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**Quantifying public health risk in the WHO  
Guidelines for Drinking-Water Quality**

A burden of disease approach

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## Abstract

The forthcoming 3rd edition of the WHO Guidelines for Drinking-Water Quality proposes a preventive management framework for safe drinking water that is similar for all types of contaminants - microbial, chemical and radiological. Descriptions of the level of risk in relation to water are usually expressed in terms of specific health outcomes (such as cancer, diarrhoeal disease, *et cetera*). A common unit for risk is essential here, since different contaminants cause health effects of widely varying severity and kinds, ranging, for example, from mild diarrhoea through crippling fluorosis to child death. This is the only way to enable comparison between the public health impact of various agents and intervention options. The purpose of this particular report is to provide a discussion paper on the concepts and methodology of Disability Adjusted Life Years (DALYs) as a common public health metric and its usefulness for drinking-water quality. The approach is illustrated for several drinking-water contaminants already examined using the burden of disease approach; preliminary data are given for several other key contaminants.

## Preface

This report was prepared by RIVM in its capacity as a WHO Collaborating Centre for Risk Assessment of Pathogens in Food and Water. It is one of a series of texts developed to support the preparation of microbial aspects of the third edition of the WHO Guidelines for Drinking-Water Quality and to provide guidance to policy makers, regulators and practitioners in aspects of planning and implementation. Marion Koopmans, RIVM, Bilthoven, the Netherlands (rota- and hepatitis viruses) and Antero Aitio, WHO/ICPS, Geneva, Switzerland (arsenic) provided essential input in the development of the numerical examples in Chapter 2.

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## Samenvatting

In de komende 3<sup>e</sup> editie van de WHO Guidelines for Drinking-Water Quality wordt een raamwerk voor het beheersen van de kwaliteit van drinkwater voorgesteld dat voor alle soorten verontreinigingen – microbiologisch, chemisch en radiologisch te gebruiken is. Drinkwaterrisico's worden meestal uitgedrukt in specifieke gezondheidseffecten (zoals kanker, diarree *et cetera*). Omdat verschillende contaminanten gezondheidsklachten veroorzaken die sterk verschillen in aard en ernst van bijvoorbeeld milde diarree tot verlamming door fluorose en kindersterfte, is een gemeenschappelijke eenheid noodzakelijk om de effecten op de volksgezondheid van verschillende agentia en interventies te kunnen vergelijken. Dit rapport beoogt materiaal aan te dragen voor een discussie over de grondslagen en methoden van Disability Adjusted Life Years (DALYs) als een gemeenschappelijke volksgezondheidsmaat en de bruikbaarheid ervan op het gebied van drinkwaterkwaliteit. De WHO maakt inmiddels uitgebreid gebruik van DALYs om prioriteiten op volksgezondheidsgebied te evalueren alsmede om de ziektelast te schatten ten gevolge van blootstelling via het milieu. Het basisprincipe van de DALY benadering is een gewicht toe te kennen aan de ernst van ieder gezondheidseffect met (meestal) sterfte als het meest ernstige effect (weegfactor 1). Dit gewicht wordt vermenigvuldigd met de duur van het effect (waarbij de duur van sterfte de resterende groeps-levensverwachting is) en met het aantal mensen dat een bepaald effect ondervindt. Sommeren over alle effecten van een bepaald ziekteverwekkend agens resulteert in een schatting van de ziektelast die aan dit agens wordt toegeschreven. Belangrijke voordelen van de DALY benadering zijn het geaggregeerde karakter waarin zowel kwaliteit als kwantiteit van leven gecombineerd worden en de expliciete erkenning van de vele aannamen, waardoor een open discussie en het verkennen van andere voorkeuren mogelijk wordt. Problemen bij het gebruik van DALYs lijken niet zozeer samen te hangen met het basisprincipe, maar veeleer met de beschikbaarheid van gegevens betreffende epidemiologie en blootstelling (zoals die eveneens worden ontmoet bij het gebruik van andere maten voor de gezondheid van populaties), en waarschijnlijk in mindere mate de beschikbaarheid van weegfactoren en informatie over ziekteduur. De methode wordt geïllustreerd aan de hand van enkele contaminanten in drinkwater waarvan de ziektelast eerder bestudeerd was, en voorlopige gegevens worden gepresenteerd voor enkele andere belangrijke contaminanten.

## Summary

The forthcoming 3rd edition of the WHO Guidelines for Drinking-Water Quality proposes a preventive management framework for safe drinking water that is similar for all types of contaminants - microbial, chemical and radiological. Descriptions of the level of risk in relation to water are usually expressed in terms of specific health outcomes (such as cancer, diarrhoeal disease, *et cetera*). A common unit for risk is essential here, since different contaminants cause health effects of widely varying severity and kinds, ranging, for example, from mild diarrhoea through crippling fluorosis to child death. This is the only way to enable comparison between the public health impact of various agents and intervention options. The purpose of this particular report is to provide a discussion paper on the concepts and methodology of Disability Adjusted Life Years (DALYs) as a common public health metric and its usefulness for drinking-water quality. WHO now quite extensively uses DALYs to evaluate public health priorities, and also to assess the disease burden associated with environmental exposures. The basic principle of the DALY approach is to weigh each health effect for its severity with (usually) death as the most severe outcome (weight 1). This weight is multiplied with the duration of the health effect ('duration' of death being the remaining group life expectancy), and with the number of people affected by the particular outcome. Summarising over all the health outcomes caused by a certain agent, this results in an estimate of the burden of disease attributable to this agent. Key advantages of the DALY approach are its aggregate nature, combining quantity and quality of life, as well as the explicit appreciation of many of its assumptions, allowing for open discussion and exploring other preferences. Difficulties in using DALYs might not so much concern its basic principle, but involve mainly data problems such as epidemiological and exposure data (also encountered when using other measures for the health status of a population), and probably to a lesser extent the availability of severity weights and durations. The approach is illustrated for several drinking-water contaminants already examined using the burden of disease approach; preliminary data are given for several other key contaminants.





# **1. Integrated assessment of the public health impact of contaminants in drinking-water**

## **1.1 Health-based targets for drinking-water quality: the WHO approach**

In the forthcoming 3rd edition of the WHO Guidelines for Drinking-Water Quality, a management framework for safe drinking-water is proposed, that consists of five key components:

1. Health based targets based on critical evaluation of health concerns;
2. System assessment to determine whether the water supply chain (from source through treatment to the point of consumption) as a whole can deliver water of a quality that meets the above targets;
3. Monitoring of the control measures in the supply chain which are of particular importance in securing drinking-water safety;
4. Management plans documenting the system assessment and monitoring; and describing actions to be taken in normal operation and incident conditions; including upgrade and improvement documentation and communication;
5. A system of independent surveillance that verifies that the above are operating properly.

The framework is similar for all types of contaminants - microbial, chemical, and radiological. Health-based targets should be part of overall public health policy based on status and trends, and take into account the contribution of drinking-water in the transmission of infectious disease and to overall exposure to hazardous chemicals. To ensure effective health protection and improvement, the implementation of health targets should be achievable within available financial, technical and institutional resources. This normally implies periodic review and updating of priorities and targets, and in turn that norms and standards should be periodically updated to take account of these factors and the changes in available information. Such norms and standards may differ between supply types or population groups to account for health priority and practical feasibility.

In many parts of the world drinking-water still is a major contributor to the community burden of enteric disease because available water sources are faecally contaminated and untreated, inadequately treated or have become contaminated during collection, handling, storage and use. Under such conditions, improvement of drinking-water quality has the potential to appreciably reduce the overall risks of enteric disease transmission. Therefore, as a first step in the application of health based targets to achieve safe drinking-water supply, a community can set as their health target a quantifiable reduction in the overall level of diarrhoeal disease. Such a reduction could be reached, for example, by the implementation of a water treatment at the household or community level (by disinfection and related processes) capable of achieving a significant reduction of pathogen loads in the water. The use of an epidemiological approach to directly measure the achievement of a health risk target is a powerful tool to demonstrate the achievement of safer drinking-water. In many situations this

can be an effective first incremental step in the eventual goal of achieving increasingly safer drinking-water.

Where the overall burden of enteric disease is low, the possible effects of water quality interventions are less easily measured by epidemiological studies. In order to relate the effects of improved drinking-water quality to health risks in the population, risk assessment models can be constructed as an alternative. Such models take into account the raw water quality, treatment effects, water quality changes during distribution and/or storage and drinking-water consumption to provide an estimate of consumer exposure to contaminants. By combining these exposure data with dose-response models, a risk estimate can be provided. Risk managers will then have to decide on the acceptability of the risk.

Decisions about risk acceptance are highly complex and need to take account of different dimensions of risk. In addition to the probability and severity of an effect, there are important socio-cultural, economic, environmental and political dimensions that play an important role in decision-making. Negotiations play an important role in these processes, and the outcome may very well be unique in each situation. Notwithstanding the complexity of decisions about risk, there is a need for a baseline definition of tolerable risk for the development of guidelines and as a departure point for decisions in specific situations. For the purpose of guideline derivation, the preferred option is to define an absolute upper level of tolerable public health risk, which is the same for exposure to each individual hazard.

Descriptions of the level of risk in relation to water are usually expressed in terms of specific health outcomes (such as cancer, diarrhoeal disease, et cetera). Given the diverse range of water-related infections and the severity of immediate and delayed health outcomes with some infections, a common exchange unit is essential in order to account for acute, delayed and chronic effects (including both morbidity and mortality). These include diverse effects; varied severity weightings; and acute versus delayed effects such as adverse birth outcomes, cancer, cholera, dysentery, infectious hepatitis, intestinal worms, skeletal fluorosis, typhoid, association of Guillain-Barré syndrome with campylobacteriosis, (mild self-limiting diarrhoea through to significant case mortality rates). This variety of health impacts also causes difficulties for making transparent decisions based on cost-effectiveness considerations, or when a particular intervention reduces the probability of one type of disease (e.g. infectious disease) but at the same time increases the probability of another illness (e.g. cancer).

This report explores a method that allows to compare between public health drinking-water risks, not only regarding mortality but also concerning a number of other relevant aspects, such as the type of adverse health outcome, its severity and duration, the size, age and other characteristics of the population involved. The method expresses the burden of morbidity and mortality in one metric -time- using disability-adjusted life years. Although the approach is still being further developed, it has gained considerable attention and significance both within and outside the WHO, and has been used in various World Health Reports. The approach is illustrated in the final paragraphs for *Cryptosporidium parvum*, thermophilic *Campylobacter* spp., Shiga-toxin producing *Escherichia coli* O157 and bromate which already have been studied using a burden of disease approach. Tentative data are also supplied for two enteric viruses (rotavirus and hepatitis-A virus) and for a chemical contaminant of drinking-water - arsenic.

## 1.2 Concepts and Methodology

The impact of inadequate drinking-water quality on human health can take numerous shapes of various severity and clinical significance, ranging from asymptomatic infections to gastroenteritis and diarrhoea to severe illness and ultimately death. At present, there is no widely accepted metric for defining and measuring health risks, whether related to drinking-water consumption or to other factors. Most risk measures that are commonly used in quantitative risk assessment and risk management fail to address the diversity of health outcomes as they are primarily geared to *probability*, rather than to the *nature* and *magnitude* of adverse health consequences<sup>1</sup>. They also give no attention to e.g. age and previous health status of the diseased or deceased. Incorporating various relevant health attributes may therefore improve the quantitative risk assessment and subsequently the decision making process<sup>2,3,4</sup>. Such an integrated risk measure would enable comparative evaluation of health risks within and between different agents ('how bad is this exposure'), and thus facilitates setting intervention priorities and evaluating the efficiency of different policy options.

### 1.2.1 An aggregate risk measure: disability-adjusted life years

In recent years several indicators have been constructed to aggregate health losses on the level of populations. Within the Global Burden of Disease<sup>5</sup> project, Murray and Lopez applied disability-adjusted life years (DALYs), in order to assess the global disease burden and consequently the health policy priorities in different regions in the world. This health impact measure combines years of life lost with years lived with disability that are standardized by means of severity weights; it thus measures health using time as the metric. The DALY is similar to another method (the quality adjusted life-year), extensively used in medical technology assessment and in clinical decision making. However, the latter primarily aims at the individual level instead of the health of a population.

The presented adaptation of the DALY-concept for use in drinking-water quality guidelines is inspired by the notion that the multiform health loss due to contaminants in water is reasonably well characterized by three dominant aspects of public health, viz *quantity* of life (measured by life expectancy and duration of disease), *quality* of life (expressed through a severity weight for the adverse health outcome), and *social magnitude* (or number of people affected)<sup>6</sup>. Thus, health loss is defined as time spent with reduced quality of life aggregated over the population involved, combining years of life lost (combining mortality and age of death data) and years lived with disability standardized by means of severity weights<sup>5,7</sup>. The diagram in Figure 1.1 sketches the basic idea behind this and comparable approaches.

Time is the unit of measurement. Based on this concept, health loss attributable to drinking-water contaminants can be assessed by:

Estimating the number of people affected (N) (based on surveys and registries, or estimated using occurrence and growth of pathogens, concentrations and exposure models, dose-response models *et cetera*);

Estimating the average duration of the adverse health response, including loss of life expectancy as a consequence of premature mortality (D);

Attributing weights for severity to the unfavorable health conditions (S), and

Calculating the health loss in DALYs, using the equation:  $DALY = N * D * S$ .



Figure 1.1 Diagram of the concept of disability adjusted life years (reproduced from De Hollander et al.<sup>6</sup>)

When assessing the burden of disease in DALYs it is often useful to distinguish between the calculation of the mortality and of the morbidity fractions of the burden of disease, respectively the Years of Life Lost (YLL) and the Years Lived with Disability (YLD), with  $DALY = YLL + YLD$ . YLL is the number of years of life lost due to mortality and YLD is the number of years lived with a disability, weighed with a factor between 0 and 1 for the severity of the disability or disease. YLL is calculated as the product of the number of deaths with the standard life expectancy at the age of death, accumulated over all the health effects an agent is causing or aggravating. YLD is calculated as the accumulated product over all diseases related to an agent, of the number of persons affected by a non-lethal disease with the duration of this disease and with a measure for its severity. If necessary, disease processes are subdivided into several stages with different duration and severity<sup>5,8</sup>. Obviously the two fractions are calculated in the same way, since remaining life expectancy can be regarded as ‘duration’ of mortality, while the severity of death is equal to 1 and therefore omitted in the calculation of YLL.

### 1.2.2 What is health?

The term ‘disability’ may sound inappropriate when it refers to weighting the severity of a disease. It has however a historic root in the original method, when trying to answer the question ‘what is health?’. This is a key question in any attempt to quantify health loss, and weighting the severity of a certain disease condition or the reduction in health and quality of life caused by it has therefore been the subject of much research and debate<sup>9,10,11,12,13,14</sup>. The concept of health may differ from era to era, from region to region, since it reflects changes or differences in social and cultural beliefs, in medical technology, and economic conditions. Already in 1946 the founding charter of the World Health Organization stated that health is not ‘merely the absence of disease and infirmity’, while in most health status measurements the central issue is an individual’s capability to function well physically, mentally, or socially<sup>15,16</sup>. Since the WHO definition brings health close to happiness<sup>17,18</sup>, this may not produce a useful tool, although it is certainly very important as a stimulating and provocative goal.

In addressing the questions of ‘what is health’ and how to measure health loss, the Global Burden of Disease (GBD) project initially applied disability weight definitions which were primarily based on functionality, the (dis)ability to perform ‘activities of everyday life’ in four domains: procreation, occupation, education and recreation<sup>19</sup>. This approach was received with a fair amount of criticism, some involving the procedures of attributing weights, other the fact that the definitions did not fully comprise important dimensions of health such as pain, distress, discomfort, anxiety and depression. Aggregated scores would not adequately reflect preferences of various ‘stakeholders’. To meet these objections in their revision of the DALY-approach Murray *et al.* applied the concept of ‘indicator conditions’<sup>20</sup>, while retaining however the term ‘disability-adjusted life year’. Using formal instruments to measure health preferences, 22 indicator conditions were given weights in a series of consensus meetings involving physicians and public health scientists from different regions. The indicator health states reflected several distinct attributes of non-fatal health outcomes, such as large physical manifestations or limitations, psychological and social limitations, pain, as well as disturbed sexual and reproductive functions (see Table 1.1).

*Table 1.1 Revised disability classes: Indicator conditions and severity weights*

Class	Indicator conditions	Weight
1	vitiligo on face, weight-for-height less than 2 SDs	0.00-0.02
2	watery diarrhoea, severe sore throat, severe anaemia	0.02-0.12
3	radius fracture in a stiff case, infertility, erectile dysfunction, rheumatoid arthritis, angina	0.12-0.24
4	below-the-knee-amputation, deafness	0.24-0.36
5	rectovaginal fistula, mild mental retardation, Down syndrome	0.36-0.50
6	major depression, blindness, paraplegia	0.50-0.70
7	active psychosis, dementia, severe migraine, quadriplegia	0.70-1.00

Source: Reproduced from Murray *et al.*<sup>5</sup>

These indicator conditions were subsequently used to attribute disability weights to most other states. This resulted in severity weights specific for age and sex for more than 100 diseases. Recent (Environmental) Burden of Disease Studies<sup>6,8,21</sup> applied rather similar approaches for somewhat different sets of diseases and environment related health outcomes.

### 1.2.3 Data needed for the calculation of DALYs

In order to calculate DALYs for each adverse outcome caused by a drinking-water contaminant or any other agent, first the *number of people* experiencing each outcome is needed. This may be derived from medical registries, surveys, *et cetera*. The number may also be estimated, either through combining attributable risks with data on the adverse health outcomes, or based on exposures and dose-response relations<sup>22,23</sup>. In the case of microbial agents, some risk assessment models use observational and experimental data together with predictive mathematical models, in order to estimate the occurrence of pathogens in raw materials, and their reduction by processing and subsequent increase by regrowth and/or recontamination. This finally leads to an estimate of the numbers of organisms ingested by consumers. Combined with dose-response models and exposure distribution data, an estimate of the number of people affected can be produced<sup>24,25</sup>. With regard to chemical agents, the number of affected people may be estimated from data on concentration, exposure distribution, and dose-response models. Which type of dose-response model to use (linear or non-linear, single-hit or threshold *et cetera*) is an important question which falls however outside the scope of this paper.

After having assessed the number of people affected, *weights for severity* need to be established. Severity weights can and have been derived through a large variety of valuation methods as mentioned before. Generally, the results of the various methods do not differ considerably, especially not when seen in the perspective of the uncertainties in epidemiological data and the various dose-response models (for an example of the latter see e.g. Melse *et al.*<sup>26</sup>).

Finally, estimates of the *durations* of the adverse health outcomes have been mostly derived through expert consultations, but hospital data and epidemiological surveys can be used as well. Establishing the durations may be skipped however, when prevalence numbers are used instead of the incidences. This is because under steady state conditions the prevalence is equal to the annual incidence times the disease duration (in years), of course under the condition that the severity weight refers to the same disease category as the prevalence. The Global Burden of Disease study is a major source of severity weights and durations for a variety of conditions<sup>5,16</sup>.

### 1.2.4 Using DALYs in setting reference levels of risks

Microbiological risks are mostly expressed as the annual individual probability of infection for a given consumption of drinking-water. Chemical risks when related to genotoxic carcinogens are usually conveyed as an increase in cancer incidence attributable to a lifetime exposure. The public health impact of these disease end points is very different and cannot be compared directly. Expressing the burden of disease in one metric (time i.e. DALYs) whatever their cause, enables comparison of the importance for public health of various microbial and chemical agents. This makes it theoretically possible to set one standard of acceptable health risk in a certain population, regardless of the type of detrimental health

effect or the nature of its cause. A widely used risk threshold in environmental cancer risk assessment is 1 death per million exposed for a lifetime. Combined with the average remaining life expectancy per death, this would lead to a corresponding threshold of  $x$  DALYs per million (in the Netherlands e.g. the average Years of Life Lost per cancer death is 13.8 years, of course equal to 13.8 DALYs since the morbidity part is left out here). Regarding this burden to health as caused by certain agents in certain doses, can finally lead to levels of exposure and concentration which are acceptable when using a specific risk threshold. As mentioned before, setting and using reference risk levels or ranges should also reckon with differences in cost-effectiveness of quality-improving activities for various agents or various agent concentrations. In the following section the possible use of DALYs in setting a common health impact based standard for drinking-water is further discussed.

## 1.3 Discussion

Protecting population health based on scientific evidence implies a pivotal role for science and scientists. Several often implicit assumptions underpin such a role of scientific counsel in the area of public health, e.g. that health is the most important human asset, that it is therefore nearly inviolable, that health can be clearly defined, and also that science should be objective and more or less free of social values. All of these assumptions need to be put in perspective. Health is not an isolated entity. The concept is very much tied up with the quality of the physical and social-cultural environment (e.g. wealth, educational status), and philosophers throughout history have emphasized the comprehensiveness and complexity of the concept of health<sup>27</sup>. Nevertheless several attempts to make the concept of health operational have been proposed in the literature, all requiring value-laden choices to be made, to which the DALY method is no exception<sup>5,12,13,28</sup>. Also, there are still many unknowns regarding the relation between environmental quality and (aspects of) health. Assessing this relation, either qualitatively or quantitatively, therefore requires several assumptions to be made, which will be influenced by personal and (scientific) group or social values<sup>29,30</sup>. Both values choice and assumptions emphasize the need for methods that foster transparency and enhance discussion.

### 1.3.1 DALYs in a public health risk context

As with every method, assessing risks through DALYs requires a careful examination of the assumptions involved. First, risks related to drinking-water can not be reduced to undesirable and quantifiable health effects alone. Besides water characteristics like taste and turbidity, risk aspects such as equity, voluntariness and nature of exposure are very important in the perception of drinking-water risks by the general public. Even when the health risks as perceived and quantified by scientific methods are the same, such risk characteristics may make a huge difference in willingness to accept exposure, as is clear from e.g. comparing smoking behavior with living under electricity power lines. Second, although the DALY method is broader than other public health indicators including both quantity *and* quality of life, to many health is much more, as is for instance clearly shown in the WHO definition of health. Both remarks do not disqualify the use of DALYs in drinking-water risk assessment, but urge for a prudent utilization and a thorough examination of assumptions and situations.

Within the framework of setting ranges of reference levels of risk for diverse pathogens and chemicals, it is tempting to follow common practice among toxicologists and cancer epidemiologists. As mentioned before, they often use a risk threshold of  $x$  deaths per million from which the corresponding acceptable health loss in DALYs can be derived using the

average lost life expectancy per cancer death, and subsequently allowable exposure and concentration levels can be established. However, these thresholds are often rather arbitrary, apparently more based upon the characteristics of our decimal system than that they are grounded on sound scientific argument and thorough public and political discussion. Since nevertheless the use of such thresholds is widely accepted, the calculation of acceptable DALYs based on such thresholds might be advocated on the basis of inclusion of otherwise left out dimensions, such as lost life expectancy and duration and severity of morbidity. When taking such an approach, it might be important to use ranges instead of exact thresholds and show the effect of the different numerical values. However, in risk *communication*, mortality per million may appear easier to comprehend than DALYs per million; calculated DALYs might have to be translated back into ‘everyday’ measures such as 10 people with cancer for a year.

Up to now, pathogen concentration standards have been mainly derived from the possible and/or reasonable level of assuring adequate control in each phase of drinking-water treatment and distribution. In every step, the effectiveness of further improvements and their costs play an important role in deciding on the required level of quality. Using the DALY methodology to obtain standards based on the population health impact, should follow the same line of argument. Setting reference risk levels or ranges suggests that rather strict lines can be drawn between good and bad, between when action is required and when not. In real life however, our actions are much more based on balancing material and immaterial pro’s and con’s than on following simple rules.

An interesting example of this can be found in Havelaar *et al.*<sup>31</sup>, studying the ozone disinfection of drinking-water (see also par. 2.2 and 2.5). Such disinfection would reduce the risk of infectious diseases, but may at the same time increase the exposure to carcinogenic by-products. Applying DALYs they showed that in the Dutch population the gain in DALYs of reducing the risk of infection with *Cryptosporidium parvum* clearly outweighs the extra health loss due to the bromate related cancer. Important to note, they stated that to a large extent this was related to a change from using conservative default assumptions as common in setting water quality standards for toxic chemicals, to a probabilistic risk assessment method aimed at estimating the actual risk. Including costs as a next step, it becomes possible to calculate the costs per DALY gained of different policy options, facilitating the decision on which one to implement. Again it should be emphasized that DALYs, and health risks in general, are not the only dimension that must be taken into account; there can very well be other reasons to choose an intervention that within a health economics perspective might not be the most cost-effective.

### 1.3.2 Sensitivity and robustness

The estimation of DALYs can be regarded as the final step in a disease model leading from concentration and exposure to symptom development and its quantification in public health terms. The usefulness of the approach also depends upon its sensitivity for changes in its parameters. Recently, Havelaar *et al.*<sup>32</sup> explicitly addressed the uncertainty and variability of various parameters by simulating different values and scenarios. In their study estimating the disease burden in the Netherlands due to infection with thermophilic *Campylobacter* spp. (par. 2.3), they concluded that the uncertainty of the estimate of total disease burden is relatively small, and mainly related to the YLD fraction due to the low incidence of fatal



cases. Using alternative assumptions resulted in total burden of disease estimates that were all within the same order of magnitude (with the highest estimate about 2.5 times the lowest). Differences in weights showed somewhat smaller effects than differences in other disease model parameters. They stated that: ‘This is related to the fact that the total health burden is based on different disease end-points, and it is unlikely that all parameter estimates for these end-points will simultaneously have an extreme value (p.519).’ (See also par. 2.2 for an illustration of the robustness of DALY estimates with regard to uncertainty in a single epidemiological estimate.)

After a limited sensitivity analysis Melse *et al.*<sup>8</sup> concluded that even in a highly developed country such as the Netherlands with extensive disease registration systems, the problem of ‘getting the numbers right’ produced a much wider range in calculated numbers of DALYs than did the uncertainty in severity weights or duration. Uncertainty and variability mainly concerned not easily explainable differences between sources of epidemiological data. An exception are diseases which are both mild and frequent, for which variation in the disability weight might lead to considerable effects on the calculated burden of disease, because the *relative* impact of a difference of e.g. 0.1 is much smaller at the severe end of the severity scale.

Hollander *et al.*<sup>6</sup> also studied the sensitivity of the DALY method when estimating the disease burden of various environmental exposures. They warned: ‘one should be very careful prioritizing environmental health issues solely based on point estimates, given the overlapping uncertainty ranges. On the other hand one can quite clearly discern groups of high-risk exposures (accidents, long-term exposure to particulates) from groups of moderate (lead, food, ETS, radon) and low risk exposures (carcinogenic air pollutants). Continuous efforts along the lines we sketched here should involve dealing with construct or model uncertainty as well, as uncertainty is another important attribute that should be of consequence in decision making’ (with references<sup>33,34,35</sup>).

This limited evidence suggests at least two messages concerning the sensitivity of the DALY approach. First, the DALY is a rather robust measure. Variations in disease model parameters are often counterbalanced by other variations, and explicitly addressing uncertainty by varying parameters does not necessarily lead to inconclusive broad ranges. Second, the major sources of variation in burden of disease estimates are to be found in the epidemiological data, and not so much in the severity weights or disease durations, except for disease both mild and frequent. It seems reasonable to conclude that possible future use of the DALY approach can not be disqualified for reasons of parameter uncertainty and data variability.

### **1.3.3 Severity and duration matter**

#### ***Availability***

In their comprehensive report on human health metrics for environmental decision support tools, Hofstetter and Hammitt<sup>36</sup> comment that ‘the availability of consistently derived quality weights for a large number of health states may be considered as a practical advantage, especially if the decision support is needed within a short time or with little resources’ (p31). For DALYs, they mention that several hundred (internally) ‘consistent disability weights are reported in Murray *et al.*<sup>5</sup> and recommended for a worldwide application. For 56 diagnostic groups separating more than 100 different disease stages disability weights for the Netherlands have been derived<sup>37,38</sup>. Environmental disease related disability weights have

been provided by Hollander *et al.*<sup>6</sup> based on Stouthard *et al.*<sup>37</sup> (and an own panel of environment-oriented physicians adjusting for the health consequences typical for environmental exposure (p34)). Anonymous<sup>39,40</sup> build on Murray *et al.*<sup>5</sup> and Stouthard *et al.*<sup>37</sup> and add some additional disability weights (by interpolation) for the specific Australian context' (p32). In the context of QALYs (quality adjusted life years), there have also been efforts to derive weights through a decomposed approach, e.g. the EuroQol<sup>41,42</sup>. In such an approach, single health dimensions such as social function, psychological function, physical function and impairment are judged and these judgements are combined into a single number. Since QALYs usually focus on medical decisions an ill individual has to make, they appear not a logical choice in a drinking-water guidelines context (see below).

Estimates of duration were also provided by Murray *et al.*<sup>5</sup>, but compared to severity weights durations may depend to a larger extent on actual local health care practices. Depending on the nature of the pollution-related condition, Hollander *et al.*<sup>6</sup> determined the duration 'from case definitions used in the epidemiological studies involved, e.g. respiratory symptoms, hospital admissions, and severe noise annoyance. In case of well-defined diseases, duration was calculated from Dutch prevalence and incidence statistics, implicitly assuming similarity among average cases and cases attributable to environmental exposures' (p610). Melse *et al.*<sup>8</sup> used prevalence instead of incidence figures, thereby excluding the need for separate disease duration estimation and assuming steady state between the compound states of a disease.

Although the number of disease states for which weights and durations are available is certainly impressive, it is likely that for application of DALYs in the context of drinking-water data for specific health effects are missing. In these cases either elicitation of the missing weights is needed, or weights for similar health states must be used, although criteria for sufficient similarity are hard to formulate. Also, it appears not always easy to find out exactly in which manner the presented severity weights -and the durations- were elicited. Durations seem easier to obtain from epidemiological data, hospital admissions *et cetera*.

### ***Age weighting and future discounting***

Two -often controversial<sup>5,43</sup>- features of the DALY measure as developed by Murray and Lopez in the Global Burden of Disease study are weighting for age and discounting of loss of healthy life in the future. Age weighting gives some ages more impact in the DALY estimates than others because of their economic and societal significance, and has been justified by the idea that everyone may eventually pass through all ages. Applying a certain discount rate for future costs and benefits compared to present ones is common practice among economists - though not so much in the public health field-, because otherwise interventions would nearly always be postponed to the future. Both features are not central to the concept of DALYs, but the decision to apply or not to apply these is again a value-laden choice that has to be made explicit and accounted for. The Annex provides 3% and 5% discounted life expectancies.

### ***Baseline health and co-morbidity***

Regarding the valuation of the severity of adverse health outcomes, important matters concern the valuation method and the issues of 'baseline health' and co-morbidity. Since the first has been discussed extensively elsewhere<sup>9-14,27</sup> this paper does not go into further detail, also because the differences in the derived weights do not appear substantial. The matter of baseline health refers to the question of how much ill health can be attributed to a specific agent. Consider e.g. the case of AIDS patients dying after infection with *Cryptosporidium*

*parvum*. It may hardly appear reasonable to count the full loss of health in death (with severity weight 1) as attributable to *C. parvum* infection. On the other hand, adverse health outcomes in already ill individuals may be much more severe than in the previously healthy. Similar arguments apply to the estimated disease duration. While a healthy person might have lived another 40 years, an already severely ill person may have a diminished life expectancy and the loss of life attributable to the infection can be consequently regarded to be much smaller. However, the duration of disease may be much longer in immunocompromised patients. Havelaar *et al.*<sup>31</sup> dealt with this by differentiating between the immunocompetent population versus AIDS patients, applying different weights, durations and life expectancies. It should be emphasized that this is not to say that the death of some individuals is less worthy to prevent than of others. DALYs and similar methods are to be used solely on a population level as a tool for public health impact quantification and an aid for policy making and evaluation, but certainly not for the valuation of individual lives.

A parallel with this discussion can be drawn concerning differences between poorer and richer countries, the poorer populations generally in poorer health and living shorter. In the Global Burden of Disease study<sup>5</sup> Murray and Lopez choose to apply the same life expectancy all over the world for reasons of equity, taking the highest life expectancy (Japan) as an approximation of the biologically possible life span. Because of actual disease course characteristics, for some conditions they applied different -usually higher- severity weight and durations in poorer regions as well as different weights and durations for untreated versus treated diseases.

#### **1.3.4 Comparison with other human health metrics**

Disability-adjusted life years are of course not the only possible human health metric which might be used to assess the health risks of drinking-water. In a recent publication on the use of such measures for environmental decision support, Hofstetter and Hammitt studied three well-known types: DALYs, QALYs (quality adjusted life years), and WTP (willingness to pay). Using the example of environmental impacts in the Netherlands of De Hollander *et al.*<sup>6</sup>, they studied whether it matters which metric is chosen, and also which are the relevant characteristics of these metrics in environmental applications. In the example the choice mattered for the ranking of the impacts, and it was also found that WTP was dominated by mortality outcomes. As earlier pointed out by Melse *et al.*<sup>8</sup>, QALYs and DALYs were sensitive to diseases both mild and frequent, of which the severity weights are also difficult to assess with the currently used elicitation methods. In order to select a metric for environmental decision-support, Hofstetter *et al.* discuss a number of relevant aspects:

##### ***Health or wealth***

Since monetary methods not only require a health-health but also a health-wealth trade-off, they are more demanding than both QALY and DALY. For comparative risk assessment in which expressing health outcomes in monetary units is seldom required, the latter may therefore be preferred. However, these usually only include the intangible costs borne by the individual.

##### ***Population choices***

Whether the value of mortality risk avoidance is age-dependent is at present unclear, and neither unweighted (QALY) or age-weighted (DALY in the Global Burden of Disease

Study), nor the assumption of an age-independent value of a statistical life are supported by evidence. Hofstetter *et al.* therefore suggest a sensitivity analysis if the age of populations affected by different decision alternatives varies. Which reference life table is to be used largely depends on both spatial and temporal characteristics of a proposed study or decision.

### ***Severity weights***

For use in environmental decision-making, Hofstetter *et al.* conclude that reasonable weights may lie somewhere between patients' values and the public's. Severity weights of patients are usually lower because the whole meaning of quality of life is redefined for ill or disabled persons (whom to compare to, coping *et cetera*). They propose to use weights as given by health professionals, who know to some extent both the societal preference and the patients' experience, and the values of which are often in-between. Since in environmental applications social rather than individual decisions are at stake, person trade-off methods as used in DALYs focussing on the health of others appear a logical weight elicitation method; standard gamble and time trade-off methods deal with the individuals' own health.

### ***Discounting***

Concerning the discounting of future health, Hofstetter *et al.* state that at present it can not be said how much the value of a DALY or a QALY (or a statistical life) changes over time. In case one DALY or QALY is considered equally valuable over time, they suggest discounting.

### ***Ethical considerations***

As mentioned before, health metrics make major and policy relevant assumptions on distributional and ethical choices. In environmental decision making it is likely that different policy alternatives affect different sub-populations. If choices concerning intra- and intergenerational equity and health shifts cannot be made *ex ante*, the authors advise that total health metric scores should be broken down for the different affected subgroups. Since most health impact measures maximize utility but most decision makers would also want to allow for how different ethical preferences would affect the outcome, the authors suggest a semi-quantitative discussion to evaluate who are the worst-off, the innocent, the ones that benefit or pay most, age-distributions, *et cetera*. Such data will support usually made policy considerations, and do not replace a utility measurement.

From this comparison by Hofstetter and Hammitt it can be concluded that the main difference between the studied health metrics lies between monetary (WTP) and non-monetary (QALY and DALY) measures. In their example, the only difference between QALY and DALY originates in the difference between the applied quality and disability weights for noise related health effects. Since these are widespread and also usually mild and therefore hard to value properly, the total burden of disease showed highly sensitive for the noise effects. In fact, the authors discuss QALY and DALY as one category of HALY (health adjusted life years), conceptually differing mainly in focus on the individual or societal level, both historical and methodological. Since using a health impact measure in drinking-water guidelines is a type of environmental application as discussed by Hofstetter *et al.*, the choice of DALYs instead of QALYs can be reasonably defended because of their societal perspective and elicitation method.

Finally, DALYs should be applied with the specific context in mind. Since data on mortality and lost life expectancy are often much easier to obtain than full data on morbidity, severity

weights and durations, first a quick scan may be performed of the extra benefits of having full DALY figures compared to calculating only mortality based Years of Life Lost. This may be for example be appropriate for some microbial agents causing high mortality amongst children, leading to huge numbers of Years of Life Lost, while morbidity appears to play a more important role in the burden of disease caused by chemical agents.

### **1.3.5 Further research**

Important areas still need further research. Useful estimates of the burden of disease and subsequent reference levels or ranges of contaminant exposure and concentration first of all require sufficient data quality. This especially concerns epidemiological information regarding morbidity (prevalence and incidence, and their changes in time) and mortality (number of deaths, age at death, population specific life tables), as well as attributable risks, dose-response relations, population exposure distributions, infection rates and concentration levels. These might be found in published comprehensive reviews, or have to be derived from scattered evidence subsequently subjected to in-depth and time-consuming meta-analysis. Research on how to use and improve scant data seems essential.

Although in numbers most likely not the major source of variation, since it has been and will be hotly discussed, the methodological and philosophical assumptions of assessing severity weights require further attention. Both weights and durations might need to be discussed further, concentrating on selected pathogens and chemicals. Other aspects such as the application of age weighting and future discounting may also need a more thorough discussion<sup>28</sup>, since DALYs in other WHO-reports<sup>44,45</sup> have been calculated using both features. Also, the assumptions of time and person proportionality central to DALYs (having the same illness for five years instead of one year makes the disease burden exactly five times higher<sup>28</sup>, and one person ill for five years equals five persons one year ill) may require further attention, both empirical and philosophical. In general, uncertainties and variations in all parameters should be identified and taken account of, e.g. by using probabilistic methods instead of fixed estimates, and discussed in a transparent manner. Finally, in order to produce widely-used guidelines for drinking-water quality in which DALYs play a role, the DALY method must not only be accepted by scientists, but also by policy makers and third parties. Conditions and prerequisites for its acceptability should therefore be carefully studied and addressed.

## **1.4 Conclusion**

Guidelines for Drinking-Water Quality aim at protecting the health of the population. It has therefore been suggested to base the guidelines on a quantification of public health risks involved in drinking-water consumption. A major advantage of the proposed method, the DALY, is that it enables a comprehensive evaluation of health gains and losses of various intervention options, in terms of established public health concepts (quality and quantity of life and social magnitude), using time as a unit of measurement. The DALY measure appears in this respect superior to the use of annual mortality rates alone, because it also includes non-lethal end points and explicitly addresses life and health expectancy. The DALY concept is in principle transparent and highly flexible. It can be used both for fairly simple comparisons of risks due to different agents as described in this paper, as well as for comparison of the cost-effectiveness of diverse policies, and also in more complex models studying specific aspects of societal values<sup>46</sup>.

Of course, there are many questions about concepts and methods underlying indicators such as the DALY. The use of composite health outcome measures implies several normative choices, such as which reference life table to use for the lost life expectancy, the severity valuation procedures, *et cetera*. The explicit introduction of values and preferences when attributing weights to different diseases may seem to add controversial dimensions, but well-established public health indicators such as mortality and morbidity also rest upon a number of assumptions (e.g. implicitly valuing death at young and old ages equally), which however often go unnoticed. Because of its transparent nature, the DALY approach allows for open discussion and evaluation of alternative preferences.

Waterborne risks often evoke strong emotional reactions in the public. Policy makers have to take these into account when deciding about acceptability of contaminants in water. Many dimensions other than health play a key role in these decisions, even if the emotions are fed by a perceived health risk. Against this background, the use of quality of life measures primarily related to health could be considered inappropriate by some, because they do not completely capture the public's values. However, both publicly and scientifically perceived or researched risks will contribute to the decision making process; a public health basis for defining acceptable risk is therefore one of the essential inputs to the policy process.

## 2. The DALY approach illustrated

### 2.1 Overview

In order to assess the burden of disease related to exposure to microbiological and chemical contaminants or conversely to apply a reference level of tolerable risk, the disease outcomes following each specific exposure and ingestion or infection have to be defined. Subsequently, their severity weights and durations must be established and the number of cases of each outcome estimated. Therefore models of the disease process have to be collected or designed, such as Figure 2.1. Transition probabilities between all blocks must be established, and each block representing an adverse health outcome has to be characterised by a weight for severity and duration. This enables partitioning an exposed population over the various blocks and calculating a burden of disease including all relevant health outcomes.

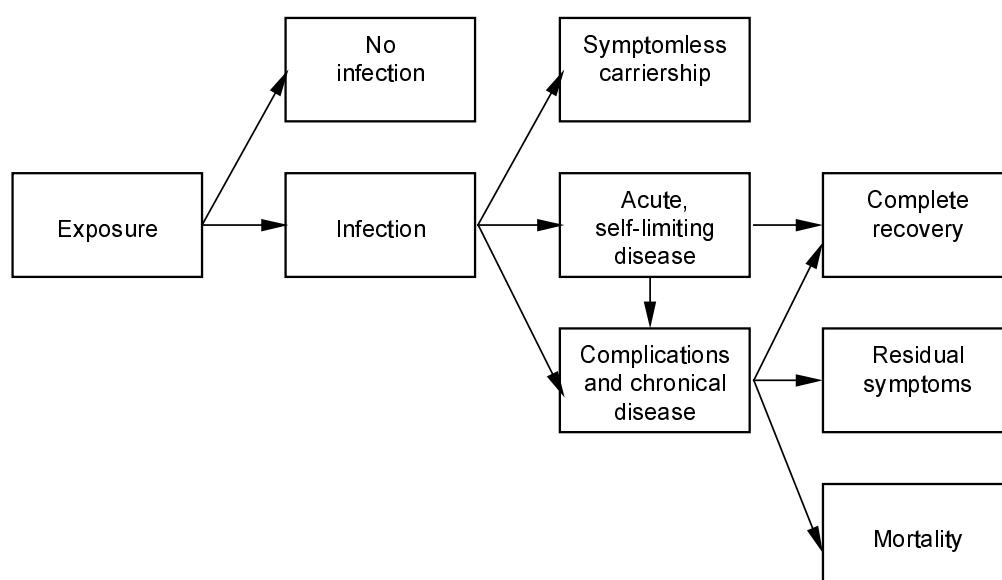


Figure 2.1 Chain model of infectious gastro-intestinal disease (reproduced from Prüss and Havelaar<sup>47</sup>)

The following paragraphs present short discussions of burden of disease calculations for *Cryptosporidium parvum*, thermophilic *Campylobacter* spp., Shiga-toxin producing *Escherichia coli* O157 (STEC O157) and bromate, based on data from published studies. For rotavirus and hepatitis A, two major waterborne causes of disease especially in developing countries, such publications were not available, as for arsenic, which in some regions has a huge effect on the population's health. Presented burden of disease calculations for these agents are meant as only an indication of how the approach might work in these cases, and numerical results should therefore be regarded with caution. Data are presented on disease burden per case for all relevant outcomes separately. They are also presented as aggregated estimates, i.e. taking into account all possible outcomes after primary exposure. For this

purpose, transition probabilities were taken from relevant epidemiological studies. These were mainly based on data obtained in or relevant for one country, the Netherlands. Application of the presented data would also be relevant for other Western countries, but for other regions of the world, country- or region-specific data would need to be substituted into the calculations.

When looking at the burden of disease calculations presented in the next paragraphs, the following remarks can be made. In the *C. parvum* study in the Netherlands, the aim was to evaluate the risks and benefits of drinking-water disinfection using DALYs. The number of persons with health effects needed for a burden of disease calculation was modelled with parameters based on Dutch data, with added international data if necessary. Possible difficulties in obtaining the correct epidemiological data for an actual situation could therewith be circumvented. The severity weight for watery diarrhoea was available from the Global Burden of Disease study. Estimates of duration were derived from the literature, as was the case-fatality ratio and thus the number of deaths. Lost life expectancy was derived from data on all gastroenteritis deaths. The burden of disease was calculated using Monte Carlo simulation, thus avoiding the misleading exactness of point estimates. This study shows that the DALYs approach could be employed, but that some assumptions on the applicability of international data to the Dutch situation and on the similarity of watery diarrhoea and *C. parvum* health effects were unavoidable.

The disease burden for thermophilic *Campylobacter* is composed of several endpoints: mortality and morbidity due to gastroenteritis and morbidity due to residual symptoms of Guillain-Barré syndrome (GBS). Even though GBS is a very rare complication of campylobacteriosis, the severity and duration of residual symptoms are such that they add significantly to the public health effects. This is an example of the need to carefully consider the impact of not only the most prevalent outcomes of exposure and infection, but also more rare, but serious outcomes.

For the STEC O157 burden of disease calculation, mortality effects dominated the disease burden. Since mortality due to *Escherichia coli* infection and its various health outcomes is not separately registered in the Netherlands, numbers of deaths had to be estimated using a disease model with transition rates based on Dutch and international data. Lost life expectancy per case had also to be estimated, since case specific data were unavailable. Also for bromate not all the required figures for a burden of disease calculation were available from registries, but had to be estimated. The more tentative, indicative examples of rotavirus, hepatitis A and arsenic present a similar picture. Establishing the epidemiological figures often required combining data of different kinds, and severity weights and durations could not always be derived directly from published sources.

All examples show that burden of disease calculations are possible but that making assumptions is unavoidable, with establishing the numbers of persons affected probably being the most important source of uncertainty. Since making assumptions is common practice in epidemiology, this does not necessarily mean that DALYs are not to be used. It emphasizes again the need for methodological ways to deal with variability and uncertainty such as simulation models. The examples also show that for complex diseases like Guillain-Barré syndrome and hemolytic uremic syndrome, simple point estimates are not sufficient to give a



valid estimate of the burden of disease. Also for this purpose, more complex simulation models are recommended.

Table 2.1 gives a summary of the data presented in Chapter 2. Again, it is emphasised that these data are only valid for certain regions of the world, and some data are only preliminary estimates. The summarised data can be used to compare the public health impact of different waterborne diseases, and for deriving water quality targets. The latter also requires information on the dose response relationship, and will not be further elaborated here. The table shows that, on a case per case basis, there are considerable differences between the health effects of different contaminants. The two selected chemical contaminants have a more severe impact per case than microbiological contaminants, mainly because of a high case-fatality ratio. This does not necessarily indicate that this is also true on a population basis, because for this comparison, the actual incidence of illness also needs to be taken into account. This is beyond the scope of the present study. There are also considerable differences between the disease burden estimates of different microbial contaminant. These are mainly related to differences in case-fatality ratio. There are only two pathogens (*C. parvum* and *Campylobacter* spp.) for which the disability burden (YLD) is higher than the mortality burden (YLL). For all other pathogens, mortality dominates and for the viruses morbidity could even be omitted from the calculations without a major effect on the outcome of the calculations. Thus, the choice between using DALYs or the more traditional public health indicator ‘Life Years Lost’ depends on the contaminant of interest. For some contaminants, neglecting the morbidity component would lead to serious underestimation of the disease burden. It is therefore recommended that a simple calculation of the relative importance of both components is made before more detailed analyses are started.

*Table 2.1 Summary of disease burden estimates for different drinking-water contaminants*

Contaminant	Disease burden per 1000 cases		
	YLD	YLL	DALY
<i>Cryptosporidium parvum</i>	1.34	0.13	1.47
<i>Campylobacter</i> spp	3.2	1.4	4.6
STEC O157	13.8	40.9	54.7
Rotavirus			
high income countries	2.0	12	14
low income countries	2.2	480	482
Hepatitis-A virus			
high income countries, 15-49 yr	5	250	255
low income countries	3	74	77
Bromate	-	10900	10900
Arsenic	-	54000	54000

## 2.2 *Cryptosporidium parvum*

The following is an extract from Havelaar *et al.*<sup>31</sup>, adapted for the purpose of the present work. Infection with *Cryptosporidium parvum* often leads to gastroenteritis. In developed countries 71% of infected immunocompetent persons develop gastroenteritis, while population-based outbreak studies and volunteer experiments report relapses of diarrhoea in 40-70% of patients. During a 1993 outbreak in Milwaukee, USA, four deaths in the non-immunocompromized population (approx. 400,000) were attributed to *C. parvum* infection. Case-fatality rates in developing countries might be higher, but data are presently not available. In immunocompromized persons, particularly in AIDS patients, infection with *C. parvum* leads to gastroenteritis in virtually all cases. Only 30% of AIDS patients have remission, the others suffer from cryptosporidiosis until death (this has however improved with the availability of triple therapy in Western countries). Because the basis for derivation of critical levels in the GDWQ does not include specific immunocompromized groups, it can be argued that the increased susceptibility of AIDS patients should not be considered further. On the other hand, in some regions the fraction of AIDS patients within the general population is considerable and can not be regarded as a minor population subgroup.

### 2.2.1 Severity weights and duration

Table 2.2 presents severity weights, durations and burden of disease per health outcome case following *Cryptosporidium* infection. The disability weight for cryptosporidiosis was taken from the Global Burden of Disease (GBD) project. The mean severity weight for watery diarrhoea is 0.067. The duration of cryptosporidiosis is usually reported as 1-2 weeks, but these estimates are based on cases detected in laboratory surveillance, and may be biased towards longer duration. In population-based outbreak studies and in volunteer experiments, the mean duration of gastroenteritis is reported to be only 3-6 days. The (distribution of) duration of cryptosporidiosis used for disease burden estimation has a mean of 7.2 days (0.02 years) and a range between 2 and 30 days. There is no information on the clinical course of cryptosporidiosis related to age. It was assumed that this information is representative for all age groups. To estimate the number of life-years lost by a fatal case of gastroenteritis, the age-distribution for all deaths of gastroenteritis in the Netherlands in 1993-1995 was used; the mean loss of life years associated with 1 fatal case of cryptosporidiosis was estimated at 13.2 years.

Table 2.2 Severity weights, durations and burden of disease following *C. parvum* infection

Outcomes	Severity	Duration	Burden of disease per case in DALYs
Watery diarrhoea	0.067	7 days	0.0013
Death	1	13.2 yrs	13.2

### 2.2.2 Calculation of the burden of disease

The mean mortality risk for cryptosporidiosis in the immunocompetent population was estimated as 1/100 000 symptomatic cases, based on experience from the Milwaukee outbreak. Using the formula DALYs = Number\*Severity weight\*Duration, the burden of mortality for developed countries based on US and Dutch data per 1000 symptomatic cases of cryptosporidiosis could be calculated as in Table 2.3.

Table 2.3 Population based estimate of disease burden of cryptosporidiosis

Outcomes	Disease burden (DALY) per 1000 symptomatic cases of (gastroenteritis)
Watery diarrhoea	$1000 \times 0.067 \times 0.02 = 1.34$
Mortality	$1000 \times 10^{-5} \text{ (mortality)} \times 13.2 = 0.13$
Total	1.47

Data based on estimates for the Netherlands, 1990-1995

Recently, Hunter and Syed<sup>48</sup> have reanalysed the estimate of the size of the Milwaukee outbreak, and have suggested that the investigators have seriously underestimated the background illness rate. Also, evidence was given for the potential of recall bias in retrospective community-based surveys of diarrhoeal illness. The actual size of the Milwaukee outbreak was suggested to be between 1% and 10% of that claimed. This analysis has a major impact on the case-fatality ratio (CFR) of cryptosporidiosis, used in our DALY estimate. If Hunter and Syed's analysis is correct, the CFR would be between  $10^{-3}$  and  $10^{-4}$ , and the relative impact of mortality on the DALY estimate would increase, giving the following results:

CFR =  $10^{-4}$ : mortality burden per 1000 cases (symptomatic):  $(1000 \times 10^{-4} \times 13.2) = 1.3$ , morbidity burden (see above) 1.3; total disease burden 2.6 DALYs.

CFR =  $10^{-3}$ : mortality burden per 1000 cases (symptomatic):  $(1000 \times 10^{-3} \times 13.2) = 13$ , morbidity burden (see above) 1.3; total disease burden 14 DALYs.

Although the disease burden estimate increases, it is noteworthy that increasing the CFR estimate by a factor of 10 from  $10^{-5}$  to  $10^{-4}$  only leads to an increase of the DALY estimate of a factor of 2, and from  $10^{-4}$  to  $10^{-3}$  to a factor 5. This illustrates the robustness of the DALY concept, due to its composite nature. Only at very high CFRs would the disease burden estimate be strongly affected. However, a CFR of  $10^{-3}$  is higher than for most bacterial pathogens, which is not in accordance with the relatively mild clinical presentation of cryptosporidiosis.

The estimates above refer to populations with only minor fractions of immunocompromised persons, which are often well localised, e.g. hospital patients. However, over 95% of the global total of all AIDS cases are in the developing world, with prevalences up to more than 10% in several African countries<sup>49</sup>. In the latter, the burden of disease for *Cryptosporidium* infection should be estimated with the adequate population composition in mind and will become a great deal higher.

### 2.3 Thermophilic *Campylobacter* spp.

The following is an extract of Havelaar *et al.*<sup>32</sup>, adopted for the purpose of the present report. Infection with thermophilic *Campylobacter* spp. (mainly *C. jejuni*) frequently leads to gastroenteritis. In developed countries, approximately one-third of all infected patients will develop diarrhoea of a watery nature, or more severe with blood and/or mucus in the faeces and/or accompanied by abdominal cramps. In developing countries, frequent exposure to *Campylobacter* spp. induces a high level of immunity, and asymptomatic or milder cases are common. Diarrhoea may lead to mortality, particularly in the elderly in developed countries and in young children in developing countries. Reliable estimates of the case-fatality ratio are

not available, some data from the US suggest that approximately 1 of every 10,000 cases of clinical campylobacteriosis dies. Several complications have been reported in the literature, of which Guillain-Barré syndrome (GBS) and reactive arthritis (ReA) are most important from a public health point of view.

GBS is an acute immune-mediated disease of the peripheral nervous system, characterized by areflexia and acute progressive and symmetrical motor weakness of more than one limb. Respiratory muscles may be affected too, and up to one-third of patients may require artificial ventilation. Approximately 1 out of every 3 severe cases of GBS and 1 out of every 5 mild cases is attributable to precedent infection with thermophilic *Campylobacter* spp. The probability of developing GBS after *Campylobacter* associated gastroenteritis is approximately 1:5000 ( $2 \times 10^{-4}$ ). Most severe cases need hospitalisation, and a sizeable proportion does not recover completely, leaving the patient with lifelong disabilities.

ReA is an immune-mediated inflammation of the joints that is associated with a recent infection at a distant site, including the gastrointestinal tract. There are few reliable data on the probability to develop ReA after infection with thermophilic *Campylobacter* spp., one of the reasons being the very diverse clinical manifestations of ReA and consequently different case-definitions that are being used by different authors. Based on outbreak studies, Havelaar *et al.*<sup>32</sup> estimated that 1-3% of patients with thermophilic *Campylobacter* spp. associated gastroenteritis would develop ReA with a duration between 3 and 9 weeks.

### **2.3.1 Severity weights and duration**

Table 2.4 presents severity weights, durations and burden of disease for different outcomes of *Campylobacter* infection. The disability weight for gastroenteritis in the general population was taken from the Global Burden of Disease study. Approximately 6% of all cases in the population suffer from more severe disease and will consult their general practitioner (GP). A severity weight for these cases was derived specifically for the study. Severity weights for GBS were also derived for the study, the weight for ReA was taken from Dutch estimates for other rheumatic diseases. The duration of gastroenteritis was taken from published studies (outbreak studies for cases in the general population, and data on duration of acute diarrhoea by all causes in general practice). For GBS, a complex model was constructed to account for the different degrees of severity, and for different clinical courses. The outcomes of such a model cannot simply be represented as the product of the mean severity and the mean duration. Therefore, only the disease burden per case, as published in the original study is reported.

*Table 2.4 Severity weights, durations and burden of disease following infection with thermophilic Campylobacter spp.*

Outcomes	Severity	Duration	Burden of disease per case in DALYs
Gastroenteritis, population	0.067	5.1 days	0.0009
Gastroenteritis, GP	0.39	8.4 days	.009
Gastroenteritis, death	1	13.2 yrs	13.2
GBS, clinical	-*	-	0.29
GBS, residual	-	-	5.8
GBS, mortality	-	18.7 yrs	18.7
Reactive arthritis	0.21	6 weeks	0.023

\*Complex combination of different disease stages (mild and severe, different clinical courses et cetera)

### 2.3.2 Calculation of the burden of disease

Since incidence and infection data for developing countries were not readily available, estimates of the burden of disease have not been calculated. For developed countries, the burden of mortality per 1000 symptomatic cases of gastroenteritis could be calculated using the formula  $DALYs = \text{Number} \times \text{Severity weight} \times \text{Duration}$  as in Table 2.5. For each disease stage, the number of cases is related to 1000 cases of gastroenteritis by multiplication with a transition probability. For example, the probability of visiting a GP for gastroenteritis is 6%, hence the number of cases is  $1000 \times 6\%$ . In the Table, the transition probabilities are indicated by a short text.

*Table 2.5 Population based estimate of disease following infection with thermophilic Campylobacter spp.*

Outcomes	Disease burden (DALY) per 1000 symptomatic cases of (gastroenteritis)
Gastroenteritis, population	$1000 \times 0.067 \times 0.014 = 0.94$
Gastroenteritis, GP	$1000 \times 6\% \text{ (GP)} \times 0.39 \times 0.023 = 0.54$
Gastroenteritis, death	$1000 \times 10^{-4} \times 13.2 = 1.32$
GBS, clinical	$1000 \times 2 \times 10^{-4} \text{ (GBS)} \times 0.29 = 0.06$
GBS, residual	$1000 \times 2 \times 10^{-4} \times 5.8 = 1.16$
GBS, mortality	$1000 \times 2 \times 10^{-4} \times 2.3\% \text{ (death)} \times 18.7 = 0.09$
Reactive arthritis	$1000 \times 2.3\% \text{ (ReA)} \times 0.21 \times 0.115 = 0.48$
Total	4.6

Data based on estimates for the Netherlands, 1990-2000

## 2.4 Shiga-toxin producing *Escherichia coli* O157

Recently, a report on the health impact in the Netherlands of *Escherichia coli* STEC O157 was published by Havelaar *et al.*<sup>50</sup>, of which the following is an extract. Infections with Shiga-toxin producing *Escherichia coli* STEC O157 may be asymptomatic, or may lead to diarrhoeal illness. In many cases (approximately 47% of endemic cases), stools are bloody and accompanied by abdominal cramps, a syndrome also known as haemorrhagic colitis. Fever, chills, nausea and vomiting also frequently occur as a consequence of STEC O157 infection. In 1985, Karmali and colleagues<sup>51</sup> reported an association between STEC and post-diarrhoeal haemolytic uraemic syndrome (D+ HUS), which occurs mainly in young children and may lead to death during the acute phase, to end stage renal disease or other outcomes. Since then, numerous studies, both in endemic and in outbreak situations have demonstrated that STEC, and particularly serotype O157, is the major etiologic agent of D+ HUS. Death as a consequence of HUS is the most severe outcome of infection, and also the most important factor in disease burden calculations. A proportion of HUS patients may develop sequelae, of which chronic renal failure (End Stage Renal Disease - ESRD) is the most important. These patients depend on renal replacement therapy (dialysis, transplantation) for the rest of their life.

Figure 2.2 presents a disease model of health outcomes following STEC O157 exposure. In outbreak situations, as much as 40% of all symptomatic children have been reported to develop HUS, but figures between 5 and 15% are more typical. In the endemic situation in the Netherlands, the annual incidence of symptomatic infections in the 0-4 year age group (about 5% of the total population) is estimated as approximately 500 cases per year, of which 250 with bloody diarrhoea. The associated incidence of HUS is approximately 12 cases per year (i.e. 2.5%). The mortality associated with the acute phase of HUS is approximately 4%, given adequate access to high care hospitals with dialysis units. An estimate of the case fatality ratio with less advanced hospital care could be based e.g. on data from the Netherlands before 1973, when 17% of cases were fatal. Up to 10% of HUS patients will develop End Stage Renal Disease, either directly or 20 years or more after initial recovery. Dialysis and renal transplantations in these patients may be associated with excess mortality and reduced quality of life. Even though the incidence of HUS is highest in children under five years of age, mortality due to HUS occurs mainly at ages above 65, due to the very high case-fatality ratio in the elderly. For ESRD mortality is more evenly distributed over all age classes leading to a higher loss of life years for ESRD cases.

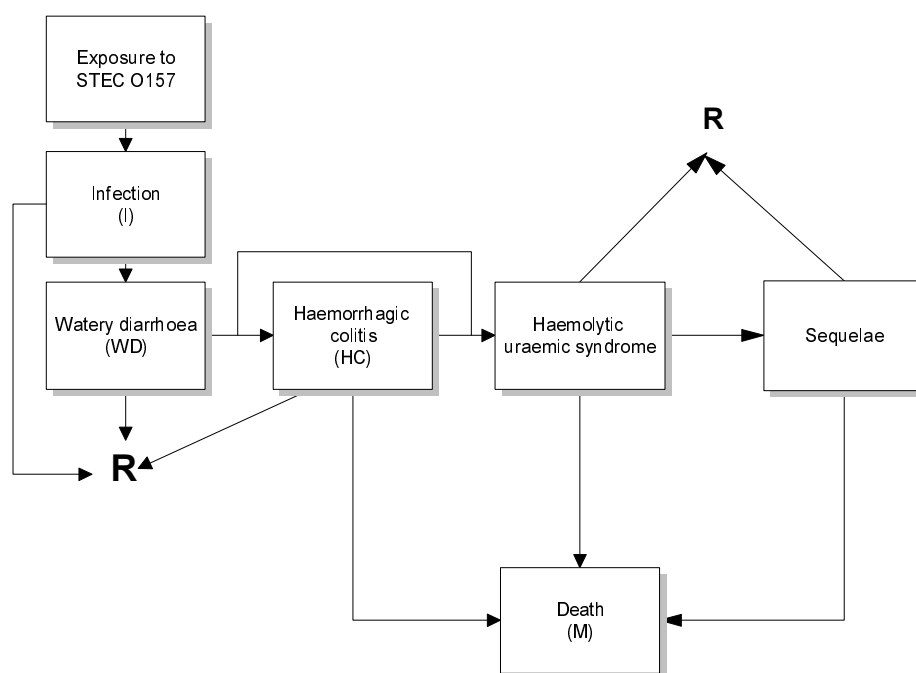


Figure 2.2 Chain model of outcomes of exposure to STEC O157 (R = recovery)

### 2.4.1 Severity weights and durations

Given the high case-fatality ratio of HUS, the mortality burden dominates the morbidity burden, as is clear from the data in Table 2.6. For ESRD, a complex model was constructed to account for the different clinical courses, including dialysis, transplantation, life with a healthy graft, graft failure, a second period on dialysis *et cetera*. The outcomes of such a model cannot simply be represented as the product of the mean severity and the mean duration. Therefore, only the disease burden per case, as published in the original study is reported.

Table 2.6 Severity weight, durations and burden of disease following Shiga-toxin producing *Escherichia coli* O157 infection

Outcomes	Severity	Duration	Burden of disease per case in DALYs
Watery diarrhoea	0.067	3.4 days	0.0006
Bloody diarrhoea	0.39	5.6 days	0.006
Death from diarrhoea	1	13.2 yrs	13.2
HUS	0.93	21 days	0.05
Death from HUS	1	26.2	26.2
ESRD	-*	-	8.7
Death from ESRD	1	34 yrs	34

\*Complex combination of different disease stages (dialysis, transplantation, life with healthy graft, graft failure, dialysis etc....)

## 2.4.2 Calculation of the burden of disease

Since incidence and infection data for developing countries were not readily available, estimates of the burden of disease have not been calculated. For developed countries, the burden of disease per 1000 symptomatic cases could be calculated using the formula

$DALYs = \text{Number} \times \text{Severity weight} \times \text{Duration}$  as in Table 2.7. It must be noted that this table is a summary of a complex simulation model. Transition probabilities (e.g. case-fatality ratio's, probability to develop HUS or ESRD) as given in Table 2.7 were calculated to fit the final results of this model and are only included here as an illustration. The input in the stochastic model was more complex, e.g. differentiating between age groups.

*Table 2.7 Population based estimate of disease burden of illness due to STEC O157*

Outcomes	Disease burden (DALY) per 1000 symptomatic cases of (gastroenteritis)
Watery diarrhoea	$1000 \times 53\% \text{ (watery diarrhoea)} \times 0.067 \times 0.009 = 0.3$
Bloody diarrhoea	$1000 \times 47\% \text{ (bloody diarrhoea)} \times 0.39 \times 0.015 = 2.8$
Death from diarrhoea	$1000 \times 2.7 \times 10^{-4} \text{ (mortality)} \times 13.2 = 3.5$
HUS	$1000 \times 10^{-2} \text{ (HUS)} \times 0.93 \times 0.057 = 0.5$
Death from HUS	$1000 \times 10^{-2} \times 1.04 \times 10^{-1} \text{ (mortality)} \times 26.2 = 27.3$
ESRD	$1000 \times 10^{-2} \times 1.18 \times 10^{-1} \times \text{(ESRD)} \times 8.7 = 10.2$
Death from ESRD	$1000 \times 10^{-2} \times 1.18 \times 10^{-1} \times 2.52 \times 10^{-2} \text{ (mortality)} \times 34 = 10.1$
Total	54.7

*Data based on estimates for the Netherlands, 1990-2000*

## 2.5 Bromate

The following is a short extract from Havelaar *et al.*<sup>31</sup>, adapted for the purpose of the present work. Bromate has been shown to induce tumours in the rat kidney, thyroid and mesothelium and is a renal carcinogen in the mouse as well. In accordance with WHO-GDWQ Volume 2 we concentrate on renal cell cancer as an outcome of chronic exposure to bromate. The survival of patients with renal cell cancer depends primarily on age, fitness for resection, post-operative survival and the presence of metastases. Patients with one or more unfavourable prognostic factors have a very short survival. Those who survive for 5 years after diagnosis have a normal life expectancy.

### 2.5.1 Severity weights and durations

The morbidity burden due to renal cell cancer is small in comparison with the mortality burden because death usually occurs within a few months after diagnosis of a fatal case, and because the quality of life after a successful operation is not negatively influenced. Therefore only mortality was considered, with severity weights equal to one. Durations (remaining life expectancies) were based on Dutch data, and presented in Table 2.8.



*Table 2.8 Severity weights, durations and burden of disease following bromate exposure*

Outcomes	Severity	Duration in years		Burden of disease per case in DALYs	
		< 70 years	70 years	< 70 years	70 years
Death	1	25	11	25	11

## 2.5.2 Calculation of the burden of mortality

Using the aforementioned data, the case-fatality ratio per age class could be calculated as outlined in Table 2.9.

*Table 2.9 Estimation of bromate related renal cell cancer case-fatality ratio*

Parameter	Age class	
	< 70 years	70 years
Percent in class	62 %	38 %
No resection	18 %	37 %
Post-operative death	4 %	4 %
Metastases	19 %	14 %
Death within 5 years (no metastases)	25 %	48 %
Total case fatality ratio	52 %	73 %

With the formula  $DALYs = \text{Number} \times \text{Severity weight} \times \text{Duration}$ , and taking into account the distribution of cases over the two age groups (58% under 70 years), this leads to a burden of disease per 1000 bromate related renal cell cancer cases of 10900 DALYs, as indicated in Table 2.10.

*Table 2.10 Population based estimate of disease burden of bromate related renal cell cancer*

Outcomes	Disease burden (DALY) per 1000 symptomatic cases of (gastroenteritis)
Age < 70 years	$1000 \times 52\% \times 58\% (< 70 \text{ years}) \times 25 = 7540$
Age 70 years	$1000 \times 73\% \times 42\% (70 \text{ years}) \times 11 = 3370$
Total	10910

*Data based on estimates for the Netherlands, 1990-1995*

## 2.6 Rotavirus, hepatitis A virus and arsenic

The above given examples of burden of disease calculations were derived from published studies. For rotavirus and hepatitis A, two major causes of disease especially in developing countries, and for arsenic that in some regions has a huge public health effect, such publications are not available. The following burden of disease calculations are therefore only

indicative of how the approach could work for these important agents, and numerical results should as such be regarded with caution.

### **2.6.1 Rotavirus**

Rotaviruses are the single most important etiologic agents of severe diarrhoeal illness of infants and young children world-wide. Although diarrhoeal diseases are one of the most common illnesses of infants and young children throughout the world, they assume a special significance in less developed countries, where they constitute a major cause of mortality among the young<sup>52,53</sup>.

Rotaviruses display a seasonal pattern of infection in temperate climates, with epidemic peaks occurring in the cooler months of the year, a pattern not distinctly observed in other climates. There are four serotypes of human rotavirus; infection with one serotype causes a high level of immunity to that serotype, and partial protection against the other serotypes<sup>54</sup>. Although all four serotypes cause disease, serotype 1 appears to be the most common cause of epidemic rotavirus diarrhoea in countries with a temperate climate. Information on the distribution of rotavirus according to serotype in the developing countries is mostly limited<sup>55</sup>.

#### ***Clinical features***

Symptoms range from sub-clinical infection to mild diarrhoea to severe and occasionally fatal dehydrating illness. In immunodeficient children, rotavirus can produce a chronic symptomatic infection or serious illness. For immunocompromised adults rotaviruses pose a special threat in causing severe gastroenteritis, but does not appear to play an important role in diarrhoea occurring in adults infected with HIV<sup>52</sup>. Rotavirus gastroenteritis severe enough to require hospitalisation occurs most frequently in children below 24 months, with lower frequencies in neonates shedding rotavirus. Malnutrition is thought to play an important role in increasing the severity of clinical manifestations of human rotavirus infection, while repeated diarrhoea may also be a precipitating factor for developing malnutrition<sup>52</sup>. Rotavirus gastroenteritis in adults is unusual, since most infections occur subclinically. In general, the disease is characterised by vomiting and watery diarrhoea for 3-8 days, and fever and abdominal pain occur frequently<sup>53</sup>.

#### ***Epidemiology***

Rotavirus is the most important cause of severe, life-threatening diarrhoea in children under 2 years of age world-wide. Nearly all children are infected at least once before the age of 2 years, and repeated infections are common. Usually only the first rotavirus infection causes significant illness. It has been estimated that world-wide about one-third of children under 2 years of age experience an episode of rotavirus diarrhoea. Rotaviruses cause 35-40% of hospitalisation due to diarrhoeal diseases during the first 2 years of life worldwide<sup>52</sup>. The highest rates of illness occur amongst infants and young children, causing the death of over 600,000 children annually worldwide<sup>53</sup>.

#### ***Developing countries***

In developing countries, rotaviruses are usually the leading cause of life-threatening diarrhoea in infants and young children. Studies in the eighties estimated the number of cases at over 125 million, of which 18 million (14.4%) were considered (moderately) severe and 873,000 die each year (case-fatality rate of 0.7% in the 80s). It was shown that 45% of children less

than 2 years of age carried rotavirus, while 20-40% of the severe diarrhoea cases were caused by rotavirus<sup>52, 55</sup>.

### ***Developed countries***

Although rotavirus diarrhoea occurs with high frequency in the developed countries, mortality is low. In 1994, the number of cases in the US has been estimated at over 1 million in the 1-4 years olds but only up to 150 deaths, a case-fatality rate of 0.015%. More recently however (1999), it was estimated that in the US the virus causes the hospitalisation of 55,000 children each year, and 40 times more cases of rotavirus gastroenteritis, i.e. more than 2 million cases<sup>53</sup>. In the early eighties about 35-60% of diarrhoeal illnesses admitted to a hospital were associated with rotavirus infection. In children below 36 months 88% of rotavirus infections were symptomatic. In another study, 16% of children with diarrhoea but not requiring hospitalisation were rotavirus-positive<sup>52</sup>.

Amongst young children, rotavirus infection is among the most common causes of hospitalisation, and may lead to dehydration<sup>56,57</sup>. In the Netherlands some 1000 cases of rotavirus infection per year were virologically established<sup>58</sup>. The number of cases of gastroenteritis in the UK and the Netherlands was 190 and 280 per 1000 persons per year respectively<sup>56,59,60</sup>. In the Netherlands, rotaviruses caused 7.3% of all gastroenteritis cases, while 8 out of 1000 persons per year sought physician consultation in the Netherlands of which 5.3% turned out to be caused by rotavirus.

### ***Severity weights, durations and disease model***

Estimates of severity weights and duration were derived as follows. The Global Burden of Disease study provides a severity weight for diarrhoeal episodes of 0.119 for under fives and 0.086-0.094 for older ages (p.412)<sup>5</sup>, while the classes approach gives 0.02-0.24 (see Table 1.1). Table 2.11 shows provisional weights and durations divided between mild and severe diarrhoea, based on their incidence fractions (14.4% severe in developing countries) and an overall weight of 0.119. An average age at death of 1 was assumed, which means a loss of about 80 years, using life tables from the Global Burden of Disease study<sup>5</sup> (see Annex). The burden of disease per case was calculated by multiplying severity weights with durations.

*Table 2.11 Severity weights, durations and burden of disease following rotavirus infection*

Outcomes	Severity	Duration	Burden of disease per case in DALYs
Diarrhoea -mild	0.10	1 week	0.002
-severe	0.23	1 week	0.004
Death	1	80 yrs	80

A model of disease and mortality following rotavirus infection is presented in Figure 2.3. Tentative transition rates were derived from the not entirely consistent evidence given above. It was assumed that after rotavirus infection 10-15% are asymptomatic, while 85-90% develop diarrhoea of which in high income countries 2.5% (based on US figures) and in developing countries 12% severe, with the rest mild diarrhoea leading to full recovery. From the severe diarrhoea cases it was assumed that in low-income regions about 5% dies and in high-income regions 0.6%, the other cases fully recovering.

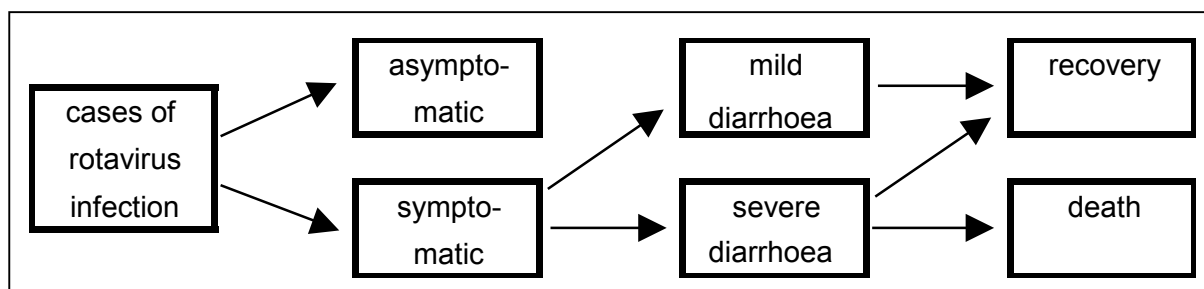


Figure 2.3 Disease model of rotavirus infection

### **Burden of disease calculation**

#### **Mortality**

In order to estimate the burden of this mortality amongst children, for the lower income countries, a case-fatality rate of 0.6% was applied (supposing some improvement since the 80's with 0.7%). For the developed countries figures for the US were used, i.e. a case-fatality rate of 0.015%. The age at death due to rotavirus infection amongst young children was assumed at 1, leaving 80 years of lost life expectancy. This resulted in a burden of disease per 1000 cases (symptomatic) as follows:

developing countries  $1000 * 0.6\% * 1 * 80 = 480$  DALYs, and for:

developed countries:  $1000 * 0.015\% * 1 * 80 = 12$  DALYs.

#### **Morbidity**

Regarding morbidity, the burden of morbidity caused by periods of rotavirus diarrhoea was calculated using the estimated severity weights and duration (see Table 2.11) and the disease model transition rates. The following point estimates were used: the fraction of infected children that becomes symptomatic: 88% in developed countries (see above), with a little higher rate (90%) in developing countries; the fraction of children that becomes infected: high income regions 14% and low income 17%, derived from the disease model; the fraction of young children (below 5 years of age) of the whole population: about 13% in lower income and 7% in high income countries<sup>61</sup>.

Tentative results for mortality and morbidity burden based on the above mentioned assumptions are summarised in Table 2.12.

*Table 2.12 Rotavirus burden of disease estimates for different sub-populations*

DALYs per 1000	Cases (sympt.)
Low income regions	
Burden of morbidity	2.2
Burden of mortality	480
Total Burden of disease	482
High income regions	
Burden of morbidity	2.0
Burden of mortality	12
Total Burden of disease	14

The burden of disease caused by morbidity in lower income countries is estimated at only 0.5% of the total burden of disease, while in developed countries this is about 15%. Such figures appear relatively negligible in the lower income region, but may be regarded as more important in the higher income regions. This shows that when a disease causes the death of large numbers of young children, the burden of disease is dominated by mortality, as can be expected using the DALY methodology.

## 2.6.2 Hepatitis A virus

### *Clinical features*

Natural infection with the Hepatitis A virus (HAV) usually follows ingestion of virus from material contaminated with faeces containing HAV. The course of viral hepatitis may be extremely variable. Anicteric hepatitis refers to patients who develop clinical symptoms, but who are not jaundiced, while icteric patients do. Patients with inapparent or subclinical hepatitis have neither symptoms nor jaundice. Patients may recover completely or develop fulminant hepatitis and die<sup>62</sup>. In general, HAV infection may result in non-specific symptoms like fever, headache, fatigue, diarrhoea, intermittent nausea and vomiting, followed by signs of hepatitis 1-2 weeks later<sup>63,64</sup>.

A short prodromal or preicteric phase, varying from several days to more than a week, precedes the onset of jaundice. In over half of the patients, the prodromal state is typically characterised by anorexia, fever, fatigue, malaise, myalgia, nausea, and vomiting. The transition from well-being to acutely ill occurs abruptly (within a period of 24 hrs) in over 60% of patients. Diarrhoea, nausea and vomiting are more frequent in children than in adults. Older children and adults often complain of right-upper-quadrant pain or discomfort as a consequence of hepatomegaly, which usually precedes jaundice by 1-2 weeks. The icteric phase (unusually coloured urine, stool, skin *et cetera*) begins within 10 days of the initial symptoms in over 85% of HAV cases. Patients often seek medical attention when jaundice becomes clinically apparent. Fever, if present, usually subsides after the first few days of jaundice<sup>62</sup>. Relapsing hepatitis occurs in 1.5-20% of HAV cases<sup>62,63,64</sup>. Hospitalisation and death due to hepatitis A is age-dependent. While Blaine Hollinger and Ticehurst write that two-thirds of the cases in the US occur in children and young adults and over 70% of deaths are observed in patients over 49 years of age<sup>62</sup>, recent CDC reports indicated that 30-40% of cases occur in children and adolescents (<20 years of age)<sup>65</sup>. The latter source will be used in

the presented calculations. Among patients with chronic hepatitis B or underlying liver disease, the mortality rate is considerably higher<sup>62</sup>.

Occasionally, patients develop fulminant hepatitis, characterised by the sudden onset of high fever, marked abdominal pain, vomiting, and jaundice, followed by the development of hepatic encephalopathy associated with deep coma and seizures, leading to death in 70-90% of cases. Mortality increases with age, survival being uncommon over the age of 45 years. This clinical pattern is rare, occurring in less than 1.5% of icteric patients hospitalised for acute viral hepatitis<sup>62</sup>.

Generally speaking, the disease is milder in children than in adults, complete recovery is the rule, and chronic outcomes have not been observed. Acute hepatitis A is usually a mild illness, preceded by typical prodromes similar to 'flu' with prominent myalgia and anorexia, a few days to two weeks before the onset of jaundice. Typical outcomes following an infection in seronegative individuals are summarised in Table 2.13.

*Table 2.13 Predicted typical outcomes following an infection with hepatitis A virus*

Parameter	Children (<5yr)	Adults
Inapparent infection	80-95%	10-25%
Anicteric or icteric disease	5-20%	75-90%
Complete recovery	99+ %	98+ %
Mortality rate <15 years		0.1%
15-39 years		0.3%
>39 years		2.1%

*Source: reproduced from Blaine Hollinger et al. p. 757<sup>62</sup>*

*Note: Mortality rate assumedly referring to symptomatic cases only.*

### **Epidemiology**

Hepatitis A has been endemic world-wide, but the incidence has decreased dramatically in many regions by sanitary measures only<sup>63</sup>. In populations with low sanitation levels and crowded living conditions, infections occur at an early age and nearly 100% of children acquire immunity. Since hepatitis A infections have become less common in developed regions, less people will acquire immunity and infections will occur more often in older age groups with more severe effects. The community incidence of hepatitis A virus varies therefore significantly by geographical region. The world-wide incidence may exceed 1.4 million cases each year, at a health cost between 1.5 and 3 billion US\$ annually<sup>62</sup>.

Patients occasionally develop fulminant hepatitis leading to death in 70-90% of cases. The risk of developing fulminant hepatitis appears much higher in case of pre-existing liver disease e.g. hepatitis C (estimated between 1% to 10%; personal communication M. Koopmans, RIVM, the Netherlands). Mortality increases with age, survival being uncommon over the age of 45 years. This clinical pattern is rare, occurring in less than 1.5% of icteric patients hospitalised for acute viral hepatitis<sup>62</sup>. More than 95% of infections in young children will not lead to symptoms and will not be detected, while in adults HAV infection may result in rather serious illness in 70-80% of persons, with a case-fatality rate of

up to 3%<sup>66</sup>. Besides the case-fatality rates mentioned above, Chin more recently presented a case-fatality rate of 1.8% for people above 50 years of age<sup>67</sup>.

In the US, about 9.5 cases HAV per 100,000 population were reported in 1993<sup>62</sup>, of which an estimated 7.3% were food- or waterborne<sup>63</sup>. In outbreak situations, up to 20% of cases are due to secondary transmission. Rates of disease are particularly high among children and young adults and in American Indians and Hispanics. The actual incidence is much higher because many persons contract such a mild form of hepatitis that they do not seek treatment, and because fewer than 12% of the hospitalised cases is reported. It has been estimated in 1990 that in the US 75,800 clinical cases occur each year, of which 11,400 are hospitalised, and 80 die from fulminant hepatitis<sup>62</sup>, while CDC recently estimated about 100 deaths due to fulminant hepatitis per year, with 33% of Americans immune<sup>64</sup>.

In England and Wales the number of reported cases has risen between 1987 and 1991 from 3.6 to 14.6 per 100,000. Incidence in low endemic is generally estimated at regions 10 per 100,000<sup>63</sup>. In the Netherlands 27% of reported cases of HAV between 1988 and 1999 was related to travelling to high-endemic regions<sup>63,68</sup>.

### ***Severity weights, durations and disease model***

For health effects due to hepatitis, the Global Burden of Disease study does unfortunately not provide severity weights or durations. For the flu-like mild form, one might look at the figures for influenza, which is however presented together with pneumonia: a severity weight of 0.28 for all age groups, treated and untreated alike (p.413<sup>5</sup>), and a duration of 7.3 days in established market and former socialist economies, and 11 days in the rest of the world. Since influenza is generally milder and more frequent than pneumonia, the weight for the mild form is here assumed to be substantially lower than the GBD-weight, with the weight for the severe form not much higher. The duration of the flu-like symptoms is assumed at 5 days with an extra 7 days for the hospitalised, with somewhat longer durations for adults (7 and 11 days). Fulminant hepatitis is a severe outcome, in the classes approach (see Table 1.1) apparently comparable to classes 5 or 6 (0.36-0.70; average 0.5); its duration was estimated at 1 month. Table 2.14 shows provisional weights and durations, together with the ages of death and remaining life expectancy using life tables from the Global Burden of Disease study<sup>5</sup> (see also Annex). The burden of disease per case was calculated by multiplying severity weight with duration for each age group.

*Table 2.14 Severity weights, durations and burden of disease following hepatitis A infection*

Outcomes	Severity	Duration by age group			Burden of disease per case by age group in DALYs		
		0-14	15-49	>50	0-14	15-49	>50
Hepatitis		0-14	15-49	>50	0-14	15-49	>50
symptomatic/flu-like	0.15	5 days	7 days	7 days	0.002	0.003	0.003
severe/hospitalised	0.35	1 week	11 days	11 days	0.007	0.011	0.011
fulminant	0.5	1 month	1 month	1 month	0.04	0.04	0.04
Death	1	74 y	50 y	20 y	74	50	20

Figure 2.4 presents a model of disease and mortality following hepatitis A infection. The model assumes that death only occurs after the development of fulminant hepatitis. As mentioned above, the incidence in low endemic regions is generally estimated at 10 per

100,000; however, the published 75,800 clinical cases in the US is then about three times too high. Without further and more in-depth studies, sufficiently consistent transition rates could not be derived from the available literature.

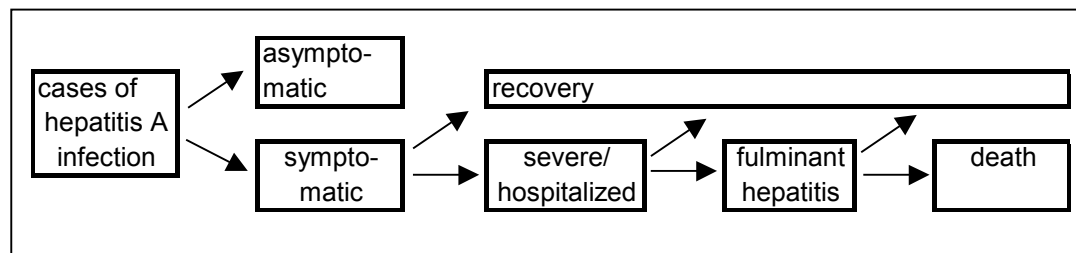


Figure 2.4 Disease model of hepatitis A infection

### **Burden of disease calculation**

The burden of disease due to hepatitis A infection has been separately estimated for mortality and morbidity, with results summarized in Table 2.15.

### **Mortality**

For the hepatitis A virus the most severe health outcome following infection is death. The most sensitive age group for infection is apparently the young children. The sensitivity for developing this most severe effect, dying from hepatitis, is however much higher in middle-aged and elderly people.

For developing countries with nearly all children infected and all adults immune, we assume that 0.1% of cases (all children) die, while for the high income region the most sensitive age group is obviously the middle-aged and elderly, with a case-fatality rate of 2%. Ages of death and remaining life expectancy for low income regions were assumed at: an age of 7.5 years at the time of death and a remaining life expectancy of 74 years; for high income countries: 62.5 years as age of death, and 20 years remaining life expectancy. This results in burden of disease per 1000 symptomatic cases with the formula

DALYs = Number\*Severity weight\*Duration as follows: developing countries (children):  $1000*0.1\%*1*74 = 74$  DALYs per 1000 cases, and developed countries (persons >50):  $1000*2\%*1*20 = 400$  DALYs per 1000 cases.

Regarding the developed countries, different age groups and their mortality rates must be dealt with (age distribution according to US data). For the age group 0-14 the same burden of mortality per case was assumed compared to the low income countries. For ages 15-49 a little higher case-fatality rate than the one mentioned for ages 15-39, say 0.5%, and a remaining life expectancy of 50 were used. This leads to a burden of mortality per 1000 cases of:  $1000*0.5\%*50 = 250$  DALYs in this age group. For ages above 50 the figures as calculated above were used (400 DALYs per 1000 cases).

For an estimate of the burden of mortality due to hepatitis A for 1000 symptomatic cases distributed over the three age groups, the estimated mortality burdens for the three age groups have to be combined with the following data: in the US 28% of cases occur amongst children and young adults (<15 years), 62% in age group 15-49 and 10% in the over 50's<sup>65</sup> (average for 1994 and 1995), and the age group population fractions are resp. 21%, 51%, 28%<sup>61</sup>. This resulted in a mortality burden of 187 DALYs per 1000 symptomatic cases.



## Morbidity

Regarding morbidity, the burden of morbidity caused by hepatitis A has been provisionally estimated using severity weights and duration (see Table 2.14) and the disease model (see Figure 2.4). Although consistent transition rates could not be derived for all steps of the model, when the published US data (75,800 clinical cases of which 11,400 are hospitalised and 80 die) were used together with the more recent number of 100 deaths and the given less than 1.5% of the hospitalised developing fulminant hepatitis and the above given figures, the morbidity burden per 1000 cases (below 15 years) could be calculated at 3.1 DALYs. Since in developing countries only young children are affected by hepatitis A, this number equals the total burden of disease per 1000 cases.

With regard to developed countries, for cases above 15 years of age the burden of morbidity could be estimated at 4.5 DALYs per 1000 cases (age groups 15-49 and >50 were taken together since for these groups the severity weights and durations are the same). When using the same approach as above with estimating 28% of cases in the under 15's, this results in 3.9 DALYs per 1000 cases as distributed over the age groups.

Results for both regions are summarised in Table 2.15. An important flaw of this approach is of course the application of epidemiological figures for developing severe and fulminant hepatitis for high income countries to low income regions. Although the evidence was not entirely consistent, estimates suggest that the morbidity burden of disease might well be below 5% of the mortality burden.

*Table 2.15 Hepatitis A burden of disease estimates*

DALYs per 1000	Cases (symptomatic)			
	total	0-14	15-49	>50
Developing countries*	total			
Burden of mortality	74			
Burden of morbidity	3			
Total burden of disease	76			
Developed countries	total	0-14	15-49	>50
(age group)				
Burden of mortality	187	74	250	400
Burden of morbidity	3.9	3	4.5	4.5
Total burden of disease	191	77	255	405

\*In developing countries, most cases occur in children under 5 years of age

### 2.6.3 Arsenic

Arsenic is a natural part of the earth's crust in some parts of the globe and may be found in water that has flowed through arsenic-rich rocks<sup>1</sup>. Drinking arsenic-rich water over a long

<sup>1</sup> Text in paragraph 2.6.3 largely extracted from: Guidelines for drinking-water quality, 2<sup>nd</sup> edition, volumes 1 and 2. Geneva, WHO 1993; [http://www.who.int/health\\_topics/arsenic/en/](http://www.who.int/health_topics/arsenic/en/); and: Smith AH, Lingas EO, Rahman M. Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. Bull WHO 2000;78:1093-103.

period is unsafe, and in some countries around the world the health effects are well known. Conditions of malnutrition and hepatitis B appear to aggravate the health effects. Delayed effects from arsenic poisoning, the lack of common definitions and poor reporting and local awareness in affected areas are major problems in determining the extent of the arsenic-in-drinking-water problem and developing adequate solutions. However, WHO has compiled reports of cases of arsenic in drinking-water in countries such as Argentina, Bangladesh, China, Chile, Ghana, Hungary, India, Mexico, Thailand and the United States of America. In Bangladesh, West Bengal (India) and some other areas, most drinking-water used to be collected from rivers and ponds with little or no arsenic, but with contaminated water transmitting diseases such as diarrhoea, dysentery, typhoid, cholera and hepatitis. Programs to provide "safe" ground drinking-water have helped to control these diseases, but in some areas they have had the unexpected side-effect of exposing the population to a new and large health problem - arsenic.

### ***Clinical features***

Early clinical symptoms of acute intoxication include abdominal pain, vomiting, diarrhoea, muscular pain, and weakness, with flushing of the skin. These symptoms are often followed by numbness and tingling of the extremities, muscular cramping, and the appearance of a papular erythematous rash. Within a month, symptoms may include burning paraesthesias of the extremities, palmoplantar hyperkeratosis, Mee's lines on fingernails, and progressive deterioration in motor and sensory responses. The latency for arsenic-caused skin lesions is typically about 10 years.

Signs of chronic arsenicalism, including dermal lesions, peripheral neuropathy, cancers of skin (with a typical latency of more than 20 years), bladder and lungs, and peripheral vascular disease, have been observed in populations ingesting arsenic-contaminated drinking-water. Dermal lesions were the most commonly observed symptoms, occurring after minimum exposure periods of approximately 5 years. Effects on the cardiovascular system were observed in children consuming arsenic-contaminated water (mean concentration 0.6 mg/litre) for an average of 7 years.

### ***Epidemiology and dose response relation***

A recent article on contamination of water supplies by arsenic in Bangladesh, states that between 35 and 77 million people of the country's total population of 125 million are at risk of exposure to arsenic in their drinking-water<sup>69</sup>. At least 100,000 cases of debilitating skin lesions are believed to have already occurred. 'Bangladesh is grappling with the largest mass poisoning of a population in history. The scale of this environmental disaster is greater than any seen before. It is beyond the accidents at Bhopal, India, in 1984, and Chernobyl, Ukraine, in 1986'. Health effects range from skin lesions to cancers of the bladder, kidney, lung and skin, neurological effects, cardiovascular and pulmonary disease, and diabetes. The diseases may develop slowly over many years. 'It is reasonable to expect marked increases in mortality from internal cancers once sufficient latency has been reached'.

Regarding skin cancer, a study of a large population in Taiwan found a clear dose-response relationship between arsenic concentrations in drinking-water and the prevalence of skin cancer. In this study, the average concentration of arsenic in water was about 500 µg/l, and by age 60 more than 1 in 10 had developed skin cancer. The lifetime risk of developing skin

cancer from the intake of 1 µg/kg body weight/day (roughly equivalent to 1 litre per day at concentrations of 50 µg/l) of arsenic in water ranges from 1 to 2 per 1000.

Using the US-EPA multistage model, the second edition of the GDWQ calculated the concentration of arsenic in drinking-water associated with an excess lifetime skin cancer risk of  $10^{-5}$  at 0.17 µg/litre (daily intake usually assumed at 2 litres/day). This value may however overestimate the actual risk of skin cancer owing to the possible contribution of other factors to disease incidence in the population, and to possible dose-dependent variations in the metabolism that could not be taken into consideration. In addition, this value is below the practical quantification limit of 10 µg/litre. With a view to reducing the concentration of this carcinogenic contaminant in drinking-water, a provisional guideline value for arsenic in drinking-water of 0.01 mg/litre has been established. The estimated excess lifetime skin cancer risk associated with exposure to this concentration is  $6 \times 10^{-4}$ .

Concerning other cancers, the second edition of the WHO-GDWQ judged data on the association between internal cancers and ingestion of arsenic in drinking-water as insufficient for quantitative assessment of risk. However, recent evidence showed the following<sup>69,70</sup>. In Taiwan populations exposed to high concentrations of arsenic in their drinking-water, containing an average of 800 µg/l of arsenic, had estimates of relative risk of bladder cancer in the order of 30 to 60. In Region II of northern Chile, 5–10% of all deaths occurring among those over the age of 30 were attributable to arsenic-caused internal cancers, in particular bladder cancer and lung cancer. Average exposures were in the order of 500 µg/l (0.5 mg/l) over 10–20 years; exposure decreased in subsequent years after remediation efforts were introduced. Long latency was apparent, and increases in mortality continued for 40 years after the highest exposures began. In Argentina, a mortality study in the arsenic-exposed region of Córdoba found increased risks of bladder and lung cancer among men and women from 1986 to 1991, although concentrations were lower (average 178 µg/l) than in Taiwan and Chile.

Using the current US Environmental Protection Agency standard of 50 µg/l, Smith *et al.*<sup>70</sup> concluded that the lifetime risk of dying from cancer of the liver, lung, kidney or bladder while drinking 1 litre a day of water containing arsenic at this concentration could be as high as 13 per 1000 persons exposed. Using the same methods, the risk estimate for 500 µg/l of arsenic in drinking-water would be 13 per 100 people. In its latest document on arsenic in drinking-water, the US National Research Council concluded that exposure to 50 µg/l could easily result in a combined cancer risk of 1 in 100<sup>69</sup>.

### ***Severity weights and durations***

Table 2.16 shows provisional severity weights, durations and resulting burden of disease per case estimates for some of the most important and likely occurring health effects following long term exposure to arsenic in drinking-water. In the Global Burden of Disease study, there is unfortunately no severity weight for debilitating skin lesions included; a point estimate was therefore based upon weights for conditions with possibly somewhat similar consequences, such as diabetic foot, amputations and osteoarthritis<sup>5</sup> (p.415-6) (resp. 0.13, 0.07-0.3, 0.16), taking the higher range values, not assuming complete recovery through treatment. For skin cancer morbidity the GBD gives a weight of 0.045, while the weight for morbidity due to other cancers was based on the weights for cancers of the liver, the trachea, bronchus and lung, and the bladder<sup>5</sup> (p.414-5), resp.0.24, 0.146, and 0.086.

Point estimates for the durations of the selected outcomes were derived as follows. It was firstly assumed that in a particular population exposure is lifelong. Subsequently, for debilitating skin lesions a latency period of ten years was assumed, leaving 72 years remaining life expectancy living with such lesions (see Annex). Obviously, this again excludes treatment and does not take into account longer latency periods (depending also on dose<sup>69</sup>) and has to be regarded as an upper limit of duration. For skin cancer and other cancers ages of death were assumed of resp. 30 and 35 year, with remaining life expectancies of 54 and 50 (27 and 26 when 3% future discounted). The average duration of cancer morbidity was derived from the GBD-study volume 2<sup>61</sup> taking values for the world and the same cancers as for the severity weights: average duration of skin cancer 4 years and other arsenic-related cancers 2 years.

*Table 2.16 Severity weights, durations and burden of disease following prolonged arsenic exposure*

Outcomes	Severity	Duration in years	Burden of disease per case in DALYs
Debilitating skin lesions	0.2	72	14
Skin cancer	-morb.	0.05	4
	-mort.	1	54
Other cancers	-morb.	0.2	2
	-mort.	1	50

*Notes: long term exposure health effects only based on the literature*

### **Burden of disease calculation**

For arsenic, the most severe health outcome following exposure and intake is obviously death. Since exposure needs to occur for at least 20 years to cause the cancers leading to death, all deaths occur in adults. With  $DALYs = \text{Number} * \text{Severity Weight} * \text{Duration}$  this results in  $1000 * 1 * 54 = 54000$  DALYs per 1000 skin cancer deaths.

Calculating a burden of disease for an actual population requires detailed information on the distribution and level of arsenic exposure and intake, population characteristics and the distribution of health effects. As examples, two provisional burden of disease calculations are presented here. First, in 1987 US-EPA estimated that in the US about 350,000 people might drink water containing more than 50 µg/l and 2.5 million water more than 25 µg/l<sup>70</sup> (population US in 1987 was 240 million). With the calculated 13 per 1000 as a lifetime risk of dying from internal cancers (still excluding skin cancer) when consuming 1 l/day with 50 µg/l and assuming a lifetime exposure of 70 years, this results in at least about 65 deaths per year in the US, equal to 3250 DALYs per year and 9 DALYs per year per 1000 exposed to 50 µg/l. This burden of disease estimate however leaves out morbidity and also skin cancer mortality.

As a second example the case of Bangladesh is used here, as described by the WHO and modelled for a period of 30 years of exposure to a mode concentration ranging from 100-290 µg/l<sup>71</sup>. Assuming a steady state of the population and the number of cases, the final prevalence (after 30 years) equals year-incidence times duration, and the burden of disease per case per year is then equal to the severity weight (duration already included in the prevalence), except for death since this is an 'incidence'. Table 2.17 shows the central

estimate of the percentages of the village population in each health state, which together with the burden of disease per case per year leads to a total burden of disease per 1000 persons exposed, of 111 DALYs per year. It was assumed that the severity of late stage keratosis is equal to debilitating skin lesions, while earlier, less severe stages were not taken into account.

*Table 2.17 Health status and burden of disease per year and total of arsenicosis in a Bangladesh village (base case incidence)*

Health outcome	Percentage of village population	Burden of disease per prevalence case (DALYs)	Burden of disease per year per 1000 population (DALYs)
melanosis and keratosis	9 %	-	-
late stage keratosis	7.5 %	0.2	15
skin cancer morbidity	0.25 %	0.05	0.125
other internal cancer morbidity	0.25 %	0.2	0.5
cancer mortality	0.18 %	52	95
total			111

*Note: the figure for cancer mortality is based on 5.5% of the village population having died after 30 years, indicating an annual 'death-incidence' of 0.18% due to arsenic-related cancers.*

## Annex

*Tables of age and sex specific standard life expectancy according to the Global Burden of Disease Study<sup>5</sup>, and (discounted) mean life expectancy in 5-year classes. (reproduced from Havelaar et al<sup>7,2</sup>)*

Age (years)	Life expectancy <sup>1</sup>		Age class (years)	Mean life expectancy <sup>2</sup>		
	Females	Males		r=0%	r=3%	r=5%
0	82.50	80.00	0-	81.25	30.42	19.66
1	81.84	79.36	1-	80.60	30.36	19.64
5	77.95	75.38	5-	76.67	29.99	19.57
10	72.99	70.40	10-	71.70	29.45	19.45
15	68.02	65.41	15-	66.72	28.83	19.29
20	63.08	60.44	20-	61.76	28.11	19.09
25	58.17	55.47	25-	56.82	27.27	18.83
30	53.27	50.51	30-	51.89	26.31	18.51
35	48.38	45.57	35-	46.98	25.19	18.09
40	43.53	40.64	40-	42.09	23.90	17.56
45	38.72	35.77	45-	37.25	22.43	16.89
50	33.99	30.99	50-	32.49	20.76	16.06
55	29.37	26.32	55-	27.85	18.88	15.03
60	24.83	21.81	60-	23.32	16.77	13.77
65	20.44	17.50	65-	18.97	14.47	12.25
70	16.20	13.58	70-	14.89	12.01	10.50
75	12.28	10.17	75-	11.23	9.53	8.59
80	8.90	7.45	80-	8.18	7.25	6.71
85	6.22	5.24	85-	5.73	5.26	4.98
90	4.25	3.54	90-	3.90	3.68	3.54
95	2.89	2.31	95+	2.60	2.50	2.44
100	2.00	1.46				

<sup>1</sup> calculated at the beginning of the age interval    <sup>2</sup> r = discount rate for future life lost

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