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Review

Disability adjusted life year (DALY): A useful tool for quantitative assessment of environmental pollution

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HIGHLIGHTS

- This review introduces the methodological framework of DALY.
- This paper reviews the basic process of environmental health risk evaluation.
- Several cases regarding environmental burden of disease studies are analyzed.
- Future directions for environmental burden of disease studies are indicated.

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ABSTRACT

Disability adjusted life year (DALY) has been widely used since 1990s for evaluating global and/or regional burden of diseases. As many environmental pollutants are hazardous to human health, DALY is also recognized as an indicator to quantify the health impact of environmental pollution related to disease burden. Based on literature reviews, this article aims to give an overview of the applicable methodologies and research directions for using DALY as a tool for quantitative assessment of environmental pollution. With an introduction of the methodological framework of DALY, the requirements on data collection and manipulation for quantifying disease burdens are summarized. Regarding environmental pollutants hazardous to human beings, health effect/risk evaluation is indispensable for transforming pollution data into disease data through exposure and dose–response analyses which need careful selection of models and determination of parameters. Following the methodological discussions, real cases are analyzed with attention paid to chemical pollutants and pathogens usually encountered in environmental pollution. It can be seen from existing studies that DALY is advantageous over conventional environmental impact assessment for quantification and comparison of the risks resulted from environmental pollution. However, further studies are still required to standardize the methods of health effect evaluation regarding varied pollutants under varied circumstances before DALY calculation.

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1. Introduction

Due to the increased attention to the impact of environmental pollutants on human health, the environmental health risk assessment has gradually become a necessary approach before risk control and risk management (Biesiada, 2000, 2001; Biesiada et al., 1999, 2001; Biesiada and Sokal, 2003). However, in the early attempts of environmental health risk evaluation, conventional risk assessment methods were usually applied to interpret risk as a probability of exceeding a standard or to take the incidence of health risk as the endpoint. Neither can the probability analysis of health risk provide a conclusive evidence of the occurrence of health damage (Geelen et al., 2009), nor can the incidence of health risk account for the severity and duration of the health impact caused by the exposure of environmental pollutants. Therefore, with regard to the health hazard induced by environmental pollution, the adoption of quantifiable indicators, such as the disability adjusted life year (DALY), is necessary for the assessment of health impact caused by environmental contaminants based on the estimation of the probability of health risk occurrence (WHO, 2002; Valent et al., 2004a, 2004b).

DALY was developed by WHO and World Bank to quantify disease burden and injury on human populations in the Global Burden of Disease Study (Murray, 1994, 1996). As a disease burden indicator, DALY combines the estimation of time lived with disability and time lost due to premature mortality with adjustment by a set of social preference values (Murray, 1994). Different weights could be given for different age groups and time periods while being addressed as age weight and discount rate, respectively, in the process of disease burden quantification. This consequently provided an objective and quantitative description of the gap between the ideal health status and actual population health status (Murray and Lopez, 1994, 1996a, 1996b). With these irreplaceable advantages, DALY method has been applied to many fields such as disease burden estimation for identifying disadvantaged groups and target health interventions, and cost-effectiveness analysis for setting health service priorities (World Bank, 1993; Jamison et al., 1993).

As exposure to contaminants may also cause health loss, DALY was used in a number of studies for quantifying the impacts of environmental pollution (Fewtrell et al., 2003; Prüss-Üstün et al., 2003; Jarosińska et al., 2006; Kim et al., 2011; Ragas et al., 2011a, 2011b; Xiao et al., 2012a, 2012b; Wei et al., 2012; Machdar et al., 2013), thus leading to a new paradigm of DALY study combining disease burden quantification with health impact/risk assessment. However, due to the complexity of environmental pollution problems and lack of standardized methodologies to transform pollution data into disease data which is an indispensable stage before DALY calculation, there have been few publications by far dealing with the whole framework of using DALY as a tool for quantitative assessment of environmental pollution.

Hence, it becomes the objective of this article to provide a comprehensive review on the current status of the DALY studies for quantitative assessment of environmental pollution with attentions paid to the disease burden caused by exposure to hazardous pollutants. In the following sections, an overview of the DALY methodology will be given and the methods applied by various studies for bridging pollution with the occurrence of diseases will be critically reviewed with introduction of real cases. The direction of future studies will also be discussed.

2. An overview of DALY methods

2.1. Development of DALY method

There has long been a need for quantitative description of the health status of people under various health outcomes caused by specific diseases using certain measurement index. Such a need stimulated studies on the burden of disease which experienced several stages (Hu et al., 2011). The first stage was before 1982 with a description of disease burden simply from the perspective of death outcome mainly as the death rates caused by specific diseases. The second stage started with the proposal of the Years of Potential Life Lost (YPLL) in 1982 by the US Centers for Disease Control (US CDC) as an indicator for evaluating disease burden in terms of the time lost due to specific diseases (Gardner, 1990; Hu et al., 2011). YPLL, as well as other indicators derived in similar ways, mainly took into consideration of the loss of individual life due to premature death, but ignored the loss due to disability (Gardner, 1990). As a symbol of the third stage, the Disability Adjusted Life Years (DALY) was proposed in 1993 through a study of Global Burden of Disease (GBD) jointly mobilized by the World Bank (WB), the World Health Organization (WHO) and the Harvard School of Public Health (World Bank, 1993; Murray, 1994; Christopher and Acharya, 1997; Wang and Xu, 2002). DALY was a comprehensive indicator of disease burden taking into account the premature death and disability caused

by specific diseases simultaneously either on individual level or population level, and was widely used in global and regional burden of disease studies. The methodology was provided by the GBD study for global and regional comparative assessment of mortality and DALYs attributable to more than 100 kinds of diseases (World Bank, 1993; Murray and Lopez, 1996a, 1996b). GBD studies were further updated in 1999, 2000, 2001, 2002, and 2004 with similar approaches using specific disease data and information collected from various countries and regions (WHO, 2013). The GBD 2001 study was particularly important for the application of DALY to disease controls which provided a guidance of decision making for health interventions, and cost–benefit analysis of specific health interventions was also made possible so as to assist health institutions to allocate health resources (López-Bastida, 2006; Jamison et al., 2006a).

Several revisions were successively made on the DALY calculation method as well as its relevant parameters. In the GBD 2010 study, a revised DALY method was adopted to rectify the shortcomings of the previous method and provide a comparable, systematic, and rigorous epidemiological assessment of the magnitude of 291 diseases and injuries as well as their associated sequelae in 21 regions over the world (Christopher et al., 2012). Revisions were also given on the establishment of a new disability weighting system and construction of a new model life table (Murray et al., 2012a, 2012b).

In the GBD studies, attention was also paid to the formulation of guidelines for the applications of DALY for resource allocation or cost-effectiveness analysis (Lane et al., 2003). Since 1999, calculation and reporting of disease burdens using DALY tools have become a routine work of WHO (WHO, 2002; Hyder et al., 1998; Murray and Acharya, 1997) which aroused increasing attentions paid to various health issues all over the world (Polinder et al., 2012). WHO is planning to continue the GDB studies till 2020 (Murray and Lopez, 1996b).

2.2. Framework of DALY analyses

Damages to human health caused by specific diseases include loss of life and loss of normal ability, both resulting in a reduction of healthy life years of individuals. As an indicator for direct measurement of health loss, DALY can be defined as the total loss of healthy life years from the onset to death (Anand and Jonson, 1995) which consists of two components, namely Years of Life Lost (YLLs) due to premature mortality and Years Lived with Disability (YLDs) combining with several social preference values, such as disability weight, age weight, and time discounting rate (Murray, 1994; Sudhir and Kara, 1997; Shen and Yun, 2002). DALY is in fact a summary metric to describe and estimate the health status of specific population when compared to a normative goal (Höll, 2002).

The basic formula for calculating DALY in terms of specific disease could be expressed as (Homedes, 2000):

$$\mathrm{DALYs} = \mathrm{YLLs} + \mathrm{YLDs}. \tag{1}$$

Several social preference values should be considered in DALY calculation, such as the disability weight with a value between 0 and 1 which reflects the severity of health hazard caused by different diseases, the age weight designed for distinguishing the relative value of life among different age groups (World Health Organization, 2004), and the time discounting rate to distinguish the relative values of healthy life lost occurred in different time periods (Murray and Lopez, 1996a, 1996b). After taking these into consideration, the complete formula for calculating DALY can be expressed as an integral form:

$$\int_{x=a}^{x=a+L} DCxe^{-\beta x}e^{-r(x-a)}dx \tag{2}$$

where, a: the age of onset or the age of death; L: the disability duration or life expectancy; D: disability weight; $Cxe^{-\beta x}$: the age weight function; and $e^{-r(x-a)}$: the time weight function. By integral calculation with introduction of an age weight adjustment factor, YLL and YLD can be obtained, respectively, as Eqs. (3) and (4) (CEDEX, 1999; Murray and Lopez, 1996a, 1996b; Christopher and Acharya, 1997):

$$\mathrm{YLLs} = \frac{KCe^{r\alpha}}{(r+\beta)^2}\left\{e^{-(r+\beta)(L+\alpha)}[-(r+\beta)(L+\alpha)-1]-e^{-(r+\beta)\alpha}[-(r+\beta)\alpha-1]\right\} + \frac{1-K}{r}\left(1-e^{-rL}\right) \tag{3}$$

$$\mathrm{YLDs} = \mathrm{D}\{\frac{KCe^{r\alpha}}{(r+\beta)^2}\{e^{-(r+\beta)(L+\alpha)}[-(r+\beta)(L+\alpha)-1] - e^{-(r+\beta)\alpha}[-(r+\beta)\alpha-1]\} + \frac{1-K}{r}\left(1-e^{-rL}\right)\} \tag{4}$$

where, K: age weight adjustment factor ($K = 1$ generally); C: a constant ($C = 0.1658$ generally); r: discounting rate ($r = 0.03$ generally); β: age weight coefficient ($\beta = 0.04$ generally).

Although the above calculations were regarded as the standard DALY method in the initial estimation of disease burden (Christopher et al., 2012), there have always been debates on whether or not the social preference values adopted are suitable and/or justifiable (Sudhir and Kara, 1998; Anand and Hanson, 1997; Williams, 1999; Murray et al., 2002; Lyttkens, 2003; Arnesen and Kapiriri, 2004; Bognar, 2008). As a result of hot debates, a simplified method was worked out for DALY calculation in which the age weight and time discounting were ignored and YLL and YLD could thus be calculated in much simpler ways (Murray et al., 2012b; Murray et al., 2012a, 2012b) as shown in Eq. (5) and Eq. (6), respectively:

$$\mathrm{YLL} = N \times L \tag{5}$$

$$\mathrm{YLD} = I \times D \times L \tag{6}$$

where, N: number of premature deaths caused by a specific disease; L: standard life expectancy loss for each death in Eq. (5) or average duration of disease in Eq. (6); I: number of disabilities caused by a specific disease; and D: disability weight (Miquel and Huertas, 2006).

2.2.1. Years of life lost in various age ranges

The concept of years of life lost due to premature mortality was introduced for evaluating the impact of diseases on human health in 1940s with a number of methods put forward (Haenszel, 1950; Kohn, 1951; Romeder and McWhinnie, 1977). For the DALY calculation, the Standard Expected Years of Life Lost (SEYLL) was chosen as the best-fit method referring to a standard model life table which was obtained from a survey of the highest national life expectancy observed in Japan (82.5 for females and 80.0 for males) in 1990 (Murray, 1994). As such a model life table was based on the highest current life expectancy, it could avoid giving any population a lower expectancy than they actually experienced, but might lead to an overestimation of the disease burden in underdeveloped countries (Sudhir and Kara, 1997; Hollinghurst et al., 1999; Homedes, 2000). It was also questioned that the rationality of setting the normative loss of years of life in terms of currently observed death rates because even for the lowest observed death rates there would be a proportion of deaths which are preventable or avertable (WHO, 2013). Therefore, in order to provide a more accurate reflection of the life expectancy for individuals in each age group under ideal health condition, the model life table was revised based on the frontier national life expectancy projected for the year of 2050 (UN Population Division, 2013). Table 1 summarizes the standard life expectancies used for the calculation of life expectancy loss caused by premature death for each age group in GBD 1990 study (Murray, 1994), GBD 2010 study (Murray et al., 2012a, 2012b) and WHO Global Health Estimates (GHE) (WHO, 2013).

2.2.2. Disability weights

In order to measure the years of life lost and years lived with a disability on the same scale, a detailed description of various disabled statuses due to specific diseases was given by the WHO expert committee, leading to a categorization of disability divided into six grades each giving a measure of the extent of loss of physical functioning and represented by a disability weight valuing between 0 and 1, where 0 represents perfect health while 1 represents death (Murray, 1994; Sudhir and Kara, 1997; Salomon, 2014). In the earliest version of the GBD 1990 study, the burden of disease was defined as loss of welfare/subjective well-being/quality of life (World Bank, 1993). However, it was argued that the health state values should reflect societal judgments of the value of averting different diseases rather than individual judgments of the disutility of the diseases. This led to the adoption of a person-trade-off (PTO) method to assess social preferences for health states (Murray and Lopez, 1994, 1996a, 1996b) and to estimate disability weights (Stouthard et al., 1997, 2000). However, there were also criticisms from commentators who thought that the disability weighting in such a way would be unethical (Arnesen and Nord, 1999). As a result the PTO method was ruled out in a European multi-country study (Schwarzinger et al., 2003) and a comprehensive re-estimation was undertaken in the GBD 2010 study (Murray et al., 2012a, 2012b) through a large scale empirical investigation with emphasis on the public responses by questionnaire survey (Salomon et al., 2012a, 2012b, 2012c), thus leading to a remarkable change in the result of disease burden study (Taylor et al., 2013).

The disability weights could also be estimated as varied values between ages, genders and health interventions (Christopher and Acharya, 1997; Jia et al., 2007; Joshua et al., 2013). As sanitation level and diagnostic criteria may also differ much among countries and regions, different disability weights should be adopted for developed and developing countries so as to avoid overestimation of disease burden (Stouthard et al., 1997; Mathers et al., 1999; World Health Organization, 2004).

2.2.3. Age weights

Age-weights allow for bias in valuing life years in different age ranges (Sudhir and Kara, 1997; WHO, 2013), and incorporating age-weights into the DALY calculation (Murray, 1994). In order to compare the relative importance of healthy life loss occurred in different ages, a standard age weight function was proposed in a form shown in Fig. 1 where larger weights were given for people between 10 and 55 years old, especially with a peak approximately in the age range of 20–30, while smaller weights were given for children below 10 years old and elder people above 55 years old (World Health Organization, 2004). Such a distribution of age weights accounts for the dependence of the younger or elder people on the middle-aged in spirit and life (Sudhir and Kara, 1997). However as DALY is used for measuring health loss rather than any broader aspect of social welfare, it is difficult to justify the inclusion of age weights in the GBD study. Therefore, the impact of age weight was ignored in the GBD 2010 study (Murray et al., 2012b; Jamison et al., 2006b), which consequently resulted in a relative increase of DALYs for younger and older populations (WHO, 2013).

2.2.4. Time preference

Time preference is used for evaluating the value of health gains at present comparing with the value attached to health gains in the future (WHO, 2013). In the original GBD 1990 study (Murray, 1994), a 3% discount rate was adopted for discounting future years of life lost (Jamison et al., 1993). This implies that one life saved today will be worth more than five lives saved in the future 55 years (Sudhir and Kara, 1998). For this assumption, the arguments were couched mainly in terms of avoiding various decision making paradoxes when future costs of health interventions were discounted (Murray et al., 2002; Murray and Acharya, 2002). It was also argued that discounting future life loss is injustice due to lack of intrinsic reason (Tsuchiya, 2002). As a result of these arguments, the discounting rate was ignored in the GBD 2010 study considering that DALY was explicitly defined as a quantification of health loss, rather than the social value of health loss (Murray et al., 2012a, 2012b). The ignorance of discounting rate could avoid the inconsistency in the original DALY method, where the start time for discounting future stream of YLDs was the year of incidence, whereas the start time for discounting YLLs was the year of death rather than the year of incidence (WHO, 2013).

DALY calculation is not complicated in most cases so that manual computations are often adopted in many studies following the standard methods. However, appropriate software has also been developed for DALY calculation in more efficient ways, such as DISMOD II used by WHO (Barendregt et al., 2003).

2.3. Usage of DALY for quantifying disease burden

2.3.1. DALY calculation for comparing disease burdens in various regions

Fig. 2 shows the latest result of disease burden among different regions and disease causes (WHO, 2013) based on the global DALY calculation results derived from six major regions of the world regarding three major types of diseases. Comparing the total DALY per thousand people in each of the region with the world average, Africa apparently has the highest disease burden – with DALY value almost double of the world average. Such a result coincides well with the backward condition in most of the African continent such as low per capita income, low accessibility to safety drinking water and proper sanitation, low level of social welfare and so on (World Bank, 1993; WHO, 2013)

Table 1
Standard life expectancy used in GBD studies and WHO GHE (Murray, 1994; Murray et al., 2012).

Age range	GBD 1990 age weighted, discounted		GBD 1990 no age weights or discounting		GBD 2010	WHO GHE
	Male	Female	Male	Female	Male & Female	
Neonatal	33.27	33.38	79.94	82.43	86.01	91.93
Post-neonatal	34.22	34.34	78.85	81.36	85.68	91.55
1–4	35.17	35.29	77.77	80.28	83.63	89.41
5–9	37.22	37.36	72.89	75.47	78.76	84.52
10–14	37.31	37.47	67.91	70.51	73.79	79.53
15–19	36.02	36.22	62.93	65.55	68.83	74.54
20–24	33.84	34.08	57.95	60.63	63.88	69.57
25–29	31.11	31.39	52.99	55.72	58.94	64.60
30–34	28.08	28.40	48.04	50.83	54.00	59.63
35–39	24.91	25.30	43.10	45.96	49.09	54.67
40–44	21.74	22.19	38.20	41.13	44.23	49.73
45–49	18.63	19.16	33.38	36.36	39.43	44.81
50–54	15.65	16.26	28.66	31.68	34.72	39.92
55–59	12.82	13.52	24.07	27.10	30.10	35.07
60–64	10.19	10.96	19.65	22.64	25.55	30.25
65–69	7.80	8.60	15.54	18.32	21.12	25.49
70–74	5.71	6.45	11.87	14.24	16.78	20.77
75–79	4.00	4.59	8.81	10.59	12.85	16.43
80–84	2.68	3.09	6.34	7.56	9.34	12.51
85+	1.37	1.23	3.82	3.59	5.05	7.60

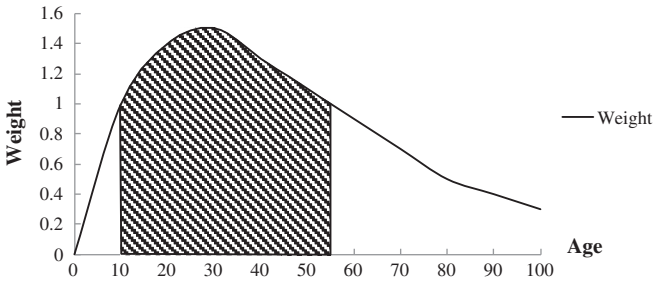

Fig. 1. Age weight function (World Health Organization, 2004).

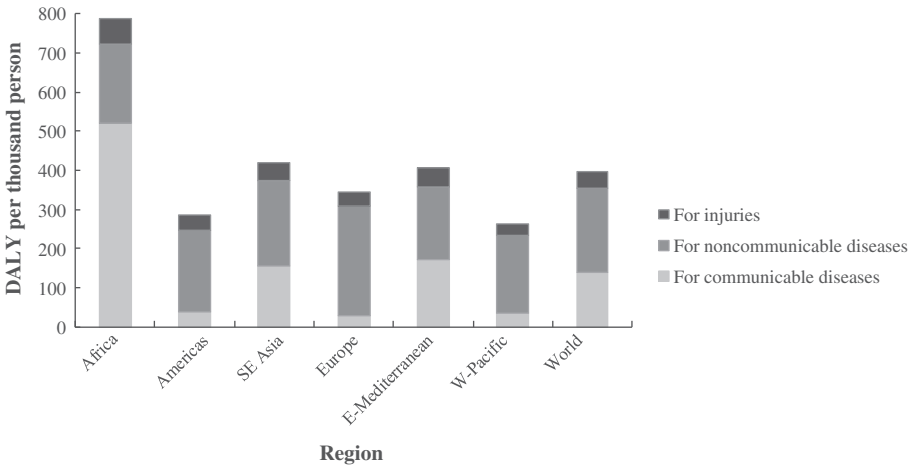

Fig. 2. Disease burden among different regions and disease causes (WHO, 2013).

which inevitably results in poor health status. In contrast to this, the lowest DALY value is in the Western Pacific region and followed by American and European regions, all lower than the world average, which coincide with the better living and welfare conditions in these regions. The DALYs calculated for Southeast Asia and East Mediterranean regions are slightly higher than the world average.

The distribution of the three major diseases, namely injuries, noncommunicable and communicable diseases, is another factor to reflect the living conditions in different regions. It is noticeable that the very high disease burden in Africa is greatly contributed by communicable diseases, i.e. illnesses caused by specific infectious agents or its toxic products which directly relate to poor living conditions. The contribution of injuries to DALY in Africa is also higher than the world average and that in other regions, indicating a poorer condition of safety protection, while regarding the non-commutable diseases, i.e. non-infectious and non-transmissible chronic diseases of long duration and slow progression, its contribution to DALY in Africa is rather lower than that in other regions. Europe is noticeably a region with the lowest injuries and communicable diseases contributing to DALY but faces with the highest disease burden due to non-communicable diseases.

2.3.2. Data acquisition and calculation procedures

The estimation of disease burden using DALY method has primarily been based on the availability and completeness of disease data from the study area (Miquel and Huertas, 2006). The age of onset or the age of death can be determined referring to the disease statistics or the death registration information from local health institutions, otherwise the median value or the starting value of each age interval can be adopted referring to previous studies (Chie et al., 2001). The disease duration is often determined based on epidemiological investigations (Murray and Lopez, 1996a, 1996b; Havelaar and Melse, 2003). Life expectancies of each age group can be calculated referring to the standard model life table (Table 1). Regarding disability weights, the recommended values can be used or practical measurement can be conducted (WHO, 2013). After the determination of these parameters, disease burden can be estimated.

Generally, a certain health problem may result in four possible outcomes such as death, disability before death, permanent disability, and full recovery after disability (Hollinghurst et al., 1999; Homedes, 2000). On the basis of epidemiological survey and demographic census, specific disease data can be input into the DALY model, and the total burden of disease can be evaluated by multiplying the disease burden per health outcome with the symptomatic cases attributed to each outcome (Miquel and Huertas, 2006).

2.3.3. Disease burden calculation

To understand better the DALY calculation procedure, the disease burden study of breast cancer in Taiwan is a typical case (Chie et al., 2001). By using the collected information up to 1994, two kinds of health outcomes were taken into account, namely permanent disability and death. Under a consideration of the characteristics of breast cancer, the age ranges were divided in a 5-year interval from 15 to 90+, and in accordance with the health outcomes, the age of onset and the age of death in each age group were selected as the median value of each age interval. Life expectancy (L for death) and disease duration (L for disability) were manipulated in the following ways: (i) L for death was calculated for each age group with reference to the model life table proposed in the GBD 1990 study, and (ii) L for disability was described as the average survival period of breast cancer patients in the study period (up to 1994) based on epidemiological investigation (Chie et al., 2001). Following Murray and Lopez (1994), the disability weight associated with breast cancer was 0.086, while it was 1 for death. Age weight coefficient and discounting rate were selected in line with the recommended values adopted in the GBD 1990 study (Murray, 1994).

In the calculations, Eq. (4) was used for obtaining the life loss per disability case (YLDs/case) with related parameters valued as $\beta = 0.04$, $D = 1$, $C = 0.1658$, and $r = 0.03$, and Eq. (5) was used for obtaining the life loss per mortality case (YLLs/case). The number of cases of life loss due to disabilities and that due to premature deaths caused by breast cancer was determined based on epidemiological survey or referred to disease statistics. By multiplying the number of cases with the calculated YLDs/case and YLLs/case, respectively, the total healthy life loss due to disability attributed to breast cancer (total YLDs) and that due to premature death attributed to breast cancer (total YLLs) was obtained. The total burden of disease (total DALYs) caused by breast cancer was finally calculated following Eq. (1) as the sum of total YLDs and total YLLs.

As shown in Fig. 3 as the final result of DALY calculation, the disease burden caused by breast cancer in Taiwan in 1994 was mainly concentrated among women in the age range of 35–54, which was the subpopulation with high incidence of breast cancer comparing with other age groups. Women in the age range of 40–44 would have the highest disease burden caused by breast cancer so that special attention should be paid in prioritizing disease prevention and treatment. Another thing understood from the result is that at least in the study area up to 1994, the disease burden caused by breast cancer attributed mainly to the outcome of death. Therefore, breast cancer seems to be a lethal disease with a high probability of death among women who suffered from this disease.

3. Health effect analyses for using DALY in environmental burden of disease study

DALY is a useful indicator for quantifying disease burden by taking "time" as a unit. This indicator can provide a quantitative measure of the decrease as life length and degradation of life quality after the outbreak of specific diseases (Miquel and Huertas, 2006). As many environmental pollutants may also cause diseases, their impacts on human health can be interpreted as disease burden as well. In this regard, DALY can provide useful tools for risk quantification of environmental pollutants. However, the application of DALY to quantitative assessment of health hazards caused by environmental pollutants requires the adoption of a series of methodologies other than DALY itself, and this has become a new research field defined as "environmental burden of disease study" (WHO, 2002).

Fig. 4 shows a framework of the environmental burden of disease study which consists primarily two parts: (i) A basic process (plots with solid lines) similar to what has been widely applied for human health risk assessment of hazards from environmental pollutants consisting of hazard identification, exposure assessment, and dose–response analysis (Haas et al., 1999). However, the outcome of the assessment is no longer merely a measure of "risk", but morbidity and/or mortality which are useful for subsequent disease burden calculation (Pruss and Havelaar, 2001); and (ii) DALY calculation process (plots with dashed lines) using the outcome from the basic process. The disability analysis result and the mortality analysis result can be used for calculating YLD and YLL respectively, and DALY can finally be obtained for the quantification of disease burden (Pruss and Havelaar, 2001; WHO, 2013).

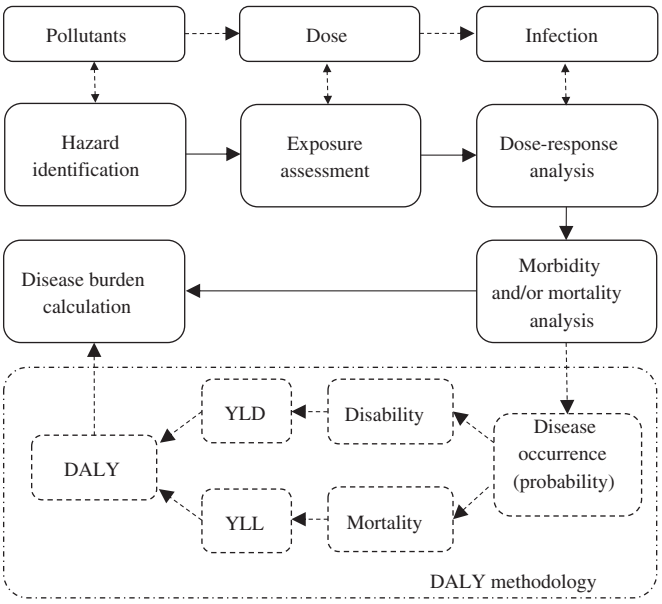

Fig. 4. Framework of environmental burden of disease study with usage of DALY.

3.1. Categories of health significant environmental pollutants

Many environmental pollutants may probably cause health hazards on human beings (Lubka, 2002). From their chemical and physical features, environmental pollutants can be generally classified into three categories, namely inorganic substances, organic substances, and microorganisms (Verhaar et al., 2000). Of the inorganic pollutants, lead, cadmium, chromium and mercury, just mention a few, are typical heavy metals, and arsenic, selenium, fluoride and cyanide are typical metalloids of health significance (Verhaar et al., 2000). Organic pollutants of health significance mainly include polycyclic aromatic hydrocarbons (PAHs), metal organic compounds, oxygen-containing organic compounds, organonitrogen compounds, organic halides, organophosphorus pesticides and so on (Verhaar et al., 2000). Microorganisms which are pathogenic include bacteria pathogens such as *Escherichia coli*, *salmonella*, *shigella*, *vibrio cholerae*, viruses such as enterovirus, hepatitis virus, rotavirus and poliovirus, protozoa such as *cryptosporidium* and *giardia*, and parasites such as ascaris and tapeworms (Kwaasi, 2003).

The majority of the inorganic and organic pollutants are identified to be toxic (Elmore and Boorman, 2013). Their hazardous effects on human bodies can be classified into various categories according to the target tissues or organs (Wright and Welbourn, 2002; Elmore and Boorman, 2013). Therefore, pollutants can also be classified according to the nature of toxic effects, such as mutagenic toxics, carcinogenic toxics, and teratogenic toxics (Wright and Welbourn, 2002; Susan et al., 2013) of which carcinogenic substances should be paid with special attention due to their severe and irreversible human health outcomes (Gehlhaus et al., 2011). A number of inorganic and organic chemicals are confirmed to be carcinogenic to human, such as arsenic, benzene, chromium VI and chloroethylene (Dhanalakshmi, 2013), or probably carcinogenic to human, such as cadmium, beryllium, cobalt, methanal and acrylonitrile (Laura et al., 2014; Gehlhaus et al., 2011).

Contacting with environmental contaminants may induce different extents of health hazards (Elmore and Boorman, 2013). For example, the ingestion of inorganic pollutants such as lead, mercury, cadmium and arsenic may cause a variety of acute or chronic effects, and consequently lead to damages on nervous system, lung, kidney, skin or bones (Yuan et al., 2014; Tore and Parvinder, 2012; Laura et al., 2014;

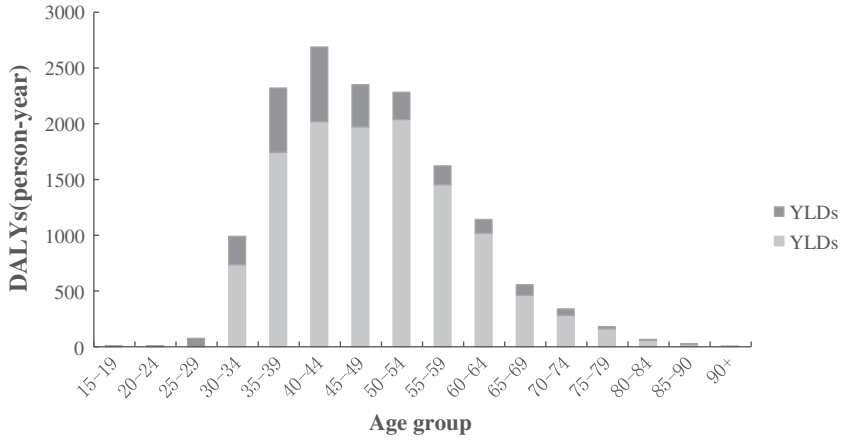

Fig. 3. Disease burden caused by breast cancer in Taiwan 1994 (Chie et al., 2001).

Zhang et al., 2013). Regarding organic pollutants such as organochlorine pesticides, PAHs, and phenolic compounds, their effects on human bodies are usually chronic including carcinogenic, teratogenic, mutagenic and endocrine disruptive effects (Gehlhaus et al., 2011). In contrast to chemicals, pathogenic microorganisms mainly induce various symptoms of acute infection, such as diarrhea or gastroenteritis caused by *E. coli* or enteroviruses, infectious hepatitis caused by hepatitis viruses, and cryptosporidiosis and giardiasis, respectively, caused by the very harmful protozoa — *cryptosporidium* and *giardia* (Toze, 2006).

The health hazards caused by specific environmental pollutants are also influenced by other factors. The exposure dose or concentration determines the rapidity of infection to a great extent (Manahan, 1992; Dai, 1996). The health impacts caused by the entrance of high dose of contaminants into human body in a short time is defined as acute health effect such as that caused by pathogenic microorganisms (Toze, 2006; Dillingham et al., 2002; Okhuysen et al., 1999), while the health impact caused by accumulation of specific pollutant in human body through long-term exposure under low doses is defined as chronic health effect (Gehlhaus et al., 2011). Carcinogenic and mutagenic effects by long-term exposure to carcinogens belong to this category. Health impact with a speed level lies between the above two conditions can be defined as sub-chronic effect, such as the typical cases of minamata disease caused by methylmercury and itai-itai disease caused by chromium (Chen et al., 2007). Table 2 summarizes the classification of environmental pollutants according to their properties and rapidity of the resulted human health impacts.

3.2. Quantification of health effects caused by environmental pollutants

As shown in Fig. 4, before disease burden calculation with application of DALY methodology, there are basically four steps, namely identification of potential harmful pollutants (Sam, 2014), exposure assessment (Gehlhaus et al., 2011), dose–response analysis (Gehlhaus et al., 2011) and morbidity/mortality analysis (Pruss and Havelaar, 2001). Following the discussion in Section 3.1 regarding hazard identification, this section deals with the three subsequent steps, all together called the quantification of health effects caused by environmental pollutants.

3.2.1. Exposure assessment

Exposure assessment includes determination of exposure pathway and calculation of exposure dose. Exposure pathway analysis is usually based on field investigation of the contaminated sites and involves four basic elements, namely, the source of pollution, the pollutant transmission medium, the exposure site and the contact pathway of contaminant to human body (Gehlhaus et al., 2011; Chen et al., 2006; USEPA, 2011). The exposure dose can then be calculated according to the stages of pollutants' intrusion into a human body to obtain either of the four categories of doses, namely, the potential dose as the amount of pollutants probably absorbed by human bodies, practical dose as the amount of pollutants actually reached the exchange boundary of the target organs/tissues, internal dose as the amount of pollutants entered the blood, and effective dose as the amount of pollutants delivered through blood to human cells or organs (Chen et al., 2006).

In the environmental burden of disease study, the internal dose or absorbed dose is adopted by means of direct measurement, biomarker method and/or model calculation (Gehlhaus et al., 2011). The direct measurement of the exposure quantities of pollutant carriers and the pollutant concentration is usually inaccurate due to the influence from many environmental factors (Hu et al., 2011) while the biomarker method, as an indirect measurement of the amount of biomarkers that exist in human metabolites may not effectively distinguish the exposure

Table 2
Categories of environmental pollutants.

Pollutants	Adverse health effects		
	Acute	Sub-chronic	Chronic
Inorganic pollutants	Hg (Susan et al., 1990; Kimberlie and Pollack, 1998); As (Kimberlie and Pollack, 1998; Michael, 2002); Cr (Dhanalakshmi, 2013); Cd (Rathishri et al., 2013; Yuan et al., 2014); Pb (Yuan et al., 2014); Fluoride (Garg et al., 2013); Cyanide (Lewis, 2006)	Cd (Rathishri et al., 2013; Anatoly et al., 2014; Yuan et al., 2014); Pb (Anatoly et al., 2014; Yuan et al., 2014); As (Zhang et al., 2013); Cyanide (Rahul et al., 2014)	Hg (Tore and Parvinder, 2012; Kimberlie and Pollack, 1998); As (Kimberlie and Pollack, 1998; Michael, 2002); Cr (Dhanalakshmi, 2013); Cd (Laura et al., 2014); Pb (Jarrar and Taib, 2012); Fluoride (Flavia et al., 2010); Cyanide (Okolie, 2000)
Organic pollutants	Endosulfan (Das and Gupta, 2013); Parathion (Sheemona et al., 2014); Dichlorvos (Sheemona et al., 2014); Chlorpyrifos (Michael et al., 2005); Dimethoate (Michael et al., 2005); Fenthion (Michael et al., 2005);	Tertiary butyl acetate (Willem et al., 2014); N-butyl acetate (David et al., 2001);	Polychlorinated biphenyls (Hsu et al., 2013); Polybrominated diphenyl ethers (Hsu et al., 2013); Leptophos (Milan et al., 2010); Methamidophos (Milan et al., 2010); Trichlorfon (Lotti and Moretto, 2005); Roxithromycin, clarithromycin, tylosin (Yang et al., 2008); Caffeine (Li et al., 2012); Carbamazepine (Clara et al., 2004; Li et al., 2010); Triclosan and triclocarban (Yang et al., 2008); Diclofenac (Schwaiger et al., 2004); Pyrene (Jignasha et al., 2013); Benzo[a]pyrene (Du et al., 2014); Ethinylestradiol (Zühlke et al., 2004); N-nitrosodimethylamine (ICEC, 2002); Chloroform (McCulloch, 2003)
Pathogen	Enterovirus (Muir et al., 2014); Hepatitis A virus (Mustafa et al., 2014); Hepatitis C virus (Chang and Chang, 2013); Rotavirus (Niwat and Pattara, 2014); Norovirus (Wu et al., 2014); Escherichia coli (Lobel et al., 2013); Campylobacteria (Rokosz et al., 2014); Cryptosporidium (Winnie et al., 1984)	–	Hepatitis C virus (Chang and Chang, 2013; Mabrouk et al., 2013); Helicobacter (Dassen et al., 2014); Giadia (Marie and Buret, 2013); Helminth (Desalegn, 2014)

doses obtained through various media and pathways (NRC, 2006). Comparing with these two methods, model calculation is more convenient for estimating the exposure dose using appropriate mathematical models which are constructed taking into account the emission concentrations, migration and transformation laws, environmental and physiological characteristic of the exposed populations and so on (Hu et al., 2011). The most widely applied model is the Average Daily Dose (ADD) model which is suitable for noncarcinogenic pollutants (Gehlhaus et al., 2011) by the following basic equation (USEPA, 2011):

$$\mathrm{ADD} = \frac{\mathrm{Intake\,Dose}}{\mathrm{Body\,Weight} \times \mathrm{Average\,Time}} \tag{7}$$

where, the intake dose is the mass of a specific pollutant ingested by one person; body weight is the average weight of an adult, usually taken as 70 kg; average time is the period of exposure counted by days. Therefore ADD is the mass of the pollutant ingested per kg of body weight per day.

Another widely used model it the Lifetime Average Daily Dose (LADD) model which is suitable for carcinogenic pollutants by the following equation (Gehlhaus et al., 2011; USEPA, 2011):

$$\mathrm{LADD} = \frac{\mathrm{Intake\,Dose}}{\mathrm{Body\,Weight} \times \mathrm{Lifetime}} \tag{8}$$

where, the lifetime is usually taken as 70 years and counted by days so that LADD is the mass of the pollutant ingested per kg of body weight per day through a lifetime.

3.2.2. Dose–response analysis

Dose–response analysis is a process to obtain the probabilistic relationship between the exposure dose and the health risk which can be ideally conducted based on epidemiological investigations (Gehlhaus et al., 2011). However, due to the limitation of available exposure information, mathematical models have to be used in most cases.

Various dose–response models have been found applicable for measuring carcinogenic risks, such as the log-normal model, Weibull model, one-hit model, multistage model and so on (Klaassen, 1996). Of them the Weibull model and multistage model are regarded as the most reliable for extrapolating health risks to low dose conditions (Gehlhaus et al., 2011). For quantifying microbial risks, a number of studies are available for estimating the effect of low dose exposures to a few pathogens (Gehlhaus et al., 2011), and exponential model and Beta-Poisson model are commonly applied (WHO, 2001a, 2001b, 2001c).

3.2.3. Morbidity/mortality analysis

Table 3 summarizes the potential human health effects as a result of exposure to various environmental pollutants. These effects can be measured as infection rate through dose–response analysis. However, the infection rate may not represent the ultimate health hazards, and further analysis should be conducted to obtain morbidity and mortality as the measures of the health outcome (Pruss and Havelaar, 2001).

Fig. 5 illustrates the general process of disease development after exposure to environmental pollutants (Gehlhaus et al., 2011). For individuals exposed to specific pollutants, because not everyone can be infected after each exposure, there are either no-infection or infection cases, and even among the infected individuals, either asymptomatic cases or symptomatic/illness cases may occur. In the symptomatic/illness cases, as the pollutants are of different concentrations in the environment and act in different pathogenesis on human bodies, different types of diseases may develop as a result. The ultimate results of infection include complete recovery, residual symptoms (disability) and even loss of life (mortality).

There are several methods to estimate morbidity rate due to certain diseases, such as epidemiological investigation, human/animal experimental analysis and probability evaluation. Epidemiological investigation is usually a general survey or sampling survey for collecting disease information, including an investigation of the routine recorded data on hospitalized proportions, disease surveillance, death registration and so on (Havelaar et al., 2000). Experimental analysis is a test on animal and/or human bodies for observing the impacts of certain risk factors on the infected objects. Although animal experiments (Yuan et al., 2014; Ruthann et al., 2014) are much easier to be conducted, there are successful cases of experimental analysis on human infection of diseases (Dietz et al., 2000). Probability evaluation is a mathematical calculation process to determine the morbidity and mortality related to disease prevalence and transmission caused by specific pollutants. The most useful equations for calculating morbidity and mortality are as below (Gehlhaus et al., 2011; Wei et al., 2012):

$$P_{\mathrm{Morbidity}} = P_{\mathrm{Infection}} \times P_{\mathrm{Ill/Inf}} \tag{9}$$

$$P_{\mathrm{Mortality}} = \mathrm{CFR} \times P_{\mathrm{Morbidity}} \tag{10}$$

where, $P_{\mathrm{Infection}}$: probability of infection with a specific pollutant; $P_{\mathrm{Ill/Inf}}$: probability of illness due to infection; and CFR: case fatality rate due to disease.

In Eq. (9), $P_{\mathrm{Infection}}$ is usually determined through dose–response analysis to distinguish the probabilities of infection between varied subpopulations in different immune conditions (Pouillot et al., 2004; An et al., 2011), while $P_{\mathrm{ill/Inf}}$ is often calculated by fitting with different statistical distributions through epidemiological investigations and disease outbreak studies. For example, in the cases of cryptosporidium infection, a β distribution was found to be suitable for characterizing the probability of gastroenteritis (Gehlhaus et al., 2011) and $P_{\mathrm{Ill/Inf}}$ was calculated as 0.71 for immunocompetent population (Havelaar and Melse, 2003) while that for immunodeficient population was 1.0 (Pouillot et al., 2004).

In Eq. (10), CFR can be determined following different statistical distributions according to disease outbreak studies (Addiss et al., 1996) or lab-surveillance analysis (Dietz et al., 2000). In this case, the β distribution is also found to be useful for evaluating CFR. For example, according to the cryptosporidiosis outbreak study for Milwaukee, USA in 1993, the CFR was fitted with a β distribution with parameters as $\alpha = 1$, $\beta = 99{,}999$ and mean value $= 10^{-5}$ for HIV-positive patients (Havelaar and Melse, 2003), while the parameters were $\alpha = 7$, $\beta = 3$ and mean value $= 0.7$ for HIV-negative patients (McGowan et al., 1993).

Regarding the health outcome of disability, its probability ($P_{\mathrm{Disability}}$) can be evaluated through disease outbreak studies or experimental analysis taking into account the pathogenic characteristics of specific contaminants and the intervention conditions of the diseases. For an area where disease outbreak occurs, the number of disabilities ($N_{\mathrm{Diability}}$) and number of premature deaths ($N_{\mathrm{Mortality}}$) can be evaluated by the following equations (Gehlhaus et al., 2011):

$$N_{\mathrm{Disability}} = N \times P_{\mathrm{Morbidity}} \times P_{\mathrm{Disability}} \tag{11}$$

$$N_{\mathrm{Mortality}} = N \times P_{\mathrm{Morbidity}} \times P_{\mathrm{Mortality}} \tag{12}$$

where, N is the exposed population referring to demographic statistics.

3.3. Selection of models

For predicting disease burdens due to exposure to specific pollutants of heath significance, due to lack of sufficient available data to generate a specific dose–response curve in most cases, existing dose–response models are often used (Gehlhaus et al., 2011). Regarding noncarcinogenic chemicals, the resulting health impacts are normally regarded as 'threshold' effects (Hu et al., 2011). In this case, a hazard index can be used calculated as below (Gehlhaus et al., 2011):

$$P = \frac{\mathrm{ADD}}{\mathrm{RfD}} \times 10^{-6} \tag{13}$$

Table 3
Common environmental pollutants and the associated potential health effects.

Group	Specific pollutant	Disease and clinical symptoms	Reference
Bacteria	Salmonella	Typhoid and diarrhea	Straub and Chandler (2003)
	Shigella	Diarrhea	Straub and Chandler (2003)
	Campylobacter	Diarrhea	Rokosz et al. (2014)
	Escherichia coli O157:H7	Acute hemorrhagic diarrhea, abdominal cramps, hemolytic uremia syndrome	Lobel et al. (2013)
Viruses	Enteroviruses	Meningitis, paralysis, rash, fever, myocarditis, respiratory disease, diarrhea	Muir et al. (2014)
	Hepatitis A and E viruses	Infectious hepatitis	Mustafa et al. (2014), Chang and Chang (2013)
	Caliciviruses	Diarrhea/gastroenteritis	Wu et al. (2014)
	Rotavirus	Diarrhea/gastroenteritis	Niwat and Pattara (2014)
	Adenovirus	Diarrhea, eye infections, respiratory disease	
Protozoa	Giardia lamblia	Chronic diarrhea	Marie and Buret (2013)
	Cryptosporidium parvum	Acute diarrhea, fatal for immunocompromised individuals	Winnie et al. (1984)
Helminths	*Ascaris lumbricoides*	Ascariasis	Desalegn (2014)
	Schistosome	Schistosomiasis	King (2010)
Inorganic chemical	Hg	Neurological damage	Tore and Parvinder (2012)
	Cr	Lung cancer, nasal septum congestion, anabrosis, respiratory complications, skin disease	Dhanalakshmi (2013)
	Cd	Itaiitai disease	Rathishri et al. (2013), Laura et al. (2014)
	Pb	Neurological damage, anemia, hypertension, chronic gastritis, liver and kidney dysfunction	Jarrar and Taib (2012), Yuan et al. (2014)
	As	Gastroenteritis, polyneuritis, liver cancer, lung cancer, renal carcinoma, skin pigmentation, skin cancer	Michael (2002), Zhang et al. (2013)
Organic chemical	*N*-nitrosodimethylamine	Liver cancer, lung cancer, kidney cancer	ICEC (2002)
	Polybrominated diphenylethers	Goiter, benign and neoplastic thyroid diseases, neurodevelopmental deficits, liver cancer, pancreatic cancer	Hsu et al. (2013)
	Polychlorinated biphenyls	Infertility, estrogenlike hormone interference and thyroid interference, neurological damage, skin disease, liver cancer, death	Hsu et al. (2013)
	Fenthion	Dysgenesis, liver disease, respiratory disease, gastrointestinal disease, cancer	Michael et al. (2005)
	Parathion	Skin diseases, respiratory diseases, gastrointestinal diseases and cancer	Sheemona et al. (2014)
	Endosulfan	Central nervous system disorder, liver, kidney, and brain damage, growth retardation, dysgenesis, death	Das and Gupta (2013)
	Dichlorvos	Central nervous system disorder, liver or kidney damage, endocrine disorder, skin disease, death	Sheemona et al. (2014)
	Caffeine	Endocrine disruption	Li et al. (2012)
	Diclofenac	Renal lesions	Schwaiger et al. (2004)
	Benzo[a]pyrene	Skin cancer, lung cancer, gastric cancer, intestinal cancer, etc.	Du et al. (2014)
	Chloroform	Central nervous system disorder, liver or kidney damage, cancer, teratogenesis	McCulloch (2003)
	Dioxin	Growth retardation, reproductive defects, immunocompromise, intelligence and movement disorders, neuropsychiatric disorders, teratogenesis, liver cancer, skin cancer, breast cancer, etc.	Pier et al. (2001)
	Pentachlorophenol	Headache, neuralgia, bronchitis, allergic dermatitis, liver or kidney damage, death	Zhang et al. (2010)

where, P: hazard index as the probability of the occurrence of certain health hazard; ADD: average daily dose ($mg/kg^{-1}\ d^{-1}$); RfD: reference dose of a non-carcinogenic chemical ($mg/kg^{-1}\ d^{-1}$) corresponding to the maximum dose of non-health-effect (Donald, 1988); 10^{-6}: threshold risk as one per million (Gehlhaus et al., 2011).

Regarding carcinogenic chemicals, the resulting health impacts may not be detected soon after exposure but certain cancers may be developed after long term exposure (Gehlhaus et al., 2011). In this case, the response to chemical dose becomes a 'risk' of cancer which has to be assessed using suitable models. Probit, Weibull,

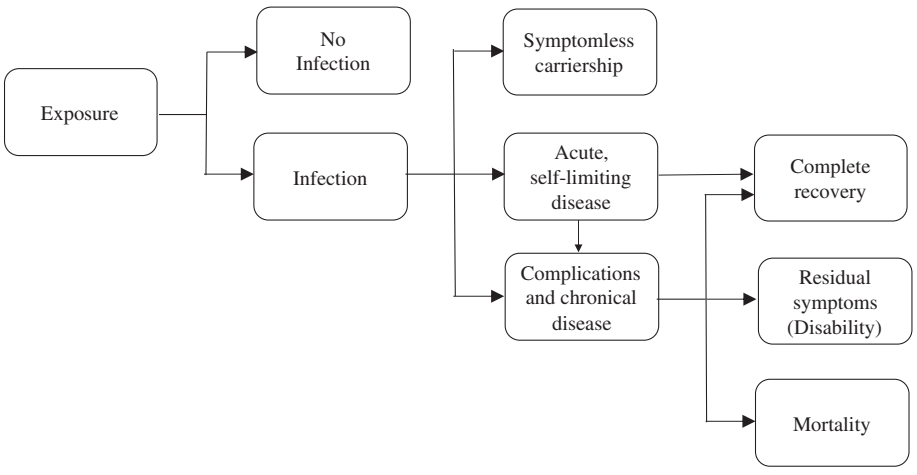

Fig. 5. General process of disease development after exposure to environmental pollutants.
Adapted from Pruss and Havelaar (2001).

One-hit, and Multi-stage models are most commonly used for this purpose (Metcalf and Eddy, 2008). As shown in Table 4, if P(D) denotes the probability of response to a dose as D, the Weibull, One-hit, and Multi-stage models have a similarity in their exponential expressions while the Probit model is differently expressed. For fitting with experimental data such as chemical dose and tumor occurrence, these models are often found to be applicable in high dose ranges but significant differences may appear when the modelling results are extrapolated to low dose ranges where human health effects are targeted (Hu et al., 2011; Adamus-Górka et al., 2011; Gehlhaus et al., 2011; Martin et al., 2011). It is recommended in the USEPA's Integrated Risk Information System that the Multi-stage model, as the safest to obtain higher risk of human cancer in low dose ranges, can be applied as the standard model for cancer risk assessment (Gehlhaus et al., 2011).

For fitting the mathematical models to experimental data on human cancers, a maximum likelihood method is recommended (Johnson et al., 1994; Adamus-Górka et al., 2011), and the goodness of data fitting to the model can be evaluated through various hypothesis testing (Baltas and Grassman, 1997; Adamus-Górka et al., 2011). To estimate the upper limit of carcinogenic risk rather than to calculate the values of health risk under low dose of exposure, a linear Multi-stage model was proposed as (Lovell and Thomas, 1996):

$$P = LADD \times CPF \tag{14}$$

where, P: the lifetime carcinogenic risk; LADD: lifetime daily dose ($mg \cdot kg^{-1} \cdot d^{-1}$); CPF: carcinogenic intensity coefficient which defines the upper limit of the excess carcinogenic risk per unit exposure dose ($kg \cdot d \cdot mg^{-1}$).

Exponential and Beta-Poisson models are commonly used for pathogenic microorganisms (Regli et al., 1991). The exponential model is derived from the one-hit model based on the assumptions that (i) microorganisms are distributed randomly and follow the Poisson distribution; (ii) for infection to occur, at least one pathogen must survive within the host; and (iii) the probability of infection per ingested or inhaled organism is constant (Metcalf and Eddy, 2008). Following the exponential relationship shown in Table 4, the probability of infection P_i depends on exposure dose N and an empirical parameter β which is a constant for any given host and given pathogen picked to fit experimental data. The Beta-Poisson model is derived based on similar assumptions as those for the Exponential model but with an additional assumption that the probability of infection per ingested organism is more relaxed, allowing the probability of infection to vary with crowds of population. In the model equation shown in Table 4, the parameter α is a constant for a given pathogen, while the median dose N_{50} depends on α and a slope parameter β in a relation as below:

$$N_{50} = \frac{\beta}{2^{1/\alpha} - 1}. \tag{15}$$

Selection of the suitable model for dose–response analysis regarding pathogenic microorganisms may require tests to validate the model with outbreak data (Eisenberg et al., 1998). According to existing studies many protozoans and viruses generally tend to follow the Exponential model (Metcalf and Eddy, 2008; Zhang and Wang, 2012, 2014), while many bacteria tend to follow the Beta-Poisson model (He et al., 2005; Zhang and Wang, 2012, 2014).

3.4. Determination of parameters

For dose–response analyses many parameters have to be determined or selected. In calculating the hazard index of non-carcinogenic chemicals (Eq. (13)), ADD should be appropriately determined, while in calculating the carcinogenic risk following the linear relation (Eq. (13)), determination of LADD is also an indispensable step. At an exposure site the concentration of pollutants can be monitored while pollutant migration and transformation models may have to be applied for predicting the concentration of pollutants to reach human body (Chen et al., 2006). To determine the intake of pollutant carriers, the ingestion rate, exposure frequency and duration under various contacting pathways should be taken into account. Detailed investigations, if possible, may be the most appropriate way to determine all these factors, but in most cases former experiences or technical guidelines can provide referential parameters (USEPA, 2011).

Regarding carcinogenic chemicals, the model parameters shown in Table 4 can be determined by fitting with available experimental data for each model adopted (Haas et al., 1999). In the case of using the linear function (Eq. 14) to calculate the carcinogenic risk, determination of the carcinogenic intensity coefficient may need sophisticated medical, epidemiological and/or toxicological studies (Haas et al., 1999). USEPA has established an Integrated Risk Information System (IRIS) in which the toxic characteristics of thousands of chemicals are reviewed and continuously updated based on latest scientific evidences and research findings (Haas et al., 1999; Gehlhaus et al., 2011).

In the two dose–response models shown in Table 4 for pathogenic microorganisms, the parameters α, β and N_{50} should be appropriately determined preferably by fitting experimental data with the Exponential or Beta-Poisson model (Haas et al., 1999). It is often more convenient to transfer the models to logarithmic forms for linear regression (Kang et al., 2000). However in many cases reliable experimental data may be unavailable or insufficient, and past experiences have to be

Table 4
Commonly used dose–response models.

Model	Equation	Characteristics	Reference
For carcinogenic chemicals			
Probit	$P(D) = \frac{1}{2}\left(1 - Erf\left[\gamma_{50}\sqrt{\pi}\left(1 - \frac{D}{D_{50}}\right)\right]\right)$	Based on an assumption that the tolerance of exposed population follows a lognormal distribution	Cocherham and Shane (1994), Pepper et al. (1996), Adamus-Górka et al. (2011)
Weibull	$P(D) = 1 - \exp(-a + bD^m)$	Applicable under the condition that the observed data are in line with Weibull distribution	Metcalf and Eddy (2008)
Onehit	$P(D) = 1 - \exp(-k_0 - k_1 D)$	Applicable for the single exposure scenario which may lead to the development of specific health hazard	
Multi-stage	$P(D) = 1 - , \exp\left(-\sum_{i=0}^{n} k_i D_i\right)$	Applicable under the condition that the formation of a tumor is the result of a sequence of biological events	
For pathogenic microorganisms			
Exponential	$P_i = 1 - e^{-\frac{N}{\beta}}$	Applicable to many protozoans and viruses	Regli et al. (1991), Cocherham and Shane (1994), Pepper et al. (1996), Metcalf and Eddy (2008)
Beta-Poisson	$P_i = 1 - \left[1 + \frac{N}{N_{50}}\left(2^{\frac{1}{\alpha}} - 1\right)\right]^{-\alpha}$	Applicable to many bacterial pathogens	

referred for choosing appropriate model parameters. Table 5 summarizes the reported dose–response models and best-fit parameter values for typical pathogens.

4. Application of DALY for real cases of environmental burden of disease study

The application of DALY for environmental burden of disease study basically follows the framework shown in Fig. 4. In this section, real cases will be analyzed on two categories of pollutants usually encountered in daily life and/or industrial activities, namely, chemical pollutants and pathogens.

4.1. Disease burden analyses for chemical pollutants

A range of health issues has so far been suspected or conformed to be related to the exposure of chemical pollutants in external environment, such as neuro-developmental disorders caused by heavy metals, dioxins, PCBs, pesticides and so on (Hall and Peters, 2004), cardiovascular diseases and peripheral vascular diseases observed in children due to consumption of arsenic-contaminated water (Havelaar and Melse, 2003), respiratory diseases and certain childhood cancers related to early life exposure to air pollutants, such as PM_{10}, benzene, and toluene (Ragas et al., 2011a, 2011b), thus drawing attentions from national/international institutions and individual researchers for qualitative and quantitative evaluation of the health impacts caused by chemical pollutants (WHO, 2009b). In many studies, DALY has been used as an indicator to quantify disease burdens caused by chemical pollutants (Valent et al., 2004b). Table 6 summarizes relevant studies on chemical pollutants of airborne, foodborne, and waterborne sources, of which the airborne chemical agents were recognized as the major sources to cause a variety of diseases which contributed much to the total disease burden (Jahnke et al., 2005).

4.1.1. Case explanations

In this subsection, three typical cases are reviewed regarding disease burdens due to exposure to chemical pollutants majorly from airborne sources as indicated in Table 6.

1) Case 1: Disease burden analysis of air pollutants from municipal solid waste incinerators in Seoul, Korea (Kim et al., 2011). The main pollutants are PM_{10}, NO_2, SO_2 and CO emitted from four incinerators for final disposal of municipal solid wastes in northwestern, northeastern, southeastern and southeastern suburbs of Seoul. The diseases suspiciously resulted from exposure to these airborne chemicals through inhalation are cardiovascular and respiratory diseases among residents in the vicinities of the solid waste incinerators. A source-specific, exposure-based population attributable fraction (PAF) was used as a measure of the impacts, and the burden of disease associated with the risk factor and the population level was then assessed in terms of DALYs. The total burden of disease was finally evaluated by multiplying PAF and DALYs. For evaluating PAF, the AMS/EPA Regulatory model was applied to predict the additional concentrations of PM_{10}, NO_2, SO_2 and CO in the ambient environment. As a result of dose–response analysis, a relative risk (RR) could characterize the response to each of the specific pollutants, leading to a quantitative evaluation of respiratory morbidity, cardiovascular mortality and all-cause mortality. It was identified that the emission concentration of NO_2 was the highest among all air pollutants and its all-cause mortality was also the highest. Although the air emissions from one risk factor (an incinerator) were small, the burden of disease can be significant to the public health when population exposure was considered.
2) Case 2: Cumulative risk assessment of chemical exposures for people living in a hypothetical urban environment equivalent to a middle-sized European city (Ragas et al., 2011a, 2011b). The case study focused on the health risks of multiple chemical pollutants for people exposed to PM_{10} and four VOCs (benzene, toluene, nonane and naphthalene), in indoor and outdoor air and six pesticides (carbendazim, chlorpyrifos, diazinon, imidacloprid and permethrin) in food. The cumulative health risk was assessed for three different target groups of young children, working adults and elderly. The study included two successive steps — exposure assessment and effect assessment. Regarding airborne pollutants, exposures in five different microenvironments (outdoors, home, office, school/kindergarten and enclosed transit) were taken into account. The average exposure concentration of an individual was calculated for each chemical separately as a time-weighted average concentration, using the relative time spent in each microenvironment as weights. Regarding pesticide residues in food, the exposure assessment was conducted using the human exposure model NORMTOX (Ragas and Huijbregts, 1998; Ragas et al., 2009) to estimate the long-term averaged daily intake of contaminants via food with food consumption data from a Dutch source (Hulshof et al., 1998) and data on pesticide residue levels in food from a German source (BVL, 2009). For assessing the mixture effects, four scenarios were defined to cover a range of options, such as to assess the potential adverse effects for each substance separately with ignorance of their mixture effects, to consider possible joint effects without interactions, to consider possible joint effects with interactions, and to calculate the number of DALYs based on the assumptions that substances have a dissimilar mechanism of action and do not interact. The DALY calculation was conducted firstly to estimate the Excess Lifetime Risk (ELR; Vaeth and Pierce, 1990), and subsequently to multiply the ELR with the average number of life years lost due to premature death and/or illness and to obtain the DALYs. The case study implied that pollutants in indoor air seemed to have a larger impact on human health than pollutants in outdoor air, and of all air pollutants studied, the health impact of PM_{10} pollution seemed to be much more serious than the others.
3) Case 3: Environmental burden of disease analysis due to lead exposure in urban children from Silesia, Poland (Jarosińska et al., 2006). In this case study, environmental burden of disease assessment was conducted on the neurotoxic effects of lead in the Polish urban children based on the data on blood lead level (BLL) of more than 8500 children in the Upper Silesia Province. By data analysis, the adjusted geometric mean BLLs combined for the studied urban area were found to be 4.9 μg/dL, a value higher than the corresponding value of 3.9 μg/dL for the WHO EurB region (Fewtrell et al., 2003).

Table 5
The reported dose–response models and their best-fit parameter values for typical pathogens.

Pathogenic microorganisms	Model	Parameter	References
Poliovirus	Exponential	$\beta = 109.87$	Crabtree et al. (1997),
Hepatitis A virus	Exponential	$\beta = 1.8229$	Crockett et al. (1996),
Adenovirus	Exponential	$\beta = 2.397$	Fewtrell et al. (2001),
Echovirus	Exponential	$\beta = 78.3$	Gerba et al. (1996),
Coxsackie virus	Exponential	$\beta = 69.1$	Haas et al. (1999),
Cryptosporidium	Exponential	$\beta = 238$	Huertas et al. (2008),
Giardia	Exponential	$\beta = 50.23$	Jolis et al. (1999),
Rotavirus	Beta-Poisson	$N_{50} = 6.17$, $\alpha = 0.2531$	Regli et al. (1991), Teunis et al. (2010),
Salmonella	Beta-Poisson	$N_{50} = 23{,}600$, $\alpha = 0.3126$	Rose et al. (1991), Wei et al. (2012),
Shigella	Beta-Poisson	$N_{50} = 1120$, $\alpha = 0.2100$	Westrell et al. (2009)
Escherichia coli	Beta-Poisson	$N_{50} = 8.60 \times 10^7$, $\alpha = 0.1778$	
Campylobacter jejuni	Beta-Poisson	$N_{50} = 896$, $\alpha = 0.145$	
Vibrio cholerae	Beta-Poisson	$N_{50} = 243$, $\alpha = 0.25$	

Table 6
Chemical pollutants as targets of disease burden studies.

Source	Specific agents	Reference
Airborne	Lead, PM_{10}, benzene, toluene, nitrogen oxides, ammonia, sulfur dioxide, styrene, 1,2-dichloroethane, acrylonitrile, tetrachloroethylene, formaldehyde, benzo[a]pyrene, carbon tetrachloride, chloroform, nickel, cadmium, chromium, vinyl chloride, dichloromethane, ethylene oxide, propylene oxide	Francesca et al. (2004), Geelen et al. (2009), De Hollander et al. (1999), Jarosińska et al. (2006), Kim et al. (2011), Knol and Staatsen (2005), Kunzli et al. (2001), Murray and Lopez (1996a), Ragas et al. (2011a, 2011b), Smith and Mehta (2003), Watkiss et al. (2005)
Foodborne	Lead, arsenic	Prüss-Ustün (2011), Fewtrell et al. (2004), Haagsma et al. (2013), Lokuge et al. (2004), Valent et al. (2004b)
Waterborne	Fluorine, arsenic, chromium	Prüss et al. (2002), Prüss-Ustün et al. (2011) Chen et al. (2008), Fewtrell et al. (2005)

The occurrence of mild mental retardation (MMR) was assessed by calculating the loss of IQ points which were assumed to be 0.65, 1.95, 3.25, and 3.5 from the original IQ points when BLLs were in the ranges of 5–10 μg/dL, 10–15 μg/dL, 15–20 μg/dL, and above 20 μg/dL, respectively. According to the BLLs and IQ distributions, number of children affected per 1000 children and the associated incidence of MMR per 1000 children were evaluated. For estimating the DALYs attributed to childhood exposure to lead, the MMR incidence estimates were used as input into the WHO template for DALY calculation (Dorota et al., 2006). As MMR does not contribute to YLL, the total DALY estimates come from YLD, calculated with the assumed discount of 3% per year and age weighting. As a result, 66 DALYs were estimated for the year 2005 assessment, while the analogous figure projected for the year 2001 was 136 DALYs, indicating that lead prevention activities resulted in significant DALY reduction in the study area.

4.1.2. Methodologies and processes of analysis

Exposure assessment, health risk estimation, and disease burden calculation are three basic steps for environmental burden of disease study. In the abovementioned three cases regarding chemical pollutants, much or slightly different methodologies were adopted in each step according to the chemicals and environmental conditions under investigation.

For exposure assessment, Case 1 dealt with airborne chemicals in the ambient air from the same source (municipal solid waste incinerators), Case 2 dealt with airborne chemicals both indoor and outdoor and pesticides in food, while Case 3 dealt with a single chemical, i.e. lead from mining industry. The exposure pathways for these chemicals in Cases 1 and 3 only included inhalation (through respiratory tract) while in Case 2 included both inhalation and digestion (through digestive tract). In Case 1, since the pollutants from municipal solid waste incinerators emitted directly into the ambient air, the AMS/EPA Regulatory Model was employed to simulate air pollutant emission and estimate their ambient concentrations (Venkatram et al., 2004; Zou et al., 2009) based on monitoring data. In Case 3, although children might expose to lead mainly through respiration, as available data were blood lead level resulted from the cumulative exposure doses entering human body over a period of time (Chen, 2009), sophisticated exposure assessment was not conducted regarding exposure pathways. Comparing with these two cases, varied methodologies were adopted for exposure assessment such as using the CAR II Model for predicting PM_{10} concentrations in streets due to traffic (Infomil, 2009), estimation of the outdoor VOC concentrations using measurement data (Rehwagen et al., 2003; Schlink et al., 2004; Strebel et al., 2007), estimation of the indoor VOC concentrations partially referring to previous studies and partially by expert judgments (Schlink et al., 2004; Matysik et al., 2007; Ilgen et al., 2001; Zuraimi et al., 2006), and derivation of the indoor PM_{10} concentrations based on an outdoor/indoor ratio for PM_{10} (Franck et al., 2006; Kingham et al., 2000) as indoor air quality is strongly influenced by outdoor air quality. Regarding pesticide residues in food, the human exposure model NORMTOX (Ragas and Huijbregts, 1998; Ragas et al., 2009) was employed based on data from German and Dutch sources. When there were no data available for specific pesticides, their concentrations in food were taken as zero. If there are sufficient scientific evidences, using different methodologies for assessing the exposure of different pollutants under different environmental conditions would be plausible. Otherwise uncertainties may increase among varied assumptions and/or mathematical models (Kingham et al., 2000; Gulliver and Briggs, 2004; Zuraimi et al., 2006) and result in over- or under-estimation of the exposure to certain chemicals especially when health impacts of different pollutants are compared as in Case 2.

For health risk estimation, the target diseases were respiratory and cardiovascular diseases in Case 1, and MMR in Case 3 so that exposure–response relationships or functions were utilized. While in Case 2 the effect of exposure was taken as an exceedance of national/international standards to indicate a safe or acceptable chronic exposure level. These led to different approaches for the quantification of health risk. In Case 1, the risk related to each health outcome due to exposure to each air pollutant was represented by a relative risk (RR) using appropriate exposure–response functions (Anderson et al., 1997; WHO, 2001a, 2001b, 2001c; Pope et al., 2002, 2008; Barnett et al., 2006). The incidence data for related diseases were referred to Korean EBD study (KMOE, 2009). Further based on local population statistics and GIS data, the morbidity and fatality attributed to air pollutants by ages and sexes were calculated. In Case 3, what utilized for health risk estimation was not exposure–response models or functions but a relation between BLL and IQ point loss according to a number of epidemiological studies (Canfield et al., 2004; Fewtrell et al., 2003; Lawes et al., 2003; Needleman, 1999; Pocock et al., 1994; Tong, 1998). The health outcome was MMR which occurred when IQ points fell into a given abnormal range. Children with different original IQ scores and BLLs may be under different MMR risks. Therefore according to the IQ distributions in human population (Valent et al., 2004a, 2004b; Lezak, 1995) and the distribution of BLL among children in the study area, the morbidity of MMR could be calculated. In contrast with these two cases, the methodology used in Case 2 was in fact a threshold method where standard values were taken as thresholds above which health hazard would occur (Hu et al., 2011). Although by definition a risk can be measured in terms of the probability of exceedance to a threshold (Ganoulis, 2005), the exposure–response analysis conducted in such a way may not be equivalent to a dose–response analysis because the relationship obtained cannot be extrapolated to a dose below the threshold. Without referring to specific diseases, the excess lifetime risk and mixture effects analyzed for Case 2 may be uncertain.

For disease burden calculation, the basic methods for DALY calculation (Murray and Lopez, 1996a, 1996b) were adopted in all these cases but with certain differences in obtaining the final results. In Case 1, DALYs attributed to PM_{10}, NO_2, SO_2, and CO were calculated for respiratory disease and cardiovascular disease, respectively, as the sum of YLL and YLD (Park et al., 2006). In YLL calculation the life expectancy at birth was determined referring to the 2007 Korean statistical data, while in YLD calculation the DISMOD II model (Barendregt et al., 2003) was used to evaluate the average age at disease onset, and the disease duration was determined referring to the Korean disability weights (Lee et al., 2003). The disease burden was expressed as the product of the number of morbidities/mortalities attributed to specific

air pollutants and the healthy years of life loss per case (DALYs/case). In Case 2, due to lack of disease-specific and age-specific data a cumulative number of days lost due to exposure to PM_{10}, benzene and toluene for 80 years at current outdoor and indoor concentrations were calculated to represent the average number of life years lost. For each air pollutant, DALY was calculated by multiplying the excess lifetime risk with the average number of life years lost (Geelen et al., 2009), and the total disease burden was obtained as the summation of the DALYs for all individual pollutants. The assumption of continuous exposure to air pollutants may be an extreme condition and the lack of morbidity/mortality analysis regarding specific diseases may result in a deviation from the reality. In Case 3, as MMR does not contribute to years of life lost, the disease burden due to lead exposure only contributed to YLD. Following the standard DALY method, a discount of 3% per year was taken into account and unequal age weights were assigned to different age groups. YLD was eventually calculated by multiplying the number of MMR cases with the disease burden per MMR case.

4.1.3. Characteristics of disease burden analysis for chemical pollutants

Although certain chemicals are acute-toxic to human body at high doses (Yuan et al., 2014), environmental disease burden analyses for chemicals usually deal with their chronic effects on human health through long term exposure (Hu et al., 2011) as indicated in the three cases. In the successive steps of analyses, exposure assessment often aims at quantifying the concentrations of specific chemicals or their distributions in the environmental medium which may carry the chemicals to human bodies through various pathways. For airborne pollutants, such as PM_{10} and other inorganic and organic chemicals analyzed in Cases 1 and 2, a good understanding of their spatial and timely distribution in ambient or indoor air is extremely important. According to the characteristics of pollutant migration and transformation as well as human activities closely related to the contact of the pollutants, mathematical models should be appropriately selected to assist the analysis. It is ideal that the model parameters can be determined by fitting with existing data. Sometimes the analyses may also depend on assumptions and/or professional judgment (Schlink et al., 2004; Matysik et al., 2007; Ilgen et al., 2001; Zuraimi et al., 2006). As individual chemical may cause various diseases and a specified disease may also occur due to exposure to different chemicals, the exposure–response or dose–response assessment often becomes a sophisticated process. A prevailing way is to analyze each individual chemical regarding each possible effect on human health, such as in Case 1 where the relative risk of each chemical on the occurrence of cardiovascular disease and that of respiratory disease were respectively analyzed (Anderson et al., 1997; Pope et al., 2002, 2008; Barnett et al., 2006). It may also be necessary to consider the mixture effect of various chemicals regarding a specific disease, such as in Case 2 where scenario analysis of chemical interactions was conducted (Ragas et al., 2011a, 2011b). In this regard, clarification of interaction mechanisms is very important. Otherwise the analysis can only be based on assumptions. The final step of disease burden calculation often follows the methods recommended by WHO (Murray, 1994, 1996). What is important in this step is to consider fully the epidemiological condition in the study area.

4.2. Disease burden analyses for pathogens

In many countries, especially in the least developed regions, pathogenic microorganisms have been identified to be the major cause of disease infection. The well documented cases are diseases resulted from foodborne pathogenic bacteria, such as *E. coli* (Havelaar et al., 2004; Van Lier and Havelaar, 2007; Haagsma et al., 2013) and its more factious serotypes, *Enterohaemorrhagic E. coli* and *E. coli* O157 (Haagsma et al., 2008; Lake et al., 2010; Havelaar et al., 2012), *Salmonella* (Van Lier and Havelaar, 2007; Haagsma et al., 2008; Lake et al., 2010; Gkogka et al., 2011; Havelaar et al., 2012), *Shigella* and *Yersinia enterocolitica* (Haagsma et al., 2013), *Listeria monocytogenes*, *Bacillus cereus*, *Clostridium perfringens* and *Staphylococcus aureus* (Havelaar et al., 2012; Haagsma et al., 2013), *Campylobacter* (Havelaar et al., 2000; Van Lier and Havelaar, 2007; Haagsma et al., 2008; Lake et al., 2010), *Cronobacter* (Reij et al., 2009; Haagsma et al., 2013), *Clostridium botulinum* (Haagsma et al., 2013), and *Brucella* (Gkogka et al., 2011; Haagsma et al., 2013). There are also reported cases of virus infections due to foodborne enteric viruses, such as enteric viruses such as Hepatitis A and E viruses (Havelaar et al., 2012; Haagsma et al., 2013), Norovirus (Haagsma et al., 2008, 2013; Lake et al., 2010; Havelaar et al., 2012; Verhoef et al., 2012), and Rotavirus (Haagsma et al., 2008, 2013; Havelaar et al., 2012), while cases of disease infection by protozoans (parasites), such as *Cryptosporidium* and *Giardia* (Havelaar et al., 2012; Haagsma et al., 2013; Torgerson et al., 2014), *Leptospira* (Haagsma et al., 2013), *Toxoplasma gondii* (Havelaar et al., 2007b, 2012; Kortbeek et al., 2009; Gkogka et al., 2011; Haagsma et al., 2013; Torgerson et al., 2014), *Ehinoccosis* (Budke et al., 2004; Torgerson et al., 2008; Gkogka et al., 2011; Haagsma et al., 2013; torgerson et al., 2014), *Taenia solium* (Praet et al., 2009; Haagsma et al., 2013; Torgerson et al., 2014), *Etamoeba histolytica* (Haagsma et al., 2013), and *Trematodes* (Furst et al., 2012; Haagsma et al., 2013), are noticeable as well. The direct reason for these disease transmissions and infections by pathogens in foods and or food products would be contamination of raw materials, insanitary conditions of food processing, and lack of hygienic knowledge in food preparation.

Although not documented as much as disease infection by foodborne pathogens, exposure to pathogens through water transmission has been most popular since early days (Havelaar and Melse, 2003; Howard et al., 2006). The recently reported cases are mostly on exposure pathways of direct drinking of contaminated water, and the diseases investigated include watery diarrhea or bloody diarrhea caused by *E. coli* O157:H7 (Genthe et al., 2013; Machdar et al., 2013) and rotavirus (Machdar et al., 2013), gastroenteritis caused by *Campylobacter*, *Cryptosporidium*, and *Giardia* (Xiao et al., 2012a, 2012b; Wei et al., 2012; Machdar et al., 2013), typhoid fever caused by *Salmonella* and bacillary dysentery caused by *Shigella* (Genthe et al., 2013), as well as ascariasis caused by Ascaris (Bundy et al., 2004). In the following subsections, discussion will be mainly on disease burden analyses of waterborne pathogens through drinking water.

4.2.1. Case explanations

The followings are three typical cases recently reported on quantitative assessment of pathogenic risk of waterborne diseases followed by disease burden analysis using DALYs.

1) Case 1: Quantitative analysis of the burden of drinking water-associated cryptosporidiosis (Xiao et al., 2012a, 2012b). On the basis of a survey on source water quality in 66 waterworks in 33 cities in China, the health risks due to exposure to *Cryptosporidium* were estimated for subpopulations of different immunities under considerations of pathogen removal efficiencies and exposure pathways such as direct drinking, ingestion of small quantities from tooth-brushing, and food and dish washing (WHO, 2009b). For exposure assessment as the first step, a negative binomial distribution (Pouillot et al., 2004) with correction according to the recovery efficiency of measurement was applied for characterizing the *Cryptosporidium* oocyst number in source water, and the oocyst removal efficiency was assumed to be 2–2.5 logs for conventional treatment plus additional 2.3–3.5 logs or 2.0 logs removal when advanced treatment was further performed using microfiltration or ozonation. The amount of un-boiled tap water consumption was assumed based on surveys in China so that the exposure dose, i.e. number of oocyst intake from drinking water, could be evaluated. The second step of dose–response analysis was conducted using an exponential model for immunodeficient individuals (Pouillot et al., 2004) and Beta-Poisson model for immunocompetent subpopulations (An et al., 2011) with diarrhea as the disease outcome. The daily risks

of infection for different subpopulations were further transferred to annual risk of infection and then annual morbidity and mortality by taking into account the probability of illness and case fatality rate (Dietz et al., 2000; McGowan et al., 1993). For DALY calculation using the WHO methods, parameter values suggested by previous studies (Morgan et al., 2002; Havelaar and Melse, 2003) were referred regarding life expectancy, disease duration, disability weight and so on. As a result, the cryptosporidiosis burden associated with drinking water treated with the conventional process was calculated as 8.31×10^{-6} DALYs per person per year, in which 66% was due to the immunodeficient subpopulation.

2) Case 2: Risk assessment of *Giardia* in rivers of southern China (Wei et al., 2012). Similar to *Cryptosporidium* in the former case, *Giardia* is also a protozoan originated from animal excretes which may enter river water through surface runoff. In this case, based on a survey of *Giardia* in several rivers in a southern province of China during the rainy season of 2008, the health risk was assessed by using DALYs for risk quantification. In addition to drinking water using these rivers as source waters, swallow by swimming in these rivers was taken as another pathway of exposure. For exposure assessment, an exponential function was used for characterizing the distribution of *Giardia* cysts in the river water. The methods for evaluating daily drinking water consumption and removal of *Giardia* cysts by treatment were similar to that used in Case 1, while for swimming in the rivers, accidental intake water volume and percent of the population who swim were evaluated following existing data (Dufour et al., 2006; Bureau, 2005). For *Giardia* infection to cause gastroenteritis and abdominal distention, the dose–response relation was supposed to follow the exponential model. The morbidity rate was taken as the same as the infection rate and the mortality rate associated with *Giardia* infection was calculated by the quotient of the probability of fatal gastroenteritis and the incidence of gastroenteritis (An et al., 2011). The simplified WHO model was applied for DALY calculation with life expectancy, disease duration and disability weight following Chinese statistical data. As a result, the health risk was quantified as 6.25×10^{-6} DALYs per person per year. It was found that the exposure pathway of swimming in the rivers contributed 79.5% to the calculated DALYs.

3) Case 3: Application of quantitative microbial risk assessment to analyze the public health risk from poor drinking water quality in Accra, Ghana (Machdar et al., 2013). Accra is a densely populated area in Ghana where the local inhabitants are exposed to five pathogens, namely *E. coli* O157:H7, *Campylobacter*, rotavirus, *Cryptosporidium* and Ascaris through drinking water supplied by various means, such as household storage, private yard taps, communal taps, communal wells and water sachets. The study was conducted following the typical quantitative microbial risk assessment (QMRA) process including hazard identification, exposure assessment, dose–response analysis and risk characterization (Haas et al., 1999), followed by DALY calculation to evaluate the reduction of disease burdens through interventions. The potential health hazards identified include watery/bloody diarrhea due to *E. coli* O157:H7, gastroenteritis due to *Campylobacter*, mild/severe diarrhea due to rotavirus, watery diarrhea due to *Cryptosporidium*, and intestinal obstruction and contemporaneous cognitive deficit due to Ascaris. The concentration of *E. coli* in drinking water was evaluated through laboratory analysis and the results were extrapolated to *E. coli* O157:H7, *Campylobacter,* rotavirus and *Cryptosporidium* by taking into account of concentration ratios suggested in literatures (Haas et al., 1999; Howard et al., 2006; Smeets, 2008; Mara et al., 2010). By field surveys and interviews with water users, information was obtained on the exposure pathways, frequency and quantity of water consumption, and exposed population. Data from literature were also used to determine the ingested volume of the contaminated water (Howard and Bartram, 2003). Dose–response equations of either the exponential model or the Beta-Poisson model were applied with parameters suggested in literatures (Haas et al., 1999; Howard and Pedley, 2004; Westrell et al., 2003). For disease burden calculations basically using the WHO methods (Havelaar and Melse, 2003; Howard and Pedley, 2004; Labite et al., 2010), different health outcomes were counted for each pathogen, such as watery diarrhea, bloody diarrhea, and death from diarrhea for *E. coli.* O157:H, gastroenteritis in population, gastroenteritis in general practitioners, and death from gastroenteritis for *Campylobacter*, and so on. The relatively short life expectancy in Ghana at birth of 57 years (WHO, 2006a) was taken into account in calculating the DALYs due to mortality. As a result, the health burdens were calculated as 4.0×10^{-1} DALYs per person per year for *E. coli* O157:H7, 8.1×10^{-2} for *Campylobacter*, 2.6×10^{-2} for rotavirus, 1.2×10^{-4} for *Cryptosporidium* and 1.4×10^{-3} for Ascaris, and household storage was found to be associated with the highest risk of infection due to all these pathogens. Options for improvement of water quality to reduce the DALYs were also compared in the study and disinfection of drinking water at household level was identified to be the most cost-effective intervention for reducing the DALYs.

4.2.2. Methodologies and processes of analysis

Generally, the basic procedures for disease burden analysis regarding pathogens are similar to those for chemical pollutants. However, as pathogens are living organisms with lifecycles of growth and decay, their actions on human bodies are somewhat different from chemical pollutants (Toze, 2006; Hu et al., 2011). Even in the three cases of disease burden analyses regarding pathogens, according to the type of pathogens and local circumstances, the methodologies adopted were slightly different.

The exposure assessment for the three cases all needed characterization of the distribution of target pathogens and evaluation of daily water intake per person. In Cases 1 and 2, as water quality surveys were conducted regarding source waters, information directly obtained from the surveys was numbers of *Cryptosporidium* oocyst (Xiao et al., 2012a, 2012b) or *Giardia* cyst (Wei et al., 2012). The oocyst or cyst numbers in drinking water were calculated according to the removal efficiency of water treatment. In Case 3 laboratory tests were conducted for enumerating *E. coli* in the collected samples (Machdar et al., 2013), and the results were then extrapolated to other target pathogens by their ratios with *E. coli* referring to literatures. Due to the custom of drinking boiled water in most cases in China, a ratio of un-boiled water intake was introduced in both Cases 1 and 2 for evaluating the daily intake of the water with pathogens (Xiao et al., 2012a, 2012b; Wei et al., 2012). However, because of the diverse means of water supply and irregular water consumption in Case 3, the daily intake was evaluated by field surveys and interviews (Machdar et al., 2013). As swimming in rivers was supposed to be another pathway of exposure to *Giardia* mainly by accidental swallow of the river water in Case 2 (Wei et al., 2012), the percent of population and the frequency for them to swim in the rivers, as well as the quantity of water swallowed were completely assumed referring to literatures. Although these methodologies and assumptions were very useful for solving the difficulties in exposure assessments due to lack of more reliable data, they inevitably led to uncertainties of the estimates of exposure doses (Petterson et al., 2012; Lieverloo et al., 2007).

For dose–response analyses, conventional methods were utilized in the three cases. However, in Case 1 immunocompetent and immunodeficient subpopulations were analyzed separately (Xiao et al., 2012a, 2012b). Although the immunodeficient patients were regarded as a minor subgroup in many studies (Vijgen et al., 2007), the proportion of HIV-positive and AIDIS patients in the total population in many countries is increasing (UNAIDS, 2011). Therefore, the health risk of this subgroup cannot be neglected but should be quantified with methodologies different from that adopted for immunocompetent subpopulations.

The direct outcomes from the dose–response analyses are usually risks of disease infection due to exposure to specific pathogens, which can be taken as the infection rates. For DALY calculation, the infection rates can provide basis to evaluate the morbidity rates and mortality rates. In Case 1, a morbidity/infection ratio of 0.71 was introduced in calculating the morbidity rates of gastroenteritis due to *Cryptosporidium* for immunocompetent population and that for immunodeficient population was fixed as 1 (Xiao et al., 2012a, 2012b). Similarly, different percentages were chosen for evaluating the morbidity cases of the infected people regarding different pathogens and different severities of the associated illnesses in Case 3 (Machdar et al., 2013). Contrast to this, the morbidity rate was taken as equal to the infection rate in Case 2 (Wei et al., 2012) which might overestimate the occurrence of the illness. For mortality calculation, similar ways were adopted in the three cases by introducing case fatality ratios referring to literatures and local health statistics.

For the final step of disease burden evaluation, the WHO methods of DALY calculation (Murray and Lopez, 1996a, 1996b), especially the simplified equations (Murray et al., 2012b; Murray et al., 2002) were used in the three cases. In Case 1, the YLL due to mortality was calculated by adding all the products of deaths and the standard life expectancies for all ages, while the YLD was calculated as the accumulated product of the number of illness, disease duration, and disability weight (Xiao et al., 2012a, 2012b). In Case 2, more comprehensive analyses were conducted in the YLD calculation by considering the portion of individuals with different severities of gastroenteritis so that the health impacts can be easily compared (Wei et al., 2012). As poorer health condition and lower life expectancy were currently faced in Ghana (Machdar et al., 2013), in Case 3 the mortality burden due to a specific pathogen was estimated at higher percent of the total infection and the years lost was based upon death occurring at the age of 1 year (Haas et al., 1999; Howard and Pedley, 2004; Howard et al., 2006). Considerations on such an extreme condition may result in an over-estimation of disease burden.

4.2.3. Characteristics of disease burden analysis for pathogens

The effects of exposure to pathogenic microorganisms are generally acute diseases such as diarrhea and gastroenteritis which may occur shortly after the exposure. Another feature of the pathogenic diseases is their quick and wide transmission among populations which is called a disease outbreak such as the cryptosporidiosis outbreak in Milwaukee, USA in 1993 where over 400,000 became ill and at least 50 people died (MacKenzie et al., 1994; Davis, 1996). The transmission mediums often include water and food to be directly digested by people, though the three cases discussed above all dealt with waterborne pathogens. For disease burden analyses due to pathogens in the environment, what to be studied may not always be a disease outbreak due to unusual exposure to high dose of specific pathogens but the risks of illness occurrence under normal conditions. Therefore, a survey on the distribution of pathogens in the environmental medium (water, food materials, etc.) is very important as what were done in the three cases for water sampling and target pathogen detections (Xiao et al., 2012a, 2012b; Wei et al., 2012; Machdar et al., 2013). Different from chemical substances, because pathogens are microorganisms which undergo multiplication and decay in their lifecycles, not only their spatial distribution but also their timely variation in concentrations needs to be characterized in the exposure analyses (Metcalt and Eddy, 2008). Taking the pathogens discussed in Case 3 as examples, *E. coli* can be taken as the pathogenic bacteria existing in any water that receives fecal pollution (Machdar et al., 2013) but *E. coli* O157:H7, as an enterohemorrhagic serotype of *E. coli,* may not always exist in fecal sources (Nala and Jagals, 2002). *Campylobacter* and rotavirus may also be source specific (Labite et al., 2010), while *Cryptosporidium* as well as *Giardia* discussed in Case 2 are often from animal feces which may enter a river mainly through surface runoff in the rainy season (Wei et al., 2012). For pathogens that intermittently or occasionally occur in the environment, it is better to study the disease burden on outbreak basis rather than annual basis unless the annual frequency of the occurrence is known. This may be the main difference between some pathogens and most chemicals which cause chronic diseases after long term exposure.

Similar to chemical pollutants, the selection of appropriate models for the study of disease burden due to pathogens is important from exposure evaluation, through dose–response analysis, to DALY calculation. However, the function of mathematical modeling dealing with pathogens differs from that for chemical pollutants to certain extent. Taking dose–response analysis as an example, in the case of carcinogenic chemicals, extrapolation of a dose–response relationship fitted from the data of experiments in a high dose range into the low dose range is extremely important (Hu et al., 2011), while in the case of pathogens, epidemiological or clinical data can be available in the study area (MacKenzie, et al., 1994; Davis, 1996; Machdar et al., 2013; Wei et al., 2012) so that the response of human to the dose is often within the range of the dose–response relationship obtained. Acquisition of epidemiological or clinical data as far as possible is always applauded for disease burden analysis for pathogens.

5. Direction of future studies on DALY application for impact assessment of environmental pollution

5.1. Perspectives and current problems

As an indicator for measuring disease burden, the advantages of using DALY for health impacts assessment of pollution are to quantify the impacts in terms of health loss caused by specific pollutants in time scale, to provide an intuitive and simple parameter for comparing the severities of health hazards caused by different pollutants, and to assist the determination of prevention targets and the allocation of health resources (Miquel and Huertas, 2006). All these may not be achieved by conventional health risk assessment with the probability of disease occurrence as the endpoint which does not relate directly to life quality and/or life length of the population under exposure to hazardous environmental pollutants. Therefore, DALY is more and more accepted by environmental researchers as a useful tool, and various methods are being developed for its application in the environmental field (Arnold, 2014).

However, although a standardized methodological framework has already been established by WHO for disease burden studies based on global and regional epidemiological statistics (Murray et al., 2002; Murray and Acharya, 2002), it cannot provide a guidance for DALY calculation directly from pollution data. As discussed in the former sections, the main task of the study on DALY application for environmental pollution assessment is to transform pollution data into related disease data useful for DALY calculations. Such a data transformation process majorly includes exposure assessment and exposure–response or dose–response analysis regarding specific diseases caused by environmental pollutants (Haas et al., 1999), which can be viewed as a conventional health risk assessment process but the endpoint is not limited to the probability of disease occurrence but the disease outcomes directly related to health status so that morbidity and mortality can be evaluated for subsequent DALY calculation. In this regard, there still exist limitations and controversies in current methodologies relating to the following three aspects.

Firstly, according to the nature of pollutants and the related mechanisms to cause diseases, exposure to a certain dose of a specific pollutant may result in different kinds and/or varied extents of health hazards to different subpopulations of different ages, genders or immune conditions. However, existing dose–response models and their associated parameters have rarely accounted these factors (An et al., 2011; Xiao et al., 2012a, 2012b). Moreover, the methods for transforming the dose–response analysis results into morbidity and mortality still largely depend on assumptions, such as taking the infection rate as an alternative of the morbidity rate and even the mortality rate (Wei et al., 2012)

especially when disease information is unavailable or insufficient. This may inevitably result in overestimation of disease burden to certain extent.

Secondly, for DALY calculations following exposure assessment and dose–response analysis, epidemiological information in the study area can provide important referential data for the selection and determination of parameters. Unfortunately, in many countries especially in the developing world basic data are often unavailable (Ragas et al., 2011a, 2011b; Machdar et al., 2013). Therefore, researchers often have to refer to recommendations by WHO or developed countries. As economic, sanitary, cultural and social conditions may differ much between countries or regions, the adoption of external data to evaluate the local health condition may inevitably result in a deviation from actual situations. For calculating the disease burden caused by disability, the disability weights are usually selected by expert judgment. However, due to different diagnosis standards in different countries, the disability weights selected may differ much and eventually affect the comparability of the calculation results between different countries and regions (Zhai and Zhao, 2006; Zhai and Zhao, 2008).

Thirdly, for certain environmental pollutants few studies have been conducted by far to provide reliable clinical manifestations and information on their infection pathways and health impact. Dose–response relationships associated with these pollutants are yet to be established. Some emerging pollutants are suspicious of toxic at trace concentrations (Hu et al., 2011), but there are still limitations in detection technologies especially when these trace pollutants coexist with other organic substances. Therefore, it is still difficult to extend DALY application to the impact assessment of environmental pollutants of this category.

5.2. Directions for future studies

Application of DALY for environmental health impacts assessment is still at the trial stage. The ultimate goal of study would be the establishment of a standard methodological framework for the whole process of disease burden calculation. Toward this goal, every step of the analyses would need to be directed to a way to obtain reliable results as inputs to the next step. As pollutants are distributed in transmittable environmental media such as air, water, food and so on which may be inhaled, digested, and contacted by human bodies (Covello and Mekhofer, 1993), an accurate prediction of the spatial and timely distribution of pollutants would be very important (Dai, 1996). Because the extents of exposure to the pollutants often vary among exposed population, to divide the exposed population into subgroups would also be required (USEPA, 2011). Similar principle is also applicable to exposure–response or dose–response analyses because people of different ages, genders, and health conditions may respond differently to the same pollutant dose (An et al., 2011; Xiao et al., 2012a, 2012b). This accordingly requires development or improvement of the dose–response models. On the other hand, the dose–response analyses should facilitate the estimation of morbidity rate and mortality rate rather than merely the infection rate (Pruss and Havelaar, 2001). In this regard, more sophisticated and comprehensive models may need to be worked out by combining dose–response analysis with the methods for morbidity/mortality calculation (Xiao et al., 2012a, 2012b; Wei et al., 2012). Dealing with human health problems, the accuracy of calculation is in any sense a deterministic factor. Therefore, sensitivity analysis would have to be introduced into the disease burden study process for controlling the key factors which may influence the results in each step of calculation (Xiao et al., 2012a, 2012b).

6. Conclusions

In this article, the framework of DALY analyses for quantifying disease burden was summarized. The research progress for the application of DALY to quantitatively assess environmental pollution was reviewed with attention paid to the associated methodologies for hazard identification, exposure assessment, dose–response analysis and disease burden calculation. Different from the global disease burden study which uses epidemiological statistics related to prevailing diseases, the application of DALY for pollution assessment requires the transformation of pollution data into disease data through a number of analysis steps. Although the process for such kind of data transformation seems to be similar to conventional health risk assessment, the endpoint is no longer merely the probability of disease occurrence but a result to facilitate morbidity and mortality evaluation. The conventional methodologies may be useful to certain extent while their limitations are apparent and need further development and improvement. As DALY is advantageous over conventional environmental impact assessment for quantification and comparison of the risks resulted from environmental pollution, further study on standardized methods of health effect evaluation regarding varied pollutants under varied circumstances is necessary.

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