11 DDT: fifty years since *Silent Spring*

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'There was a strange stillness. The birds for example — where had they gone? Many people spoke about them, puzzled and disturbed. The feeding stations in the backyards were deserted. The few birds seen anywhere were moribund: they trembled violently and could not fly. It was a spring without voices ... only silence lay over the fields and woods and marsh.'

The book *Silent Spring* by Rachel Carson is mainly about the impacts of chemicals (in particular in particular dichlorodiphenyltrichlorethane also known as DDT) on the environment and human health. Indeed, the close association between humans and birds remains very apt. Representing the only two warm-blooded groups of life on Earth, mammals and birds share the same environments and threats.

Carson's claim that she lived in 'an era dominated by industry, in which the right to make a dollar at whatever cost is seldom challenged' still resonates strongly with the problems that societies face all over the world. One chapter heading, 'The obligation to endure', derived from the French biologist and philosopher Jean Rostand's famous observation that, 'the obligation to endure gives us the right to know'. United States President John F. Kennedy responded to the challenge posed by Carson by investigating DDT, leading to its complete ban in the US. The ban was followed by a range of institutions and regulations concerned with environmental issues in the US and elsewhere, driven by public demand for knowledge and protection.

DDT was the primary tool used in the first global malaria eradication programme during the 1950s and 1960s. The insecticide is sprayed on the inner walls and ceilings of houses. Malaria has been successfully eliminated from many regions but remains endemic in large parts of the world. DDT remains one of the 12 insecticides — and the only organochlorine compound — currently recommended by the World Health Organization (WHO), and under the Stockholm Convention on Persistent Organic Pollutants, countries may continue to use DDT. Global annual use of DDT for disease vector control is estimated at more than 5 000 tonnes.

It is clear that the social conscience awakened by Rachel Carson 50 years ago gave momentum to a groundswell of actions and interventions that are slowly but steadily making inroads at myriad levels. Chapter 17 of her book, 'The other road' reminds the reader of the opportunities that should have been seized much earlier. With more than 10 % of bird species worldwide now threatened in one way or another, it is clear that we missed early warnings or failed to act on them. Will we continue to miss signposts to 'other roads'? Are our obligations to endure met by our rights to know? As Carson said 50 years ago: 'The choice, after all, is ours to make.'

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11.1 Introduction

> 'There was a strange stillness. The birds for example — where had they gone? Many people spoke about them, puzzled and disturbed. The feeding stations in the backyards were deserted. The few birds seen anywhere were moribund: they trembled violently and could not fly. It was a spring without voices. ....only silence lay over the fields and woods and marsh.'

This narrative by Rachel Carson in *Silent Spring* (1962) ([2]) of an imagined town and surroundings, representing thousands such all over America, frames the context of one of the 20th century's most powerful books on humans and the environment. Fifty years on, with an enduring and strengthening message, Rachel Carson's *Silent Spring* is an unmistakeable icon for early environmental awareness and current concern.

Silent Spring is mainly about the impacts of chemicals — with an emphasis on dichlorodiphenyltrichloroethane (DDT) — on the environment and human health. Its impact is as strong now as then. Indeed, the close association between humans and birds remains very apt; representing the only two warm-blooded groups of life on earth — mammals and birds — we share the very same environments and threats. Carson's realisation of humankind-in-nature, arguably as important as humankind-in-cosmos, contributed significantly to modern and enduring environmental and even social movements, resulting in regulations and restrictions on activities and practices that now exceed chemicals alone. In her second chapter, *The obligation to endure*, Carson points a finger which then, and indeed still now, resonates strongly with problems that societies face all over the world, 'it is also an era dominated by industry, in which the right to make a dollar at whatever cost is seldom challenged'. Carson took her chapter heading and context from the French biologist and philosopher Jean Rostand's famous thought, 'the obligation to endure gives us the right to know'. United States President John F. Kennedy responded to the challenge posed by Carson by investigating DDT, eventually leading to its complete ban in the United States. Despite many counter-claims and arguments from various sources, the ban on DDT and other chemicals resulted in the return of the bird chorus to affected areas. The ban was followed by a range of institutions and regulations concerned with environmental issues in the United States and elsewhere, driven by a public demand for knowledge and protection.

The right to know and the willingness to endure, so crucial to advancing civilisation and freedom, poses interesting and challenging issues that continue to face humanity on many economic, political, social, and environmental fronts. Indeed, DDT remains part of the conundrum of 'enduring yet knowing', a situation described in more detail below.

11.2 History

The DDT molecule was first synthesized in 1873 (Zeidler, 1874), a time when organic chemistry was still a young discipline, and the synthesis was performed to study what happens when different reagents are mixed under specific conditions with no notion of what the product could be used for. It was not until 1939 that Paul Müller showed the insecticidal property of DDT (Nobelprize.org, 2012a). The first DDT formulations marketed in the United States against a variety of insect pests drew the attention of the military; means to combat insect-borne diseases in the theatres of World War II were in great demand. The key event to popularise DDT was an outbreak of typhus in Naples, Italy, in October 1943. By January 1944, and after treating 1 300 000 people over a three week period with DDT, the epidemic was brought under control (Nobelprize.org, 2012b). Based on work by De Meillon (1936), indoor residual spraying (IRS) with DDT to interrupt malaria transmission was introduced in South Africa in 1946, achieving complete coverage of malaria areas by 1958 (Sharp and le Sueur, 1996).

Paul Müller was awarded the Nobel Prize for Medicine or Physiology in 1948, but already in the prize presentation speech, problems with flies developing resistance to DDT were mentioned. However, resistance development was not viewed in any environmental light but rather as an opportunity to develop new chemical pesticides to solve the problem (Nobelprize.org, 2012b). There was no mention in the prize presentation speech of potential environmental concerns, rather, the persistence of DDT, today considered as one of the main environmental concerns, was viewed as positive for the practical use of the insecticide (Nobelprize.org, 2012b), and the early recommendations on how to use DDT were, to modern eyes, staggeringly

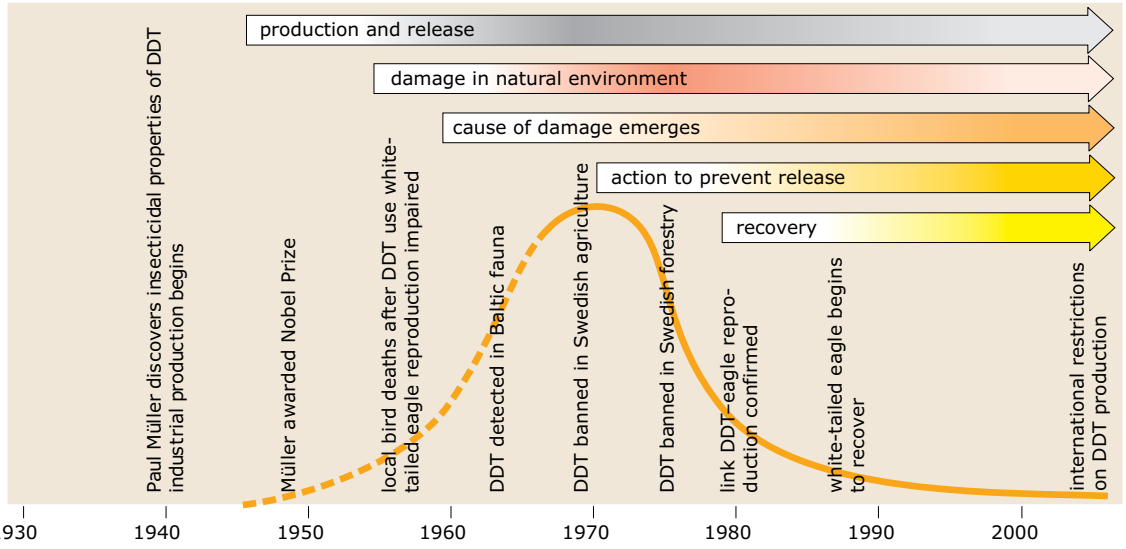
([2]) All quotations are taken from the 1972 reprint of *Silent Spring* by Hamish Hamilton, London.

indiscriminate, with much dusting of both individuals and food without any precaution (West and Campbell, 1946). However, some restrictions on indiscriminate use came already in 1948, the same year as the Nobel Prize, when use of DDT inside dairies was prohibited (American Journal of Public Health, 1949). In Sweden, cases in the 1950s were reported of flies dying after contact with dairy products with very high DDT content (Löfroth, 1971).

Arguably, the publication of *Silent Spring* (Carson, 1962) triggered the development of environmental chemistry as an academic discipline. Technical developments in analytical chemistry during the 1950s were prerequisites for development of the discipline, and, indeed, for the writing of the book, as these instrument developments were necessary to identify DDT and other organochlorine pesticides as potential environmental problems. However, it was *Silent Spring* that made the potential environmental problems everyone's concern and pressured resource allocation into environmental chemistry. In Sweden, for example, the government gave special funding to Stockholm University to set up a laboratory for the analysis of DDT in the environment (Bernes, 1998). These activities started in 1964, less than a year after the book was published in Swedish, and led, inter alia, to the identification of polychlorinated biphenyls (PCB) as environmental contaminants in 1966 (Jensen, 1966). It is difficult to envisage this development had it not been for the impact of *Silent Spring*.

That DDT was the first organic environmental pollutant that came under scrutiny was probably not only due to it being the first organochlorine pesticide to gain wide use. Another reason was probably that the negative effects first reported were on birds as many people were (and are) interested in birds, particularly large birds, and declines in the populations of birds of prey were observed in many places of the world and tied to eggshell thinning after bioaccumulation of DDT (Bernes, 1998; Bernes and Lundgren 2009). In addition, DDT was a pesticide deliberately released into the environment, which is why its presence in the environment was no great surprise. In comparison, PCB was put into production earlier than DDT, but as it was used in industry and not actively released into the environment, its presence in the environment was much of a surprise. In addition, there was no great incentive among the public to observe the negative effects of PCB as these were most severe in fish-eating mammals such as seals (Bernes, 1998; Bernes and Lundgren, 2009). The only people to regularly observe seals were fishermen, who mainly regarded them as a pest that competed for the fish. Thus, looking at the time-line for DDT and PCB (Figure 11.1), DDT was identified as a

Figure 11.1 The development of DDT concentrations in the Baltic Sea in relation to historical events, the development of environmental awareness and legal measures restricting their use



Note: The dashed portion of the line is estimated from museum material (seals), while the solid lines are based on data on Guillemot eggs analysed in the Swedish National Environmental Programme. Most uses of DDT were banned in Sweden around 1970.

Source: Bernes and Lundgren, 2009.

possible environmental problem much sooner after it was taken into use than PCB. In addition, although DDT and PCB were banned at about the same time in Sweden, the decline of DDT concentrations was more rapid as there were many remaining diffuse sources of PCB contamination, but for DDT the only use was as an insecticide (Bernes, 1998; Bernes and Lundgren, 2009).

Based on the increasing amount of data on environmental effects, restrictions on the use of DDT were put in place in different countries from the early 1970s, but the use and misuse of DDT continued. In Bangladesh, for example, fish intended for human consumption was until recently dried in DDT to avoid fly infestation in the market (Amin, 2003), even though DDT was banned in Bangladesh. With the Stockholm Convention on Persistent Organic Pollutants (Stockholm Convention, 2004), which came into force in 2004, new means to assist developing countries to reduce problems with DDT and other persistent organic pollutants (POPs) have come into place. However, the convention recognises the need to use DDT for malaria vector control until other practical and economically viable methods have been developed.

11.3 Current uses

11.3.1 DDT and malaria control

DDT was the primary tool used in the first global malaria eradication programme during the 1950s and 1960s. The insecticide was used to spray the walls and ceilings of houses and animal sheds with coverage of entire populations. Early mathematical modelling had convincingly shown that indoor residual spraying with insecticides, such as DDT, to kill adult mosquitoes had a major impact on malaria transmission (MacDonald, 1956). The insecticides prevented the female mosquitoes from surviving long enough to become infective, since it takes around 12 days for malaria parasites to migrate to the mosquito's salivary glands and, hence, only mature female mosquitoes can infect humans. Malaria has been successfully eliminated from many regions, but remains endemic in large parts of the world (Mendis et al., 2009).

The development of insect resistance to DDT, reported as early as 1951 (with even earlier indications in 1948 house flies in Sweden), became an obstacle in the eradication of malaria, and was one of the reasons behind the abandonment of the global malaria eradication campaign in 1969 (Najera et al., 2011). Amidst concerns about the safety of DDT during the 1970s, the insecticide was banned for use in agriculture in many countries. Nevertheless, DDT remained effective in a number of countries and continues to be used for malaria control today (van den Berg et al., 2012).

The negotiations that led to the inclusion of DDT as one of the initial twelve chemicals restricted under the Stockholm Convention sparked a debate about the continued need for DDT to control malaria (Curtis and Lines, 2000). An important series of developments took place over the same period. After South Africa had banned the use of DDT for malaria control in 1996, the highly effective malaria vector *Anopheles funestus* was able to reinvade the country because it had developed resistance to the pyrethroids that were being used, but not to DDT (Hargreaves et al., 2000). This situation, which was unique to South Africa, resulted in serious outbreaks of malaria, forcing the government to revert to DDT, after which the number of malaria cases declined. When simultaneously a global ban on DDT use was being proposed, fierce debates emerged over the benefits and adverse effects of DDT (The Lancet, 2000). In the final negotiations that led to the Stockholm Convention, an exception was made for DDT with an acceptable purpose for use in disease vector control. Thus, under the Stockholm Convention, countries may continue to use DDT, in the quantity needed, provided that the guidelines and recommendations of the World Health Organization (WHO) and the Stockholm Convention are met, and until locally appropriate and cost-effective alternatives become available for a sustainable transition from DDT.

DDT is one of the 12 insecticides, and the only organochlorine compound, currently recommended by the WHO for use in indoor residual spraying for disease vector control (WHO, 2006). Other recommended compounds are organophosphates, carbamates and pyrethroids. DDT has the longest residual efficacy, reportedly from 6–12 months, when sprayed on the walls and ceilings of traditional housing and, hence, one or two applications per year suffice to provide continuous protection to populations at risk. In the past few years, however, increased monitoring has shown that resistance of malaria vectors to DDT, and to other available insecticides, is now widespread in sub-Saharan Africa and India (WHO, 2011a).

11.3.2 Trends in production and use

Currently, DDT is produced only in India, from where it is exported as a pure (also called 'technical')

or as a commercially formulated product to other, mostly African, countries (UNEP, 2010). China has recently stopped production of DDT but South Africa formulates DDT using technical product from India, and exports the formulated product to several other African countries. DDT can be produced at low cost, which is relevant because it has been recommended for use at a dosage that is on average 60 times higher than that for pyrethroid insecticides. As a consequence of these differences in application rates, 71 % of the global annual amount of insecticides used for vector control is DDT, even though pyrethroids are much more widely used in terms of surface area covered (van den Berg et al., 2012). DDT is used mostly for malaria control, but 19 % of the global share is sprayed to control leishmaniasis transmission by sandflies.

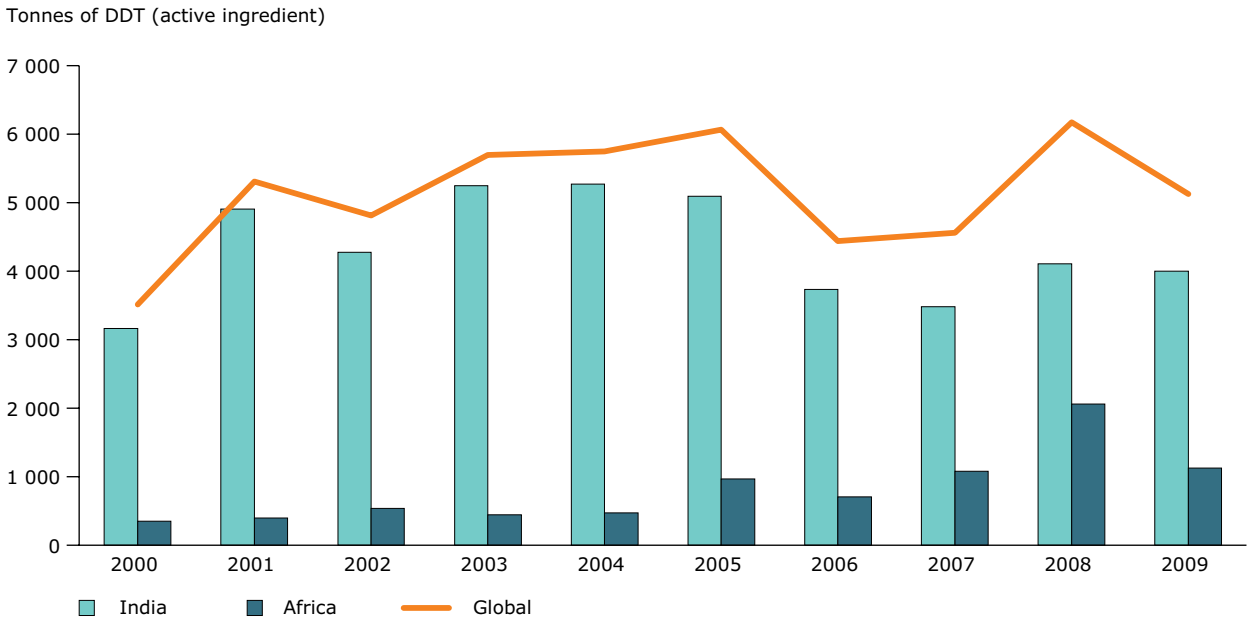
Global annual use of DDT for disease vector control is estimated at more than 5 000 tonnes of active ingredient. The amount has fluctuated during the past decade but has not declined substantially since the Stockholm Convention was enacted (van den Berg et al., 2012). India has the lion's share, with 82 % of global use. African countries also significantly increased their DDT use until 2008 (Figure 11.2) because of countries either scaling-up indoor residual spraying programmes using DDT or re-introducing its use. Only four African countries reported using DDT in 2000, compared to nine in 2008: Eritrea, Ethiopia, Mauritius, Mozambique, Namibia, South Africa, Swaziland, Uganda and Zimbabwe (WHO, 2011b). More recently, however, Ethiopia, Mozambique, and Uganda have reportedly stopped using DDT because of either policy change away from DDT or the development of insecticide resistance. It remains to be seen whether the decline in DDT use in Africa in 2009 is part of a new trend.

In DDT-using countries, it is of utmost importance that DDT is used for its acceptable purpose only. However, a recent global survey in countries at risk of vector-borne diseases revealed critical deficiencies in the capacity for regulatory control and management of pesticides, which include DDT, thus increasing the risks of adverse effects on human health and the environment (Matthews et al., 2011; van den Berg et al., 2011). For example, there are clear indications that DDT has been illegally traded on local markets for use in agriculture and termite control and there is also information to suggest that DDT is, or has been, widely used in agriculture in the Democratic People's Republic of Korea (van den Berg, 2009).

11.4 Current human health concerns

Carson (1962) devoted Chapter 12 of *Silent Spring* to a summary of the environmental health

Figure 11.2 Trends in the global use of DDT



Source: van den Berg et al., 2012.

effects associated with DDT, as then known. Very perceptively, Carson said, 'even research men suffer from the handicap of inadequate methods of detecting the beginnings of injury. The lack of sufficiently delicate methods to detect injury before symptoms appear is one of the great unsolved problems in medicine'. Since then, research men and women have added much to the arsenal of tools available, and a short summary of some follows.

The Agency for Toxic Substances and Disease Registry (ATSDR) report on DDT (2002) discussed in detail the acute exposure effects on the nervous system, the effects of chronic exposure to small amounts of DDT being almost limited to changes in liver enzymes. However, in the environment DDT is transformed to DDE which is even more persistent, leading to concerns that elevated concentrations of *p,p'*-DDE in human breast milk shortened the period of lactation and increased the chances of a pre-term delivery (see Box 11.1 for terminology on DDT and its related compounds). The International Agency for Research on Cancer (IARC) classified DDT as possibly carcinogenic to humans. Two recent publications extensively reviewed the human health consequences of DDT exposure (Eskenazi et al., 2009) and the human health aspects of IRS associated with DDT use (WHO, 2011). When the transplacental transfer of DDT and the exposure of the new-born child through breast milk became clear, there were concerns that DDT or its metabolites might affect, in particular, the reproductive and nervous systems. Moreover, some of these health effects may not become evident immediately but only long after exposure. Carson said, 'when one is concerned with the mysterious and wonderful functioning of the human body, cause and effect are seldom simple and easily demonstrated relationships. They may be widely separated in space and time'.

11.4.1 Breast cancer

The human female breast seems particularly vulnerable to environmentally-induced carcinogenesis during several critical periods such as *in utero* and before puberty (Eskenazi et al., 2009). Evidence that adult DDT exposure is associated with breast cancer was equivocal until Cohn et al. (2007) reported DDT levels in archived serum samples collected between 1959 and 1967, peak years of DDT use, from pregnant women participating in the Child Health and Development Studies (CHDS). Considering women ≤ 14 years old in 1945 when DDT was introduced, subjects with levels in the highest tertile were five times more likely to develop breast cancer than those in the lowest tertile. Moreover, in women exposed after the age of 14, there were no associations between the risk of breast cancer and *p,p'*-DDT levels. Therefore, exposure to *p,p'*-DDT during the pre-pubertal and pubertal periods is the critical exposure events to risk the development of breast cancer later in life.

11.4.2 Endometrial cancer

Sturgeon et al. (1998) reported on possible associations between endometrial cancer (cancer that starts in the lining of the uterus) and DDT serum levels, but the findings were inconclusive (Sturgeon et al., 1998). However, Hardell et al. (2004) found weak but significant associations with serum DDE levels and the topic needs further investigation.

Box 11.1. DDT-compounds

When DDT is produced the technical mixture, 'technical DDT', mainly consists of two compounds, approximately 80% *p,p'*-DDT (1,1,1-trichloro-2,2-*bis*(4-chlorophenyl) ethane), the insecticidal component, and 15% *o,p'*-DDT (1,1,1-trichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl) ethane). The major degradation products in the environment of *p,p'*-DDT are *p,p'*-DDE (1,1-dichloro-2,2-*bis*(4-chlorophenyl) ethene) and *p,p'*-DDD (1,1-dichloro-2,2-*bis*(4-chlorophenyl) ethane). The major degradation products of *o,p'*-DDT are *o,p'*-DDE (1,1-dichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl) ethene) and *o,p'*-DDD (1,1-dichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl) ethane).

In environmental samples the concentrations of all these compounds are often added to a total DDT (ΣDDT) concentration. Generally, the *p,p'*-isomers are more persistent than the *o,p'*-isomers, and *p,p'*-DDE is the most persistent of all these compounds. Therefore, high DDT/DDE or DDT/ΣDDT ratios indicate a recent release of DDT while low ratios are typical of old releases of DDT or that DDT has undergone long-range transport.

11.4.3 Male reproductive effects

There is increasing evidence suggesting that DDT and metabolites have harmful effects on the quality of human semen and sperm function, particularly in young adult healthy men from an endemic malarial area with very high DDT and DDE levels (Aneck-Hahn et al., 2007). Sperm DNA integrity in this population was also adversely affected (De Jager et al., 2009).

Bornman et al. (2010) determined the association of external urogenital birth defects (UGBD) in newborn boys from DDT-sprayed and non-sprayed villages in a malarial area. Between 1995 and 2003, mothers living in villages sprayed with DDT had a 33 % greater chance of having a baby with a UGBD than mothers whose homes were not sprayed. A stay-at-home mother significantly increased the risk of having a baby boy with a UGBD to 41 %. Further studies are necessary to determine possible causal relationships with DDT and any possible genetic or epigenetic predispositions.

11.4.4 Testicular germ cell tumours

Concentrating on a selection of recent studies, McGlynn et al. (2008) found some evidence of an association between DDE and testicular germ cell tumours. There was a positive, but not statistically significant, association between DDE and testicular cancer. However, similar associations were also found for other chemicals such as chlordane, PCB, and some insecticides (Purdue et al., 2009). Therefore, the implications of DDE associated with testicular germ cell tumours need further studies. Cohn et al. (2010) examined maternal serum levels of DDT-related compounds in relation to sons' risk of testicular cancer 30 years later. Mothers of testicular cancer cases had lower levels of *p*,*p*′- DDT, *o*,*p*′-DDT and *p*,*p*′-and DDE, but a higher DDT/DDE ratio, than their matched controls. However, the possible role of DDT in the development of testicular cancer is still not clear (Hardell et al., 2006).

11.4.5 Diabetes

Various studies reported findings suggesting that body burdens of DDT and/or DDE may be associated with the prevalence of diabetes (1980 Morgan et al., 1980; Rylander et al., 2005; Rignell-Hydbom et al., 2007). However, a variety of other persistent environmental chemicals are also associated with diabetes prevalence and the WHO (2011d) concluded that the evidence is inconclusive. Nevertheless, the findings of Turyk et al. (2009) of an association between DDE exposure and diabetes incidence warrants further research to define the specific contributions of DDT and DDE.

Ukropec et al. (2010), in a cross-sectional study from Eastern Slovakia, investigated possible links between environmental pollution and pre-diabetes/diabetes (Type 2 diabetes). The prevalence of pre-diabetes and diabetes increased in a dose-dependent manner, with individuals with highest DDT levels showing striking increases in prevalence of pre-diabetes. PCBs showed comparable associations, but increased levels of hexachlorobenzene (HCB) and β-hexachlorocyclohexane β-HCH seemed not to be associated with increased prevalence of diabetes. The synergistic interaction of industrial and agricultural pollutants in increasing prevalence of pre-diabetes or diabetes is likely. For Type 1 diabetes, Rignell-Hydbom et al. (2010) found no evidence that in utero exposure to DDT could predispose the development of the disease.

11.4.6 Pregnancy

Women exposed to DDT had shorter menstrual cycles (Onyang et al., 2005) and both DDT and DDE reduced progesterone and estrogens (Windham et al., 2005; Perry et al., 2006). Other studies, however, found no relationship between menstrual abnormalities or cycle length and DDE or DDT exposure (Yu et al., 2000; Chen et al., 2005). There is limited evidence that DDT/DDE can increase the risk of miscarriage and the risk of preterm delivery. In the U.S. Collaborative Perinatal Project, high DDE concentrations were associated with an increased risk of foetal loss in previous pregnancies (Longnecker et al., 2005). Each 1 ng/g increase in serum DDE was associated with a 1.13 increased odds of miscarriage (Korrick et al., 2001). Venners et al. (2005) studied Chinese textile workers with comparable DDE concentrations and reported a similar increased odds of 1.17 for each 10 ng/g serum increase in total DDT. Together the two cohort studies (Longnecker et al., 2005; Venners et al., 2005) indicated an association between increasing DDT and DDE levels and foetal loss. In the Longnecker et al. (2001) study, the odds of preterm delivery were 3.1 times higher in women with serum DDE ≥ 60 μg/L than in those with DDE < 15 μg/L during pregnancy. Inconsistent results on the possible association between DDT/DDE levels and gestational age were reported in other studies.

Taken together, the positive dose-response relationships for these endocrine-regulated

end-points raise concern for effects of exposure to DDT on female reproductive health. It should be noted that the 'high' DDE serum may be substantially lower than in populations where indoor residual spraying is still occurring, emphasising the need for research in the context of IRS (WHO, 2011d). In some studies the onset of menopause was associated with DDT/DDE studies (Cooper et al., 2002; Akkina et al., 2004; Eskenazi et al., 2005), but in the Agricultural Health Study DDT exposure was associated with slightly older age at menopause (Farr et al., 2006).

11.4.7 Breast milk

DDT may shorten (Gladen and Rogan, 1995; Kostyniak et al., 1999; Rogan et al., 1987; Rogan and Gladen, 1985), prolong (Weldon et al., 2006), or have no effect (Cupul-Uicab et al., 2008) on the duration of lactation, due to the endocrine disruptive properties of DDT isomers (Wetterauer et al., 2012). It is not clear whether DDT or DDE exposure per se is linked to the duration of lactation. However, a recent study from an area where DDT is sprayed as IRS for malaria control showed no differences in lengths of lactation between three DDT sprayed villages and a reference village where no DDT has ever been applied (Bouwman et al., 1012).

Infant exposure to DDT is directly related to intake through breast milk and milk levels are linked to IRS spraying for malarial vector control. Bouwman et al. (1990b) analysed breast milk from mothers visiting baby clinics, in one regularly IRS controlled area and in a control area, ten years after DDT use in agriculture was banned in South Africa. Parity, maternal age, infant age, and percentage of milk fat between the two groups were similar. DDT was detected in all samples analysed, while DDE levels were significantly lower in the non-exposed group. It should be noted that in South Africa, as in many parts of Africa, extended periods of breastfeeding (up to two years) seems the norm in rural communities (Bouwman et al., 2006). Since there is no maximum residue level (MRL) for breast milk (FAO, 2005), comparing it to bovine milk MRLs found that, based on the volume of 800 mL of breast milk consumed by a 5-kg infant, the MRL for total DDT (ΣDDT) in cow's milk is notably exceeded (Bouwman et al., 2006).

First-born infants receive much higher levels of DDT in breast milk than their siblings (Bouwman et al., 2006; Gyalpo et al., 2012; Harris et al., 2001), but recently it became clear that there are also differences in pollutant levels and effects on male and female infants (Gascon et al., 2011; Grimalt et al., 2010; Jackson et al., 2010; Jusko et al., 2006; Ribas-Fitó et al., 2006). Therefore, infant gender may somehow affect levels of pollutants in breast milk by a mechanism that is not immediately clear. One gender being exposed to higher levels than the other would add to concern about possible effects of DDT on development as result of endocrine-disruptive properties of DDT chemicals, a situation already suspected in South Africa (Bornman et al., 2010). A recent study has shown indications of gender involvement (Bouwman et al., 2012).

11.4.8 Neurodevelopment

The main mode of action of DDT as an insecticide is disruption of the nervous system. In other animal studies, DDT is a neurodevelopmental toxicant (ATSDR 2002). In mice, particular exposure to DDT during sensitive periods such as prenatal (Craig and Ogilvie, 1974) and neonatal periods (Eriksson and Nordberg, 1986; Eriksson et al., 1990; Johansson et al., 1996) affected development of the nervous system and caused behavioural and neurochemical changes into adulthood (Eskenazi et al., 2009). Eskenazi et al. (2006) was the first study to show that prenatal exposure to DDT, and not only to DDE, was linked to neurodevelopmental delays during early childhood. Ribas-Fito et al. (2006) assessed neurocognitive development relative to DDT levels in cord serum of 475 children. At age 4, the level of DDT at birth was inversely associated with verbal, memory, quantitative and perceptual performance skills, and the associations were stronger among girls. Torres-Sanchez et al. (2007) found that the critical window of exposure to DDE *in utero* may be the first trimester of the pregnancy, and that psychomotor development in particular is targeted by the compound. The authors also suggested that residues of DDT metabolites may present a risk of developmental delay for years after termination of DDT use.

Sagiv et al. (2008) demonstrated an association between low-level DDE exposures and poor attention in early infancy. In a follow-up study, they found that prenatal organochlorine DDE was associated with attention deficit hyperactivity disorder (ADHD) behaviour in childhood (Sagiv et al., 2010).

11.4.9 Immune effects

Cooper et al. (2004) demonstrated that DDE modulates immune responses in humans with evidence of potential immunosuppression and

immune-mediated health effects such as infectious diseases and autoimmune diseases. Higher levels of prenatal DDE were associated with an increased incidence of otitis media in a study of Inuit infants (Dewailly et al., 2000). Workers directly exposed to DDT and lindane for 12–30 years, compared to a control population of individuals, had a higher prevalence of infectious diseases and of upper respiratory tract infections such as tonsillitis, bronchitis, and pharyngitis (Hermanowicz et al., 1982).

11.4.10 Recent health assessments of DDT

Two recent assessments of DDT and human health indicated issues that need attention. Eskenazi et al. (2009) found after reviewing 494 recent studies: 'The recent literature shows a growing body of evidence that exposure to DDT and its breakdown product DDE may be associated with adverse health outcomes such as breast cancer, diabetes, decreased semen quality, spontaneous abortion, and impaired neurodevelopment in children'. Focusing on DDT used in IRS, Bouwman et al. (2011) found that: 'The evidence of adverse human health effects due to DDT is mounting. However, under certain circumstances, malaria control using DDT cannot yet be halted. Therefore, the continued use of DDT poses a paradox recognized by a centrist-DDT position. At the very least, it is now time to invoke precaution. Precautionary actions could include use and exposure reduction.' They concluded that 'There are situations where DDT will provide the best achievable health benefit, but maintaining that DDT is safe ignores the cumulative indications of many studies. In such situations, addressing the paradox from a centrist-DDT position and invoking precaution will help design choices for healthier lives.' This was however, challenged by others (Tren and Roberts, 2011).

11.4.11 Carson on human health

The following quotations from Carson (1962) on the relationship between humankind and chemicals illustrate the concerns that are still with us today, but care should be taken not to interpret them out of context.

'Their [chemicals including pesticides] presence casts a shadow that is no less ominous because it is formless and obscure, no less frightening because it is simply impossible to predict the effects of lifetime exposure to chemical and physical agents that are not part of the biological experience.'

'The whole problem of pesticide poisoning is enormously complicated by the fact that a human being, unlike a laboratory animal living under rigidly controlled conditions, is never exposed to one chemical alone.'

'Some of the defects and malformations in tomorrow's children, grimly anticipated by the [US] Office of Vital Statistics, will most certainly be caused by these chemicals that permeate our outer and inner worlds.'

'The most determined effort should be made to eliminate those carcinogens that now contaminate our food, our water supplies, and our atmosphere, because these provide the most dangerous type of contact — minute exposures, repeated over and over throughout the years.'

11.5 Current human exposure

11.5.1 DDT used for indoor residual spraying

Following the essentially global ban on DDT use in agriculture, the only remaining repeated exposure of people to DDT is via IRS. It is otherwise assumed that illegal use is irregular and decreasing as stocks are dwindling. With between 2–3 grams of DDT applied per square metre on indoor walls, rafters, and outside under eaves, an average house may receive between 64–128 g/year, applied prior to the malaria transmission season. As DDT is long-lasting, the residual effect interrupts malaria transmission from an infected to an unaffected person by killing the female mosquito vector that rests indoors. It also acts as a contact irritant or spatial repellent (Grieco et al., 2007).

Arguably, the millions of people living in dwellings treated by DDT to protect them from malaria could be the largest non-occupationally exposed community in the world. The exposure is non-intentional, but inevitable (Bouwman et al., 2011). A closer look at how people are exposed in a domestic environment may indicate options for reduction in exposure and amounts applied. Such an exercise would be generic for any chemical used in similar ways. Again, despite the decades of DDT used as IRS, very little has been published on this subject.

11.5.2 DDT in air

DDT in ambient air is decreasing worldwide as its production and use has decreased dramatically

with the ban on its use in agriculture (Schenker et al., 2008). Background levels in air for the general population are therefore low, with a concomitant reduction in risk. However, DDT, applied repeatedly on various indoor and associated surfaces of dwellings as IRS, remains continuously available. Because DDT has to interrupt transmission by the vectors, it must remain bio-available for six months or longer. Sereda et al. (2009) proposed a process of continuous indoor sublimation, revolatilsation, and re-deposition of DDT, effectively redistributing the DDT throughout the treated dwelling. Transport via air, airborne dust, as well as regular sweeping and removal of house dust to the outside results in DDT pollution of the outdoor environment. Applied DDT therefore, does not remain stationary. For spatial repellence of mosquitoes to remain effective for months also implies that DDT remains in the indoor air for substantial periods. Van Dyk et al. (2010) presented evidence that DDT remains detectable in indoor air for at least 84 days after application. DDT in indoor air, and probably at lower concentrations in outdoor air near the homesteads, therefore remains chronically available for inhalation by all homestead residents. Recently, Ritter et al. (2011) modelled air and human intake in an IRS situation and found inhalation exposure to DDT as an important route of uptake. A particular concern are individuals who remain close to home for long periods, such as infants, children, the elderly, pregnant mothers, and those with domestic responsibilities.

11.5.3 DDT in food and water

Van Dyk et al. (2010) reported on levels of DDT in various environmental matrixes, food, and human serum from a DDT-sprayed village in South Africa. High levels of DDT were found, especially in food items such as chickens and outdoor soil, but less so in vegetables and water. The patterns of DDT, DDD, and DDE (breakdown products of DDT; DDD is dichlorodiphenyldichloroethane) were also such that it seems far more likely that DDT in humans was derived from home-produced animal foods and outdoor soil rather than from air, indoor dust, and water. Elsewhere it was also found that DDT in fish was less likely to contribute towards DDT burdens in humans under IRS conditions (Barnhoorn et al., 2009; Bouwman et al., 1990a). DDT uptake by humans living in dwellings treated by IRS with DDT is therefore mainly through DDT entering the food chain in the immediate environs of the sprayed dwellings themselves. This differs from the situation where DDT is used on crops as insecticide, and the human route of uptake is mainly via treated crops, dairy products, or contaminated fish. A situation can be envisaged where both types of exposures occur, but large commercial agriculture was and is rarely found in malaria areas. It seems that people living in DDT-treated dwellings have a greater DDT burden than those exposed otherwise (Eskenazi et al., 2009). Gyalpo et al. (2012) using models based on data showed that primiparous mothers have greater DDT concentrations than multiparous mothers, which causes higher DDT exposure of first-born children. The DDT in the body mainly was found to be mainly from diet, likely derived from the immediate environment of the homestead (van Dyk et al., 2012).

The results presented in the previous paragraph point towards options for exposure reduction to all chemicals used in IRS, not only DDT. For such options to be investigated, the dynamics of the IRS chemicals, inhabitants, and vector mosquitoes need to be better understood. The procedures involving IRS have remained static since their introduction in the early 1940s. In the meanwhile, much more knowledge has become available about environmental chemistry, health impacts, and vector behaviour. It is clear that, where possible, all measures should be taken to reduce the exposures of the inhabitants to IRS chemicals as far as possible. A Total Homestead Environment (THE) approach has been proposed whereby these interactions are studied with the aim of identifying opportunities of exposure reduction (Bouwman et al., 2011; Bouwman and Kylin, 2009; Sereda et al., 2009).

11.5.4 Legacy issues

Except for use in disease vector control, any other current use of DDT is illegal (Section 1.3.2). Although global production of DDT may gradually be declining, legacy sources remain a problem. With vast amounts of DDT having been manufactured in industrial countries, it comes as no surprise that wastes and emissions resulted in large pollution problems near factories that are now closed down. On the Pine River in Michigan, United States, for instance, even though a Superfund site, DDT is still found in the environment, and health concerns persist (Eskenazi et al., 2009). A no-consumption of fish advisory is still in effect, and clean-up of nearby residential properties is scheduled for 2012, among a whole range of other protective and mitigating measures (EPA, 2012c). Likewise, previous mitigation of sediments at the DDT formulation site of United Heckathorn Co. in Richmond Harbor, California,

which went bankrupt in 1966, seems not to have been as effective as anticipated and high levels of DDT in sediments and water persist (EPA, 2012b). An advisory against fish consumption (initially due to mercury but now for multiple pollutants) has been in effect since 1972. A search of the EPA Superfund site (EPA, 2012a) reveals 213 sites under United States jurisdiction that list DDT in one way or another at various stages of intervention.

Other legacy issues remain. DDT can undergo long-range transport via, air, water, and biota, contaminating areas where it has not been used or released (Bailey et al., 2000; Beyer et al., 2000; Iwata et al., 1993; O'Toole et al., 2006). Residues in glaciers are now being released as a result of climate change (Bettinetti et al., 2008; Geisz et al., 2008).

11.5.5 Effects of mixtures of chemicals

Legacy situations relating to DDT and malaria control hardly ever concern DDT only. With many commercial chemicals available, DDT now occurs together with many other pollutants in all manner of media and biota. Carson, after deliberating on combinations of pesticides in a common salad bowl said: 'Residues well within legally permissible limits may interact.', then said: 'What of other chemicals in the normal human environment? What in particular of drugs?' Later she brought in other chemicals: 'Added to these are the wide variety of synthetic oestrogens to which we are increasingly exposed — those in cosmetics, drugs, food, and occupational exposures. The combined effect is a matter that warrants the most serious concern.' Now, 50 years later, the issue of mixture effects, referred to in the Stockholm Convention as 'toxicant interactions', pharmaceuticals and personal care products (PPCPs) is a major area of research.

Scientific advances are finding ever more effects associated with chemicals in more and more biological systems; some effects such as endocrine disruption was barely understood at the time of Rachel Carson. This is evident from her statement: 'The ultimate answer is to use less toxic chemicals so that the public hazard from their misuse is greatly reduced. Such chemicals already exist. … the pyrethrins, rotenone, ryania, and other derived from plant substances.' We now know that even pyrethroids have health concerns (Bouwman and Kylin, 2009) and may interact with DDT (Eriksson et al., 1993). Even if DDT is not the major component of the cocktail of pollutants in many areas, it poses a legacy that cannot be ignored. Now that DDT is universally distributed in the biosphere, its interactions with other pollutants cannot be ignored, and will occupy science for many years to come, long after the final batch of DDT has been produced.

11.6 Future directions

11.6.1 Malaria, DDT, and the Stockholm Convention

Carson devoted relatively little space to DDT and malaria, but highlights the problem of development of resistance to DDT: 'Malaria programmes are threatened by resistance among mosquitoes.', and describes a number of instances around the world, including behavioural resistance. 'Apparently the adult mosquitoes had become sufficiently tolerant of DDT to escape from sprayed buildings.' The reverse of this situation, of pyrethroid-resistant mosquitoes re-invading South Africa when DDT was withdrawn, puts this issue into a new context. DDT had to be re-introduced to return to pre-1996 levels of morbidity and mortality. DDT resistance in South Africa and many other African countries was absent, not detected, or not strong enough to result in a breakdown of control. Whether behavioural resistance to DDT — where mosquitoes leave treated houses or fail to enter — effectively interrupts transmission is still not adequately resolved.

As described in Sections 11.2 and 11.3.1 above, DDT is one of the chemicals restricted by the Parties to the Stockholm Convention. The text of the convention is provided in Box 11.2. The provisions in the Convention regarding DDT can be seen as balancing the need for the continued use of DDT for malaria control where alternatives are not yet effective or proven, with an (undated) eventual aim of banning it. However, the experience in South Africa with pyrethroids (Maharaj et al., 2005) failing as an alternative to DDT in IRS has probably increased the threshold of expectation of proof of sustainability, especially regarding the requirements of viable alternatives listed in paragraph 5 (b) of the Stockholm Convention (see Box 11.2). No Party would want to revert to DDT if the alternatives are not as effective or better, measured by increased morbidity and mortality. The Stockholm Convention is driving various activities that can be followed on their website (www.pops.int).

11.6.2 Integrated vector management

The urgency of developing and establishing suitable alternatives to DDT for disease vector control is now widely recognised. Indeed the need for alternatives

Box 11.2 DDT in the Stockholm Convention, Annex B. Restriction, Part II

1. The production and use of DDT shall be eliminated except for Parties that have notified the Secretariat of their intention to produce and/or use it. A DDT Register is hereby established and shall be available to the public. The Secretariat shall maintain the DDT Register.
2. Each Party that produces and/or uses DDT shall restrict such production and/or use for disease vector control in accordance with the World Health Organization recommendations and guidelines on the use of DDT and when locally safe, effective and affordable alternatives are not available to the Party in question.
3. In the event that a Party not listed in the DDT Register determines that it requires DDT for disease vector control, it shall notify the Secretariat as soon as possible in order to have its name added forthwith to the DDT Register. It shall at the same time notify the World Health Organization.
4. Every three years, each Party that uses DDT shall provide to the Secretariat and the World Health Organization information on the amount used, the conditions of such use and its relevance to that Party's disease management strategy, in a format to be decided by the Conference of the Parties in consultation with the World Health Organization.
5. With the goal of reducing and ultimately eliminating the use of DDT, the Conference of the Parties shall encourage:
   (a) Each Party using DDT to develop and implement an action plan as part of the implementation plan specified in Article 7. That action plan shall include:
      (i) Development of regulatory and other mechanisms to ensure that DDT use is restricted to disease vector control;
      (ii) Implementation of suitable alternative products, methods and strategies, including resistance management strategies to ensure the continuing effectiveness of these alternatives;
      (iii) Measures to strengthen health care and to reduce the incidence of the disease.
   (b) The Parties, within their capabilities, to promote research and development of safe alternative chemical and non-chemical products, methods and strategies for Parties using DDT, relevant to the conditions of those countries and with the goal of decreasing the human and economic burden of disease. Factors to be promoted when considering alternatives or combinations of alternatives shall include the human health risks and environmental implications of such alternatives. Viable alternatives to DDT shall pose less risk to human health and the environment, be suitable for disease control based on conditions in the Parties in question and be supported with monitoring data.
6. Commencing at its first meeting, and at least every three years thereafter, the Conference of the Parties shall, in consultation with the World Health Organization, evaluate the continued need for DDT for disease vector control on the basis of available scientific, technical, environmental and economic information, including:
   (a) The production and use of DDT and the conditions set out in paragraph 2;
   (b) The availability, suitability and implementation of the alternatives to DDT; and
   (c) Progress in strengthening the capacity of countries to transfer safely to reliance on such alternatives.
7. A Party may, at any time, withdraw its name from the DDT Registry upon written notification to the Secretariat. The withdrawal shall take effect on the date specified in the notification.

to DDT has been one of the drivers that led the WHO to develop a global strategic framework on integrated vector management (IVM) (WHO, 2004). IVM is a strategy for the optimal use of vector control methods, procedures and resources aiming to improve the efficacy, cost-effectiveness, ecological soundness and sustainability of vector control (WHO, 2012). Development of alternative insecticides is one way to address the problem of insecticide resistance, and it is probable that improved formulations of existing insecticide molecules will be available soon although new insecticide molecules will take considerably longer to come to the market (Hemingway et al., 2006). However, evolutionary selection for resistance will continue against any new modes of action unless the selection pressure on vector populations is substantially reduced (Read et al., 2009).

It is therefore critical that the choice of vector control methods should be carefully based on the evidence of their effect on transmission reduction and their appropriateness in the local context. Combinations of methods, including house screening, environmental management, repellents, trapping, and biological

control, with insecticide-treated bed nets or indoor residual spraying, may provide superior control while reducing reliance on single modes of action (Takken and Knols, 2009). For example, the use of IRS or insecticidal bed nets could usefully be complemented by larval source management or repellents, particularly where part of the vector population bites outdoors (Fillinger et al., 2009; Hill et al., 2007).

In its implementation, vector control should not be combined only with disease control programmes. Integrated vector management would benefit substantially from integration within the health sector, collaboration between sectors and active participation of communities (WHO 2012; Chanda et al., 2008; Beier et al., 2008).

11.6.3 Malaria, DDT, and the World Health Organization

The WHO has a major commitment to combating malaria using prompt treatment of cases, and vector control by insecticide-treated bed nets and IRS, implemented within an integrated vector management strategy. The summary of the latest WHO position statement on DDT (WHO, 2011c) is provided in Box 11.3, confirming that DDT is still required for malaria control. The WHO also introduced a global strategic framework for integrated vector management, expanded on in the previous section.

Recent unease with safety issues about DDT also prompted the WHO to reassess the potential health impact of DDT used for IRS (WHO, 2011d). The Consensus statement concluded: 'For households where IRS is undertaken, there was a wide range of DDT and DDE serum levels between studies. Generally, these levels are below potential levels of concern for populations. Considering the ranges of exposures in treated households that are summarised in Table 11.1, in some areas, the exposures in treated residences have been higher than potential levels of concern. Efforts are needed to implement best practices to protect residents in treated households from exposures arising from IRS. Of particular concern would be women of childbearing age who live in DDT IRS-treated dwellings and transfer of DDT and DDE to the fetus in pregnancy and to the infant via lactation.' The WHO has a number of initiatives and programmes relating to malaria control and IRS, which can be followed on their website (http://www.who.int/malaria/en/).

11.6.4 Likely future developments

It is clear that there is a roadmap for the exit of DDT. There remains the need to find, further refine, convincingly demonstrate sustainability, and implement alternatives. Although there is a roadmap, there is no timetable. The pieces need to be found and fitted within the budgetary constraints and competing agendas. Given the current climate regarding research and development budgets and interfacing political agendas, the final demise of DDT still seems some way off. However, DDT has taught us a lot. It is probably the most widely known quintessential environmental pollutant. It will remain a model molecule and benchmark against which many others will be compared. It has shown the good and bad side of what can be done by chemicals. One thing is for certain — DDT will remain a source of contention for some time to come. It will probably remain in inert environmental media for decades to come, but there may come a time when it will only be found in books, such as *Silent Spring*, to be read in gardens with birds.

11.7 The legacy of Rachel Carson

It is clear that the social conscience awakened by Rachel Carson 50 years ago gave momentum to a groundswell of actions and interventions that is

Box 11.3 Global Malaria Programme: The use of DDT in malaria vector control. WHO position statement, 2011

DDT is still needed and used for disease vector control simply because there is no alternative of both equivalent efficacy and operational feasibility, especially for high-transmission areas. The reduction and ultimate elimination of the use of DDT for public health must be supported technically and financially. It is essential that adequate resources and technical support are rapidly allocated to countries so that they can adopt appropriate measures for sound management of pesticides in general and of DDT in particular. There is also an urgent need to develop alternative products and methods, not only to reduce reliance on DDT and to achieve its ultimate elimination, but also to sustain effective malaria vector control (WHO, 2011e).

slowly but steadily making inroads at a myriad of levels addressing human and environmental concerns about chemicals. Reading *Silent Spring*, one is struck by how modern and current many of the issues that she raised are, although some are now described by other terminology. Resistance development, genetic damage, genetic modification, cancer, effects of mixtures, the need for more and improved biomarkers, sterile male techniques, push-pull biological control, ethical choices, and the need for concerted action at all levels, are just some of these. Although not yet aware of endocrine disruption as a mode of action of pesticides, effects such as cancer involving reproductive hormones was one of the issues she addressed. Not only did she attack the indiscriminate use of pesticides, she also proposed forms of integrated pest/vector management and biological control in chapter 17 that seem so modern and obvious today, but conceptually are more than 50 years old. Long-range transport of chemicals through air was also not well understood at the time of *Silent Spring*.

The heading of Chapter 17 — The Other Road — elicits a strong feeling that we have not taken the road that we should have taken much earlier on, an opportunity that was missed, an option not taken that will resonate for decades to come. Carson opined in her last sentence of *Silent Spring*: 'The concepts and practices of applied entomology for the most part date from the Stone Age of science. It is our alarming misfortune that so primitive a science has armed itself with the most modern and terrible weapons, and that in turning them against the insects it has also turned them against the earth.' Applied entomology has long since incorporated pest control measures other than chemicals and one can but ponder how much this was due to *Silent Spring*?

With more than 10 % of bird species worldwide now threatened in one way or another, and some already gone since *Silent Spring*, the silence that Carson called upon to illustrate the impact of chemicals has now also crossed into other realms of environmental impact. Radiation (also addressed by Carson), climate change, habitat destruction, economic mismanagement of the environment, human population expansion, and more — all of them have Other Roads, and we missed the obvious early signposts or failed to act upon them. Will there be more signposts to Other Roads that we will miss? Two final thoughts on this. Paraphrasing Jean Rostand; are our obligations to endure met by our rights to know? As Carson said 50 years ago: '*The choice, after all, is ours to make*.'

Table 11.1 Early warnings and actions

1873	The DDT molecule was first synthesised
1939	Paul Müller showed the insecticidal property of DDT
1943-44	Typhus broke out in Naples, Italy in October 1943. By January 1944, and after treating 1 300 000 persons over a three week period with DDT, the epidemic was brought under control
1946	Indoor residual spraying (IRS) with DDT to interrupt malaria transmission was introduced in South Africa
1948	Paul Müller was awarded the Nobel Prize for Medicine or Physiology. Already in the prize presentation speech problems with flies developing resistance against DDT was mentioned
1948	Use of DDT inside dairies in the US was prohibited
1950s-60s	DDT was the primary tool used in the first global malaria eradication programme. The insecticide was used to spray the walls and ceilings of houses and animal sheds with coverage of entire populations
1951	First reports of the development of insecticide resistance to DDT. This became an obstacle in the eradication of malaria, and was one of the reasons behind the abandonment of the global malaria eradication campaign
1958	Complete coverage of malaria areas in South Africa via indoor residual spraying with DDT achieved
1962	The novel *Silent Spring* was published, drawing attention to the impacts of chemicals on the environment and human health. Special emphasis was given to DDT
1964	Stockholm University, Sweden, set up a laboratory for the analysis of DDT in the environment. These activities led, inter alia, to the identification of polychlorinated biphenyls (PCB) as environmental contaminants
1970s	Based on the increasing amount of data on environmental effects, restrictions on the use of DDT were set in place in different countries, but still, the use and miss-use of DDT continued. Amidst concerns about the safety of DDT, the insecticide was banned for use in agriculture in many countries
1996	South Africa discontinued the use of DDT for malaria control and introduced pyrethroids on a large scale
2000	South Africa re-introduced DDT after failure of pyrethroids in many areas. Pyrthroids are used where viable
2004	The Stockholm Convention on Persistent Organic Pollutants came into force eliminating the production and use of DDT except for disease vector control where safe, effective and affordable alternatives are not available
2010	DDT is now only produced in India, from where it is exported to other, mostly African, countries. China has recently stopped its production of DDT. South Africa formulates DDT with the technical product from India, and exports the formulated product to several other African countries.

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