of their cultivation to biofortified crops; instead, they may grow different varieties in parallel. Therefore, the share of biofortified crops in consumption can be approximated by the coverage rate for the cultivation of the crop in question. Hence the new composition value can be multiplied by the coverage rate and applied to all consumers across the board.

Issues of producer and consumer acceptance must be considered when the agronomic or sensory characteristics of biofortified varieties differ from those of non-biofortified varieties. Although detectable sensory changes are not expected in crops biofortified with iron or zinc, increasing the beta-carotene content will cause the crop to become yellow, more yellow, or even orange. A close examination of case studies and pilot testing are possible means to arrive at defendable assumptions. Where these do not exist, expert opinions can be sought.

Multiplying the (expected) percent increase in the micronutrient content of the crop with the (assumed) coverage rate and adding this value to the micronutrient intake of the *status quo* yields the intake under the "with" scenario. The resulting modified micronutrient intake can then be used to derive the new prevalence rates for the diseases that are related to micronutrient deficiency. (Here the assumption is that the bioavailability of the micronutrient does not change).

4.2 Cut-off levels for iron intake and prevalence rates of IDA

This section describes how to obtain cut-off levels for iron intake to derive new prevalence rates of moderate and severe IDA. For IDA this approach is appropriate because there are several levels of severity – mild, moderate and severe. While there is insufficient scientific evidence to attribute adverse functional outcomes to mild IDA, the use of moderate and severe IDA takes account of the nonlinear association between health outcomes and increased iron intake. Because zinc and VA deficiency do not have such a classification system, the approach described in Section 4.3 has to be applied.

If, as in the case of India, detailed household data from representative surveys are available, each individual's iron intake can be computed (via the construction of adult equivalents). This intake data can then be used to rank individuals in each target group (according to the proportion of the recommended dietary allowance (RDA) for iron they attain with the current diet). The individual with the lowest intake is assumed to be the most deficient individual, the 10 percent of the individuals with the lowest intakes are assumed to be the most deficient 10 percent, etc.

Because the calculations are based on representative data, the prevalence rate for both moderate and severe IDA can be applied to each ranked target group. This approach will determine the individuals who have either moderate or severe IDA. If, say, the prevalence rate for severe IDA in the target group aged 6–14 years is 3 percent, then the 3 percent of children with the lowest iron intakes are assumed to suffer from severe IDA. The iron intake of the next individual (ranked 3 percent plus 1) can be taken as the cut-off for iron intake for this target group below which severe IDA can be expected.

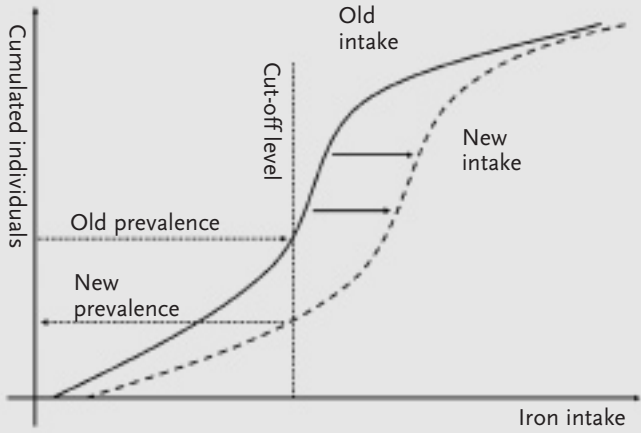
Figure 2 (p. 22) depicts the approach of deriving new prevalence rates from improved iron intakes. The individuals are ranked according to their iron intake; the prevalence rate determines up to which intake (cut-off level) of iron an individual is considered to be deficient. Improving the iron intake shifts the curve to the right, which implies that more individuals have intakes above the critical cut-off level. The individuals who remain below the cut-off level determine the new prevalence rate. This exercise needs to be carried out for the prevalence rates of both moderate and severe IDA for all target groups. These new prevalence rates can then be used in the calculation of the DALYs lost under the "with" scenario.

If individual-level dietary intake data are not available, or if the analysis is being done with average intakes only, the "dose-response" has to be considered when

relating the increased iron intake to improved functional outcomes in order to account for the assumed nonlinear association between iron intake and health outcome. This concept is described in the following section.

FIGURE 2

DERIVING ONE EXEMPLARY CUT-OFF LEVEL FOR IDA FROM IRON INTAKE



Source: Own illustration.

4.3 The concept of dose-response and the impact of biofortification

The principal issue associated with the concept of the dose-response is the nonlinearity and concavity of the association between micronutrient intake and f unctional outcome. For example, if two individuals consume the same amount (dose) of a bioavailable micronutrient, the individual with the higher level of deficiency is expected to show a relatively bigger, positive response with regard to his or her health status than the individual with the lower level of deficiency. This is explained in Zimmermann and Qaim (2004) and applied to VA; for iron, the association is given in Hallberg et al. (2000, Fig. 3, p. 665). According to the experts at the Kathmandu meeting, a similar relationship can also be assumed for zinc. In the following, for simplicity, the procedure is described for zinc only.
To measure the impact of biofortification on the health effects of zinc deficiency it is important to determine how much an incremental increase in zinc intake decreases the adverse functional outcomes caused by the deficiency. The concept of dose-response can be applied to capture the magnitude of the effect of biofortification on health outcomes; Figure 3 (p. 23), adapted from Zimmermann and Qaim (2004), shows this association.

If the intake of zinc is below the RDA, an increase in intake (through the consumption of biofortified crops) decreases the magnitude and/or severity of the adverse health outcomes of zinc deficiency.[26] At the other end of the scale, the tolerable upper limits for zinc intake are 2 to 4 times higher than the corresponding RDA levels (for infants and adults respectively) (IOM 2002); hence, negative health effects are not expected because such levels cannot be attained though biofortification.[27]

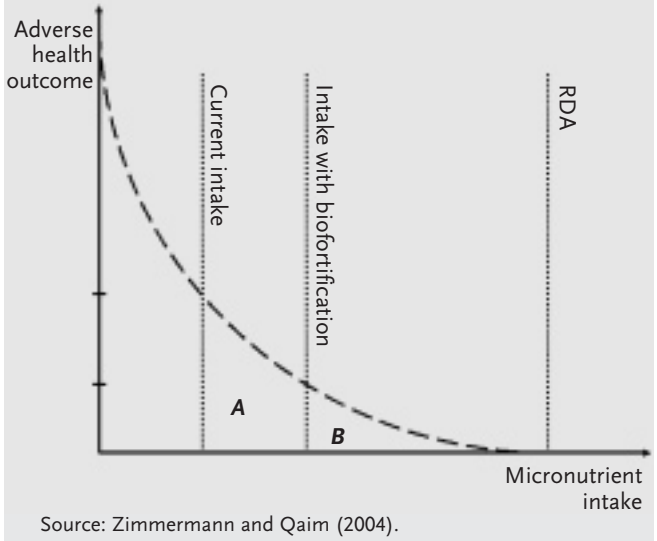
Given the shape of the curve, the efficacy of biofortification can be calculated as the ratio of area A divided by the combined area of $A + B$ (Figure 3, p. 23). Thus the efficacy "can take any value between zero and one, whereby it is positively correlated with the convexity of the curve" (Zimmermann and Qaim 2004, p. 158).

[26] Here the RDA is not seen as the point where there is no risk at all, but – following the definition of RDA levels – as point where the greatest majority of the population is not at risk.

[27] In the case of vitamin A, the amount of beta-carotene that the human body converts into retinol is homeostatically controlled, which means the body does not convert more than it needs and, except for cases involving rare conditions, toxicity from food is unknown. Similarly, uptake of dietary iron is homeostatically controlled and no negative health effects have been reported for increased intakes of iron from plant food sources, certainly not at the intake levels that can be reached with biofortified food. Dangerously high levels of iron can accumulate in the body due to accidental ingestion, which usually occurs when young children take iron pills prescribed for their mothers; the Centers for Disease Control and Prevention state that accidental iron poisoning is one of the leading causes of poisoning in children (Litovitz et al. 1992). Otherwise, iron overload is associated with several genetic diseases including hemochromatosis, which affects approximately 1 in 250 individuals of northern European descent (Burke et al. 2000). This is because individuals with hemochromatosis absorb iron very efficiently, which can result in a build-up of excess iron and can cause organ damage (IOM 2002, Bothwell et al. 1979, Bothwell and MacPhail 1998, Halliday 1998, and Brittenham 1994). Iron supplementation – in which much higher doses of iron are delivered than by fortified food or even by biofortified food – may accelerate the effects of hemochromatosis, an important reason why adult men and postmenopausal women who are not iron deficient should not take iron supplements. Individuals with blood disorders who require frequent blood transfusions are also at risk of iron overload and should not take iron supplements. However, this says nothing about the much lower quantities absorbed from (biofortified) food. Iron supplementation has also been shown not to increase the risk of developing infections (Gera and Sachdev 2002).

FIGURE 3

RELATIONSHIP BETWEEN MICRONUTRIENT INTAKE AND HEALTH OUTCOME



Source: Zimmermann and Qaim (2004).

In the absence of a universally accepted, concrete specification for this curve (for either iron or zinc), we follow Zimmermann and Qaim (2004) and use

$$H(x) = 1/x - 1/RDA$$

where *H* denotes the adverse health outcome and *x* is the micronutrient intake. The efficacy (*E*) can then be calculated as the ratio of the areas *A* and *A* + *B*, where these areas are calculated using integrals; the solution is:

$$E = \frac{\ln\left(\frac{BI}{CI}\right) - \left(\frac{BI - CI}{RDA}\right)}{\ln\left(\frac{RDA}{CI}\right) - \left(\frac{RDA - CI}{RDA}\right)}$$

where *CI* is the current intake and *BI* is the intake with biofortification.

This formula can be applied to the intake data of each observation to obtain the efficacy of the biofortified crop for each individual.[28] Calculating the efficacy of the biofortified crop for each individual observation takes account of differing consumption patterns, whereas applying the formula to average data results in a loss of the information conveyed through the disaggregated data. Again, multiplying the (expected) percent increase in the zinc content of the crop with the (assumed) coverage rate and adding this value to the zinc intake of the *status quo* yields the intake under the "with" scenario. In the end, the average efficacy of the biofortified crop for the target group can be applied to the incidence rates of the adverse health outcomes that were specified above and the new incidence rates for the "with" scenario can thus be established.

4.4 Absolute health gains and the cost per DALY saved

Sections 4.2 and 4.3 both described ways to calculate the impact (response) of an increase in the intake (dose) of iron or zinc on health outcomes that are related to iron or zinc deficiency. The new incidence and prevalence rates derived for the "with" scenario are lower than those of the initial *status quo*. Hence, using these new rates in the calculation of the burden of iron or zinc deficiency will give a lower number of DALYs lost for the situation "with" biofortification. The difference between the number of DALYs for the situations with and without a particular biofortification intervention corresponds to the benefit – expressed in DALYs saved – of the intervention.

In discussing discounting (Section 2.2), we pointed out that the discount rate can have a considerable impact on the calculated result of an intervention, i.e., on the number of DALYs gained. One way to circumvent this drawback is to express the absolute number of DALYs gained as a fraction of the burden of a disease, i.e., of DALYs that are lost in the *status quo*, because the discount rate does not change this relative value. Hence, to present the result in an objective manner, it is recommendable to (also) report the relative reduction of the burden of the disease that can be achieved by the intervention. This type of reporting makes it possible to make statements regarding the benefits of

[28] In applying the formula one has to be careful that, by definition, for $CI \geq RDA$ the efficacy equals zero, while for $CI < RDA$ *and* $BI > RDA$ the figure for *BI* has to be replaced with *RDA*.

biofortification, for example "biofortification can reduce IDA by *X* percent". Such statements can clearly and persuasively convey the benefits of biofortification.

Once the number of DALYs saved has been established, the (discounted) costs of biofortification (c.f. Section 2.5) can be divided by the (discounted) number of DALYs saved to obtain their net present value – the "price" per DALY saved. Or, the other way around, the effectiveness of the intervention can also be expressed in DALYs saved per dollar spent. This measure can not only be quite compelling if it shows – if this is indeed the case – that saving one healthy life year can cost as little as a few dollars or even cents, it also circumvents the critical and ethically dubious issue of attaching a monetary value to a DALY, as is necessary in a conventional cost-benefit analysis. Nevertheless, cost-benefit analyses have a role to play; they should be carried out and their results should be reported (in a separate, additional chapter) in any analysis of biofortified crops. We suggest that these analyses cover 30 years; this is a reasonable time horizon for carrying out the R&D, testing and dissemination activities. In addition, after 30 years future costs and benefits are greatly diminished through discounting.

4.5 Monetary valuation of health gains and cost-benefit analyses

As has already been mentioned in Section 2.5, different approaches can be used to value a DALY:[29] (i) a standardized value such as US$1,000, as suggested by the World Bank (1994), or a value of US$500 can be used, (ii) country-specific annual per capita incomes can be used, as done by Zimmermann and Qaim (2004), or (iii) an approach based on value of life estimates can be used, e.g., "values of a statistical life" (VSL) and "values of a statistical injury" (VSI), which are ultimately founded in people's willingness-to-pay (WTP) for incremental reductions in their risk of dying or of suffering a non-fatal injury.

To make studies and results comparable across countries, as is the objective of the analyses of biofortification in the framework of HarvestPlus, using a standardized value for a DALY seems to be the most appropriate approach. Otherwise, from the viewpoint of total dollars saved, it would always be preferable to carry out interventions in richer countries and to neglect the poorer ones; this could certainly not be justified on ethical and equity grounds. On the other hand, attaching a monetary value to one DALY saved is not done to place a value on life as such; it is merely a pragmatic approach to be able to assess, compare and prioritize interventions that involve human life and health on the basis of familiar cost-benefit analyses and indicators: giving the "price" that has to be paid per DALY saved is certainly very obvious and striking, but it might be quite "abstract" for policy and decision makers who have to consider different interventions (not all being expressed in "dollars per DALY") and who are accustomed to absorbing information in monetary terms and to looking at rates of return first.[30]

It would, of course, be desirable to save all DALYs that can potentially be saved worldwide, but this is not feasible. Therefore, it seems reasonable to attach a value to a DALY that approximately reflects the (economic) possibilities of the countries in question. Looking at the per capita gross national product of developing countries makes values of US$500 and US$1,000 per DALY look plausible; in the case of India the GNI per capita for 2002 was US$480 (World Bank 2004). Zimmermann and Qaim (2004) used a value of US$1,030 (the annual per capita income in the Philippines).

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[29] For a current discussion that touches on this issue and for examples of the different approaches, see the Challenge Papers of the Copenhagen Consensus: for US$1,000 see Collier and Hoeffler (2004), for US$500 see Rijsberman (2004), and for the per capita approach as well as for the WTP approach see Mills and Shillcutt (2004). Two other relevant papers are Behrman et al. (2004) and Appleton (2004).

[30] This was, for example, underlined by Rosenberg (2002, pp. 369 and 371): "There are many ways to estimate the economic return on medical research investments [...] I was stunned by these results. I knew, of course, that research had given us longer and more productive lives. But I was always taught to consider these outcomes as incalculable. To have an economic value put on our national investment and to find that it was so large was surprising and exhilarating". It was also noted by Yip (2002, p. S804): "Most policy makers who shape decisions on funding and commitment to health programs do not have nutrition or health backgrounds. More likely, these policy leaders are versed in economics. For this reason, putting the principle argument in economic terms, rather than health or nutritional terms, may prove to be more useful to this particular audience".

However, the choice of the value to attach to one DALY can have an important impact on the size of the benefits and, consequently, on both the results of a cost-benefit analysis and on the magnitude of the rate of return. Therefore, to make this choice transparent (and to ensure broader comparability of the results with other, initially unrelated studies) we suggest using both US$500 and US$1,000 when carrying out cost-benefit analyses and when computing rates of return.

5 | Conclusion

This handbook was written to give an overview of the information requirements, possible approaches and reasonable assumptions needed to calculate the burden of iron-, zinc- and VA-deficiency in a region and to carry out an *ex ante* analysis of the costs and benefits of biofortification of staple food crops. The outlined framework is currently being used for *ex ante* evaluations of several crops and countries within the HarvestPlus mandate areas. Preliminary results indicate that the burden of the deficiencies considered amounts to several million DALYs lost per year, and that biofortification could save hundreds of thousands of DALYs.

Continuation of these analyses following a common framework should strengthen this evidence and more firmly establish the potential impact of biofortification. Such studies can help to (i) analyze the economic feasibility of biofortification, (ii) create awareness of this type of intervention and its potential benefits, (iii) direct research priorities, and (iv) identify problems and constraints early on. *Ex ante* analyses of the biofortification of staple food crops with iron, zinc and beta-carotene of the type proposed here will therefore provide valuable information to the research community, donors and policy makers alike.

Given that our own analyses are on-going, the approach proposed in this handbook is a work in progress and hence is prone to changes and modifications.

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Annex 1: Checklist of the sources needed to conduct the analysis

- Population surveys, demographic statistics, census data
- Standard life tables
- Nutrition and health surveys, health statistics
- Expert input from (local) medical doctors and/or nutritionists
- Food consumption data
- Food composition tables
- Expert input from breeders
- Expert input from extension agents and/or breeders

Annex 2: Checklist of the data requirements to calculate DALYs for iron deficiency

Functional outcomes related to IDA	Target groups	Size of target gr.	Mortality rate	Remaining life expect'y	Incidence rate	DA-weight	Duration of disease	Discount rate	Average age of death	Average age of onset	Average life expect'y
Impaired physical activity (moderate)	children ≤ 5	*Get from appropriate statistics.*	N/A	N/A	*Get from appropriate statistics, derive from prevalence rates or get serious estimates.*	0.011	*Calculate from average age of onset of disease for target group until end of target group or, until end of life.*	3%	N/A	6 months	*Use standard life tables.*
	children 6-14		N/A	N/A		0.011		3%	N/A	6 years	
	women 15+		N/A	N/A		0.011		3%	N/A	15 years	
	men 15+		N/A	N/A		0.011		3%	N/A	15 years	
Impaired physical activity (severe)	children ≤ 5		N/A	N/A	*"Moderate" and "severe" functional outcomes correspond to incidence rates of moderate and severe IDA.*	0.087		3%	N/A	6 months	
	children 6-14		N/A	N/A		0.087		3%	N/A	6 years	
	women 15+		N/A	N/A		0.090		3%	N/A	15 years	
	men 15+		N/A	N/A		0.090		3%	N/A	15 years	
Impaired mental development (moderate)	children ≤ 5		N/A	N/A		0.006		3%	N/A	5 years	
Impaired mental development (severe)	children ≤ 5		N/A	N/A		0.024		3%	N/A	5 years	
maternal mortality (IDA)	(live) births		*5% of all maternal mortality*	*Calculate from average age of death for target group and the average life expectancy.*	N/A	N/A	N/A	3%	*Use average age at delivery.*	N/A	
Stillbirth	pregnancies of women who died in childbirth b/c of IDA	*Get from maternal mortality (IDA) above.*	*30% of maternal mortality*		N/A	N/A	N/A	3%	0 years	N/A	
Child mortality			*share of exclusively breastfed infants * 0.13 * under-5-mortality * 0.7 of maternal mortality (IDA)*		N/A	N/A	N/A	3%	< 1 year	N/A	

Normal font = generally applicable, *italic = use of or association with country-specific data necessary.*

Annex 3: Checklist of the data requirements to calculate DALYs for zinc deficiency

Functional outcomes related to ZD	Target groups	Size of target gr.	Mortality rate	Remaining life expect'y	Incidence rate	DA-weight	Duration of disease	Discount rate	Average age of death	Average age of onset	Average life expect'y
Diarrhea	infants <1	*Get from appropriate statistics.*	N/A	N/A	2.6 * 0.18	0.2	3/365	3%	N/A	N/A	N/A
	children 1-5		N/A	N/A	1.3 * 0.18	0.15	4/365	3%	N/A	N/A	N/A
Pneumonia	infants <1		N/A	N/A	0.29 * 0.41	0.3	4/365	3%	N/A	N/A	N/A
	children 1-5		N/A	N/A	0.29 * 0.41	0.2	4/365	3%	N/A	N/A	N/A
Stunting	infants <1		N/A	N/A	*a) < 60 µg/dL serum zinc b) < -2 SD height-for-age*	a) 0.001 b) 0.0001	*remaining life expect'y*	3%	N/A	6 months	N/A
Increased mortality	infants <1	*Get from appropriate statistics, mind reference to life births.*	*0.04 * group-specific mortality rate*	*Calculate from average age of death and the average life expectancy.*	N/A	N/A	N/A	3%	8 months	N/A	*Use standard life tables.*
	children 1-4		*0.04 * group-specific mortality rate*		N/A	N/A	N/A	3%	2 years	N/A	

Normal font = generally applicable, *italic = use of or association with country-specific data necessary.*

Annex 4: Checklist of the data requirements to calculate DALYs for VAD

Functional outcomes related to VAD	Target groups	Size of target gr.	Mortality rate	Remaining life expect'y	Incidence rate	DA-weight	Duration of disease	Discount rate	Average age of death	Average age of onset	Average life expect'y
Nightblindness	children ≤ 5	*Get from appropriate statistics.*	N/A	N/A	*1.0 of all nightblindnes*	0.05	1 year	3%	N/A	N/A	N/A
	pregnant women		N/A	N/A		0.1	5/12	3%	N/A	N/A	N/A
	lactating women		N/A	N/A		0.1	0.5 years	3%	N/A	N/A	N/A
Corneal scarring	children ≤ 5		N/A	N/A	*0.1 of all corneal scarring*	0.2	*remaining life expect'y*	3%	N/A	1 year	*Use standard life tables.*
Blindness	children ≤ 5		N/A	N/A	*0.1 of all corneal scarring*	0.5	*remaining life expect'y*	3%	N/A	1 year	
Measles	children ≤ 5		N/A	N/A	*0.1 of all measles*	0.35	10/365	3%	N/A	N/A	N/A
with complications	children ≤ 5		N/A	N/A	*0.1 of all measles*	0.7	20/365	3%	N/A	N/A	N/A
Increased mortality	children ≤ 5		*<u>status quo</u>: 0.03 * group-specific mortality <u>with biofortification</u>: 0.02 * group-specific mortality rate + 0.01 * group-specific mortality*	*Calculate from average age of death and the average life expectancy.*	N/A	N/A	N/A	3%	1 year	N/A	*Use standard life tables.*

Normal font = generally applicable, *italic = use of or association with country-specific data necessary.*

Annex 5: Determining disability weights

The GBD protocol includes two questions to determine disability (DA) weights. Arnesen and Nord (1999, p. 1424) judge the second question to be more appropriate:

> "In the second person trade-off question (PTO2) subjects are asked to value cures for different chronic conditions relative to interventions that extend life. For instance, how many people cured of blindness does the respondent consider equal to prolonging the lives of 1000 people? If the response is 5000, the corresponding disability weight of blindness is 1000:5000 = 0.2. This question raises the kind of issue that may occur in 'real world' priority setting. [...] the second [question] does not presuppose that the lifetime of disabled people is devalued."

Reversing this relationship of the PTO2,[31] the table below gives an overview of the GBD's implicit assumptions regarding how many people cured in the different disability classes[32] are considered equal to prolonging the lives of 1,000 healthy people.

Equal health gains from people cured and healthy lives prolonged

	Disability classes						
	1	***2***	***3***	***4***	***5***	***6***	***7***
Healthy lives prolonged	1,000	1,000	1,000	1,000	1,000	1,000	1,000
People cured	∞	49,999-	8,332-	4,166-	2,777-	1,999-	1,428-
	50,000	8,333	4,167	2,778	2,000	1,429	1,000
Resulting weights	0.00-	0.02-	0.12-	0.24-	0.36-	0.50-	0.70-
	0.02	0.12	0.24	0.36	0.50	0.70	1.00

Source: Disability classes and corresponding weights from Murray (1996, p. 40).

The other person trade-off question (PTO1) asked by Murray (1996, p. 91) could, perhaps, be understood as a question asking for the conditions under which two alternative interventions are perceived to yield an equal "amount" of health gained':

> "You are a decision maker that has enough money to buy one of two mutually exclusive health interventions. If you purchase intervention A, you will extend the life of 1000 healthy individuals for exactly one year, at which point they will all die. If you do not purchase intervention A, they will all die today. The alternative use of your scarce resources is intervention B, with which you can extend the life of n individuals with a particular disabling condition for one year. If you do not buy intervention B, they will all die today; if you do purchase intervention B, they will die at the end of exactly one year."

[31] 1,000 / DA-weight = number of people cured

[32] "We arbitrarily divided the spectrum from health to death into seven disability classes, [shown in the table below]. The classes are exclusively defined by a range of disability weights; there are no longer any word definitions for each class. [...] each class includes 2–3 indicator conditions. The number of disability classes and the range of disability weights used to define these classes are entirely arbitrary. The classes and the benchmark conditions in each class are needed to facilitate a shortcut approach to estimating disability weights for [...] other conditions" (Murray 1996, pp. 39/40).

DA-class	*DA-weights*	*Indicator conditions*
1	0.00-0.02	Vitiligo on face, weight-for-height less than 2 SD
2	0.02-0.12	Watery diarrhea, severe sore throat, severe anemia
3	0.12-0.24	Radius fracture in a stiff cast, infertility, erectile dysfunction, rheumatoid arthritis, angina
4	0.24-0.36	Below-the-knee amputation, deafness
5	0.36-0.50	Rectovaginal fistula, mild mental retardation, Down syndrome
6	0.50-0.70	Unipolar major depression, blindness, paraplegia
7	0.70-1.00	Active psychosis, dementia, severe migraine, quadriplegia

In an iterative process the respondents have to reach a point at which they are indifferent between the two alternatives given. For instance, if extending the life of 1,000 healthy people yields as much "health" as extending the life of 8,000 people with a severe disability, the weight assigned to that particular disability is equal to
1 – (1,000/8,000) = 0.875.
As for the PTO2, this relationship can be reversed to show the number of extended disabled lives that equal the amount of health of 1,000 extended healthy lives for a given disability weight (cf. table below).[33]

Equal health gains from disabled and healthy lives extended

	Disability classes						
	1	***2***	***3***	***4***	***5***	***6***	***7***
Healthy lives extended	1,000	1,000	1,000	1,000	1,000	1,000	1,000
Disabled lives extended	1,000-1,020	1,021-1,136	1,137-1,316	1,317-1,563	1,564-2,000	2,001-3,333	3,334-∞
Resulting weights	0.00-0.02	0.02-0.12	0.12-0.24	0.24-0.36	0.36-0.50	0.50-0.70	0.70-1.00

Source: Disability classes and corresponding weights from Murray (1996, p. 40).

To be consistent, the two results need to conform to the equation.

$$PTO2 = 1000 / (1 - 1000 / PTO1)$$

[33] 1,000 / (1 – DA-weight)= number of disables lives extended

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HarvestPlus is generously supported by: The Bill and Melinda Gates Foundation, Danish International Development Assistance (DANIDA),the Department for International Development of the United Kingdom(DFID), Canadian International Development Agency (CIDA), Austrian Ministry of Finance, United States Agency for International Development (USAID), and The World Bank.