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Quantitative risk assessment of food borne pathogens – a modeling approach

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Introduction

There is always a certain probability that the consumption of food leads to a reduced health status due to microbial contamination, however small this risk may be. One of the most frequently occurring effects of food infection or food poisoning is the occurrence of gastroenteritis. Usually this means an acute and temporary reduction in health status at the individual level, although also chronic effects and even death may occur. In this contribution we would like to describe:

- how frequently gastroenteritis occurs and which micro-organisms are involved;
- in what way we may get insight into means to control or, preferably, reduce health damage due to food-borne pathogens.

Quantitative microbiological risk assessment will be introduced. More specifically we will present work on modeling the fate of pathogens along the production chain, dose response and disease burden.

How frequently does gastroenteritis occur?

To obtain an estimate on how many cases of gastroenteritis occur in the Netherlands, data from several monitoring and registration systems are available. However, each system will lead to a different estimate, because mostly only a certain part of the human population is investigated (Figure 1). Using a population-based cohort study would allow for an estimate of the total number of patients involved. In the early nineties such a population study was performed in four regions in the Netherlands (Hoogenboom-Verdegaal et al. 1994) and more recently, in 1999, a second population study was done (De Wit et al. 2001b). The gastroenteritis incidence was estimated at 283 per 1,000 person-years in this last study (about 4.5 million cases per year in the Dutch population of 15.6 million).

A second way to obtain an estimate of the number of patients is through monitoring how many patients consult their general practitioner with gastroenteritis complaints using sentinel general practices (GP). The Netherlands Institute for Health Services Research maintains a network of sentinel general practices that participate in a continuous morbidity registration. Recent results show that about 220,000 persons consult their general practitioner each year for gastroenteritis, which corresponds to about 5% of people with gastroenteritis (De Wit et al. 2001a; De Wit 2002).

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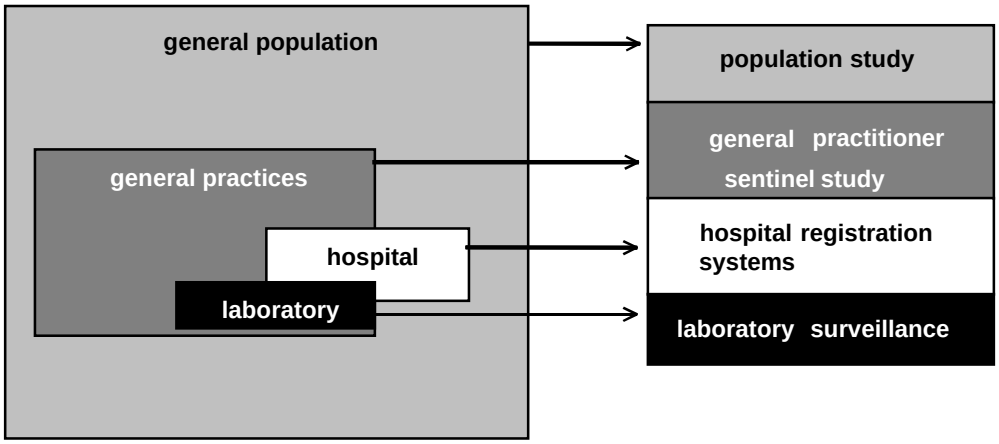

Figure 1. The various systems to obtain data on frequency of gastroenteritis.

In addition to only a minority of patients with gastroenteritis seeking medical care, only in a minority of cases the attending physician requests for microbiological testing, of which only a proportion leads to a positive result. In the Netherlands a laboratory-based surveillance system exists for some bacterial pathogens. This is a continuous system, suited to investigate trends. Other existing registration systems are: registration of hospital discharge diagnosis, mortality registration, statutory notifications, registration of outbreaks through the Municipal Health Services and through the Inspectorate for Health Protection and Veterinary Public Health.

In the recently performed sentinel GP study, De Wit et al. (De Wit et al. 2001a) found that *Campylobacter* could be detected most frequently (10% of cases), followed by *Giardia lamblia* (5%), rotavirus (5%), Norwalk-like viruses (5%) and *Salmonella* (4%). A pathogen could be found in almost 40% of the gastroenteritis patients. The ranking of the various micro-organisms found was different in the population-based study (De Wit et al. 2001b), where viral pathogens were the most prominent pathogens, detected in 21% of cases, with Norwalk-like viruses as the most frequent ones (11%).

The total number of salmonellosis cases as estimated in the population study is about 3 per 1,000 person-years, indicating a number of about 50,000 cases annually in the Netherlands (De Wit et al. 2001b). The total number of laboratory-confirmed salmonellosis cases in the Netherlands has since long been decreasing (Van Pelt et al. 1999). The incidence of *Campylobacter*-associated gastroenteritis is estimated at 6.8 per 1,000 person-years, indicating a number of about 100,000 cases annually in the Netherlands (De Wit et al. 2001b).

The food-attributable fraction in campylobacteriosis cases is estimated at > 90% (*Voedselinfecties* 2000). From a review (Altekruse et al. 1999) it can be estimated, mainly based on case-control research, that 70-90% of the *Campylobacter* infections are associated directly or indirectly with poultry meat. However, more recently there are indications that other transmission routes may be more important than originally thought (Havelaar et al. 2000). During the dioxin crisis in Belgium in 1999, when Belgian poultry was withdrawn from the market, the number of campylobacteriosis cases was reduced by 40% (Vellinga and Van Loock 2002).

The number of pathogens that may infect people through food is large and the same is true for the number of food items in which pathogens can be found (De Boer 2000). As resources are limited and information scarce the Inspectorate for Public Health Protection and Veterinary Public Health needed tools how to select the most

important micro-organisms among the ones present. Research aimed at prevention of existing and (re-)emerging problems could then be more focussed than hitherto. To this end a discussion group was formed that came up with criteria and weighing methods (Themarapport Gezonde Voeding & Veilig Voedsel, in preparation). The following five selection criteria were used: frequency of occurrence; severity when occurring; chance for explosions; is the disease endemic or can it become endemic; and whether or not there are specific research needs.

Although information on food-borne infections is becoming available as indicated above it is still scarce (*Voedselinfecties* 2000). Risk analysis is advocated as a means to come to objectives for food-safety control.

Risk analysis and risk assessment

Risk analysis consists of three coherent activities: risk assessment, risk management, and risk communication (*Proposed draft principles and guidelines for the conduct of microbiological risk assessment* 2001). Risk assessment is a scientifically based process, consisting of Hazard Identification (identification of the agent causing adverse health effects), Exposure Assessment (evaluation of the intake of the agent), Hazard Characterization (evaluation of the nature of the adverse health effects), and Risk Characterization (estimation of occurrence and severity of the adverse health effects) (*Codex Alimentarius Commission. Appendix II: Draft principles and guidelines for the conduct of microbiological risk assesment* 1998).

The functional separation of risk assessment from risk management helps assure that the risk-assessment process is unbiased. However, certain interactions are needed for a comprehensive and systematic risk-assessment process. The benefits of the use of risk assessment, or more specifically of quantitative microbiological risk assessment (QMRA), is in our view threefold:

- it results in an estimate of the health risk of a certain pathogen / product / population combination. This provides an alternative to epidemiological research;
- it is possible to make comparisons of the relative importance, in terms of public health, of e.g. different pathogens in a product, or of a certain pathogen in different products; and
- most importantly, it provides estimates of the effect of a certain intervention, again in terms of public health.

We implement risk assessment by starting with an exposure-assessment model, which has an exposure estimate as an output (e.g. the number of pathogens per serving and the probability of contaminated servings combined with the number of servings per day). This is then the input of a hazard-characterization model which converts the exposure into an estimate of the public health risk of the considered pathogen / product / population combination.

At the beginning of a risk-assessment project, the specific purpose of the particular risk assessment being carried out should be clearly stated as the statement of purpose. The output form and possible output alternatives of the risk assessment should be defined. In addition, the statement of purpose should usually also contain detailed demarcations to obtain a realistic project size (Nauta et al. 2001). These are:

- product definition: exactly which product (including details on production and processing) is considered;
- species/serotype definition: exactly which type or set of types is to be considered; and

– interventions: which interventions are to be considered, as the mathematical model to be developed must be able to include these interventions.

Exposure assessment

A first example of exposure-assessment modeling is a model for the transmission of *Salmonella* through the poultry meat production chain (Nauta, Van De Giessen and Henken 2000). The model first describes the situation before intervention (1997) in terms of *Salmonella* prevalences at flock level and some transmission parameters. The model input parameters were derived from expert opinion as research data were lacking. The effects of two intervention strategies for the Dutch poultry industry were predicted.

A general framework for performing exposure assessment, the Modular Process Risk Model (MPRM), was recently proposed (Nauta et al. 2001; *Risk assessment of food borne bacterial pathogens: quantitative methodology relevant for human exposure assessment* 2003). At the heart of the proposal is the suggestion that to each of the steps or key activities at the various intermediary stages of a farm-to-fork chain at least one of six basic processes can be assigned. These basic processes are the six fundamental events that may affect the transmission of any microbial hazard in any food process. There are two 'microbial' basic processes, growth and inactivation, and four 'food handling' processes, mixing and partitioning of the food matrix, removal of a part of the units, and cross-contamination.

In microbial risk assessment, calculations with numbers (N) of micro-organisms are to be preferred to concentrations (C). The rationale of using N instead of C in the calculations is that one is forced to do realistic calculations with discrete numbers, which is particularly relevant when N is small. For each step in the food pathway we are interested in the input-output relation for the number of cells per unit of product, *N*, the fraction of contaminated units (the prevalence), *P*, and the unit (Figure 2). The unit is a physically separated quantity of product in the process, for example an animal or a bottle of milk. Units might have to be redefined for each stage.

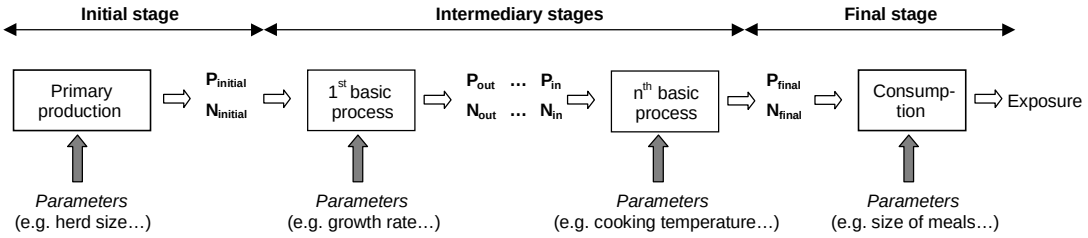

Figure 2. Schematic representation of a food pathway split up into different steps, each represented by an input-output basic process. P and N are prevalence and level of contamination, respectively (*Risk assessment of food borne bacterial pathogens: quantitative methodology relevant for human exposure assessment 2002*; modified).

The MPRM approach presented above was applied to Shiga toxin-producing *Escherichia coli* O157 (STEC O157) in steak tartare patties (see Figure 3) (Nauta et al. 2001). As slaughter practices may differ, three routes of exposure were compared, separating 'industrial' and 'traditional' ways of both slaughter and subsequent processing. Also, three preparation styles of the steak tartare patties (raw, medium and well done) were considered. As for a large part of the model parameters the

information required to estimate their values was lacking, an expert elicitation workshop was organized. The model was implemented in @Risk (an Add-In of Excel) and analysed using Monte Carlo simulations.

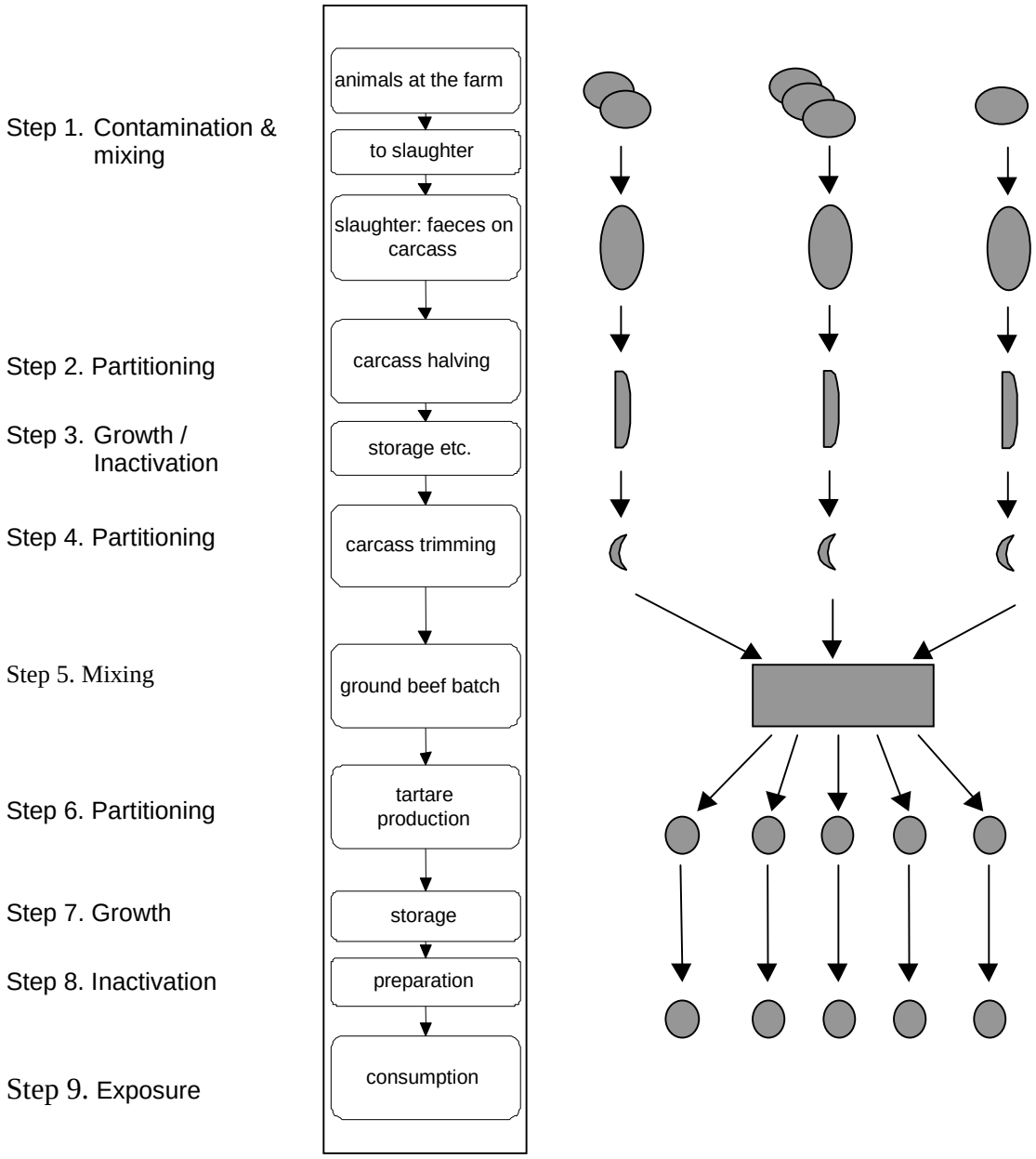

Figure 3. Food pathway of steak tartare. The pathway is split up into nine modeling steps. A basic process is assigned to each step. The illustration shows how the units are formed by partitioning and mixing.

The exposure model predicts that about 0.3% of the raw steak tartare patties is contaminated with STEC O157. Of these contaminated patties, a large fraction (>60%) is contaminated with one colony-forming unit (cfu) only. High contamination levels are rare, with for example only 7% of the contaminated raw steak tartare patties containing more than 10 cfu. As a comparison, in a microbiological survey it was found that one out of 82 raw steak tartare patties (1.2%) was positive for STEC O157. Knowing that the probability of detection of single cfus in such a survey is small, this

suggests that the model prediction is an underestimation of the actual level of contamination of steak tartare patties.

Two important general aspects related to QMRA will be considered. The first is variability versus uncertainty. The probability distributions used in stochastic risk models may represent uncertainty as well as variability. In this context, uncertainty represents the lack of perfect knowledge of a parameter value, which can be reduced by further measurements. Variability, on the other hand, represents a true heterogeneity of the population that is a consequence of the physical system and irreducible by further measurements. Separation of variability and uncertainty in QMRA models (so-called second-order models) has up to now rarely been made, a reflection of the fact that this can be a daunting task. However, neglecting the difference between them may lead to improper risk estimates (Nauta 2000) and/or incomplete understanding of the results (Vose 2000). Apart from these considerations, modeling variability has priority over modeling uncertainty. Furthermore, one must realize that in addition to the parameter uncertainty referred to here, uncertainty also includes scenario uncertainty and model uncertainty.

The second aspect is the considerable data need (*Risk assessment of food borne bacterial pathogens: quantitative methodology relevant for human exposure assessment* 2003). Data will be needed on environmental conditions (e.g., temperature, pH) and (handling) practices (e.g., duration of transport, storage) at the various processing steps. To validate the model, data are needed on N, unit size and P at the beginning and end of all steps. Another category of data that is needed concerns the description of the food pathway. Experience showed that a description in quantitative terms (number of animals and their destination or their origin (national, import), number and weight of carcasses and their destination or their origin, etc.) is not easily obtained. Moreover, when the model is to be used also to gain insight into risk reduction scenarios, data on alternative food pathways and/or steps will be needed. A third category of data is consumption data. For exposure assessment, data on prevalence and level of pathogens are not sufficient. Exposure can only be estimated if data on amount and frequency of food intake in the given population or subpopulation are available. It will be clear that in principle a large amount of data is needed to perform a risk assessment. Usually a large amount of data is available for any particular subject. However, these data were usually not collected for the purpose of risk assessment and therefore often of little use.

Hazard characterization

Exposure assessment is followed by hazard characterization, which can be implemented by an effect model. An effect model consists of a dose–response model, which translates the ingested dose into a probability of infection, and a disease-burden model, which estimates the probability of each of the relevant diseases, given infection. Each disease contributes to the disease burden, which can be expressed in an integrated measure, e.g. DALYs (see below).

The *E. coli* study mentioned above (Nauta et al. 2001) included not only exposure assessment, but also effect modeling, distinguishing three age classes in the human population (1-4 years, 5-14 years and 15+). The number of STEC O157 infections by steak tartare consumption per year in the Netherlands was predicted with the baseline model at 2,300, and the number of cases of gastroenteritis at about 1,300. The latter equals an incidence rate of 8 per 100,000 person years. This result can be compared with an independent point estimate of the total incidence of STEC O157-associated

gastroenteritis in the Netherlands based on epidemiological data: 2,000 cases or 13 per 100,000 person-years. This would imply that a large fraction of the cases is a consequence of steak-tartare consumption. As many more routes of exposure to STEC O157 are known, the large attributable fraction of steak-tartare consumption (that is the high contribution to the total incidence), seems to be an overestimation. However, one should realize that comparing the model and epidemiological estimates is questionable, as the uncertainty in both these estimates is large.

Analysis of alternative scenarios shows that the uncertainty in prevalence and concentration of STEC O157 at farm level may have a large effect on the final model estimates. The same holds for uncertainty about growth and inactivation of STEC O157 on the carcass. In contrast, the effect of growth of STEC O157 during retail and domestic storage is negligible and the effect of advocating the consumption of 'well done' steak tartare patties is questionable. This suggests that intervention at farm level or at slaughter is more likely to be effective as a strategy to reduce STEC O157-associated risks than intervention at the consumer level.

We will use research on *Campylobacter* (Teunis and Havelaar 2000; Havelaar 2002) to illustrate effect modeling in some more detail. As stated above, one part of effect modeling is dose response modeling. Many models are available for dose response modeling, but data are scarce. A theoretically well defensible model is the hypergeometric model. The mathematical formula for this model can be derived on the basis of the following assumptions:

- each individual micro-organism is able to infect a human (the single-hit hypothesis);
- individual micro-organisms do no interact (hypothesis of independent action);
- the probability of infection per micro-organism varies (following a beta distribution), e.g. because of variation in pathogen virulence or host susceptibility.

Figure 4 shows the result of fitting the hypergeometric model to experimental data with human volunteers.

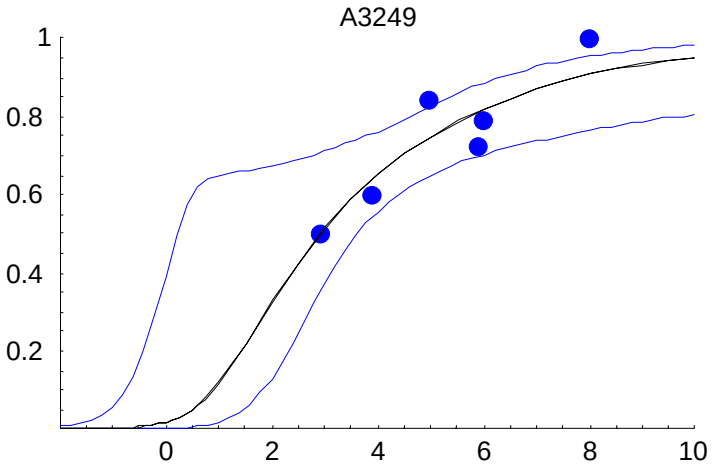

Figure 4. Hypergeometric dose–response model, fitted to data from Black et al. (1988) on *Campylobacter jejuni* A3249. X axis: ^{10}log of the dose; Y axis: fraction of infected persons. Middle curve: best fitting curve; outer curves: limits of the 95% confidence interval.

The second part of effect modeling is disease modeling: estimating the probability of diseases occurring once infection has taken place (Havelaar 2002). *Campylobacter* infection can remain without indications of disease, but frequently it will lead to gastroenteritis, characterized by diarrhea, stomach pain, fever and less frequently vomiting and blood in the stool. Less frequently, more serious disease symptoms will occur, of which the Guillain-Barré syndrome (GBS) and reactive arthritis (ReA) are the most important (Havelaar et al. 2000). Death can occur as a consequence of gastroenteritis (especially in the elderly) and as a consequence of GBS; no deaths have been reported as a consequence of ReA. Combination of the models for the probability of infection and the probability of disease in infected persons leads to a model for the probability of diseases as a function of the ingested dose.

An integrated measure for comparison of reductions in health status is the DALY (Disability-Adjusted Life Year) (Murray and Lopez 1996; Van der Maas and Kramers 1998). The principle is that mortality as well as morbidity is expressed in (healthy) life years lost: Years of Life Lost (YLL) and Years Lived with Disability (YLD), respectively. Thus life years can be lost by premature death (the loss is equal to the theoretical remaining life expectancy at the time of death, had the disease not occurred) and some proportion of time lived because disease or infection reduces the quality of life. This proportion depends on the severity of the disease.

An example of application of DALYs is an epidemiological study on the disease burden of thermophilic *Campylobacter* species in the Netherlands (Havelaar et al. 2000). The results are given in Table 1. It appears that the main determinants are acute gastroenteritis in the general population, gastro-enteritis related mortality and residual symptoms of Guillain-Barré syndrome.

Table 1. Disease burden due to infection with thermophilic *Campylobacter* spp. in the Netherlands (Havelaar et al. 2000).

Population	**YLD**	**YLL**	**DALY**
Gastroenteritis			
General population	291	419	710
General practitioner	159		159
Guillain-Barré syndrome			
Clinical phase	16	25	41
Residual symptoms	334		334
Reactive arthritis	159		159
Total	**959**	**444**	**1403**

Campylobacter Risk Management and Assessment (CARMA)

The studies cited above were mainly focused on development of the risk-assessment methodology. Integration of risk assessment, risk management and risk communication will enhance the usefulness of a risk-analysis project. In the CARMA project (Figure 5) (Havelaar 2002) this will be attempted. Risk assessment models will be integrated with economic models and policy analysis to provide an optimal basis for risk-management decisions. The social and health effects of disease will be expressed in the disease-burden model as DALYs, and in the economic model the costs due to disease will be calculated. In consultation with risk managers and stakeholders, intervention scenarios will be selected and it will be investigated in

which way these will lead to changes in the risk-assessment model. Autonomic developments will be taken into account when choosing the intervention scenarios.

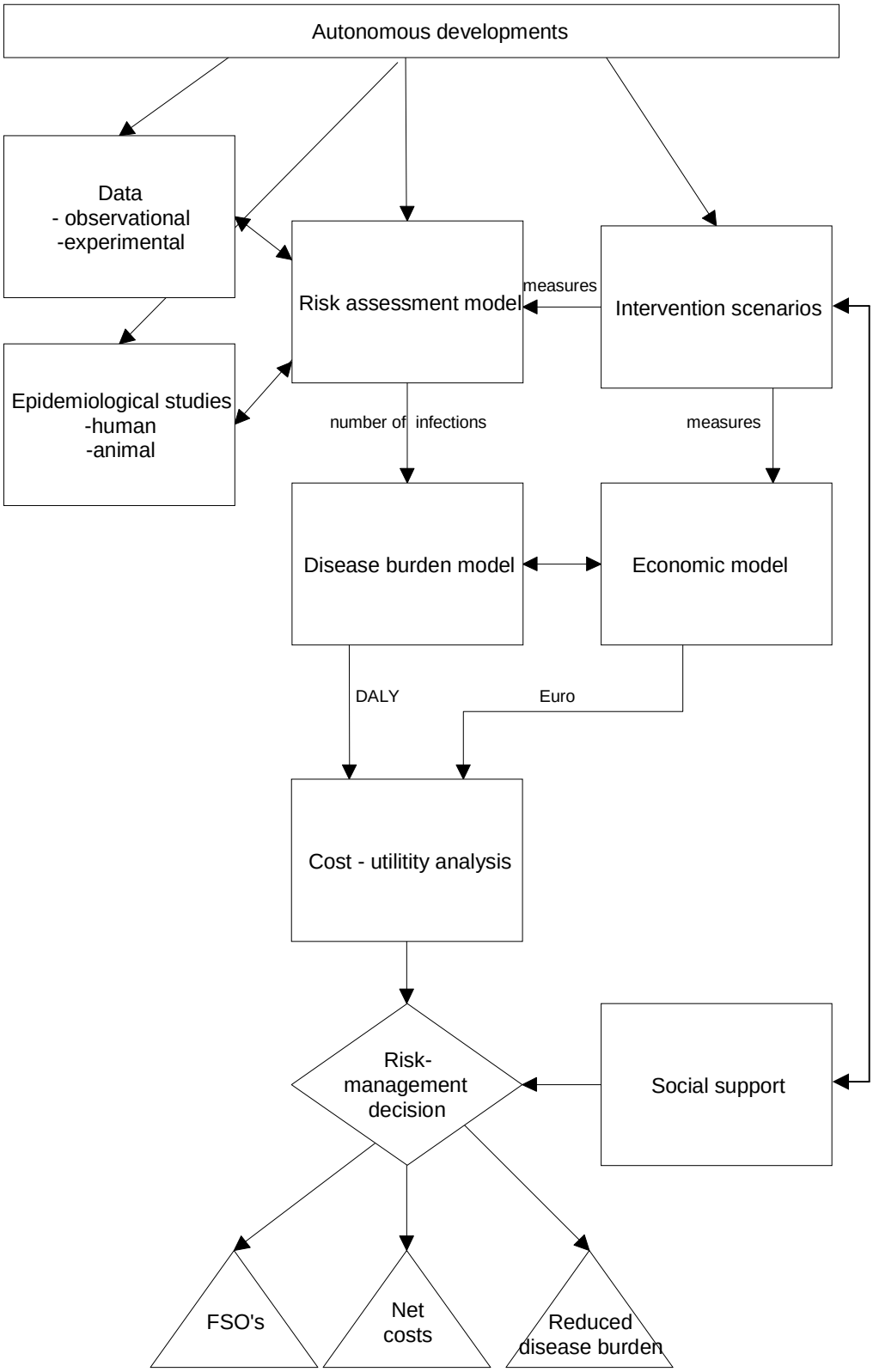

Figure 5. General setup of the CARMA (*Campylobacter* Risk Management and Assessment) project. FSO = Food Safety Objective.

Reduction of disease will lead to a reduction of disease burden and the costs involved. Besides this, the costs of intervention will be calculated. Together, all these estimates are the basis for a cost-utility analysis, with which different interventions will be compared on the basis of their net cost per DALY gained, the cost-utility ratio. The calculated effects, costs and cost-utility ratios are the basis for policy decisions. However, other social and political factors also play an important role in these decisions. In this project, these factors will also be listed, in a format that is useful for the decision process.

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