Growing Burden of Diabetes in Sub-Saharan Africa: Contribution of Pesticides?

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Abstract: The diabetes burden is growing in Sub-Saharan Africa (SSA). The low overall access to health care has been documented to contribute to the high diabetes-related mortality. Due to economic, demographic, epidemiological and nutrition transitions in SSA, the growing prevalence of diabetes appears to be related to obesogenic lifestyles and the intergenerational impact of malnutrition in women of childbearing age. Both overnutrition and undernutrition have been associated with the development of diabetes and other chronic diseases. Africans are also suspected of being genetically predisposed to diabetes. According to existing data in developed countries, exposure to pesticides, particularly organochlorines and metabolites, is associated with a higher risk of developing type 2 diabetes and its comorbidities. In African countries, pesticide exposure levels often appear much higher than in developed countries. Furthermore, undernutrition, which is still highly prevalent in SSA, could increase susceptibility to the adverse effects of organic pollutants. Therefore, the growing and inadequate use of pesticides may well represent an additional risk factor for diabetes in SSA. Additionally, high exposure to pesticides in African infants *in utero* and during the perinatal period may increase the intergenerational risk of developing diabetes in SSA.

INTRODUCTION

Diabetes is a public health problem in Sub-Saharan Africa (SSA); the prevalence is growing and mortality is high. In most cases, the disease is diagnosed late and often at the stage of crippling complications. The diabetes burden in SSA occurs in a context of poverty where access to health care is limited [1]. Diabetes is also an economic burden for SSA [2]. According to the International Diabetes Federation (IDF) projections, SSA is the region where diabetes prevalence will have the greatest increase by 2030 [1-3]. In SSA, diabetes is implicated in the double nutritional burden issue, with concurrent nutrition-related non-communicable diseases (NCDs) and malnutrition in the same populations. However, limited attention has been given so far to NCDs such as diabetes, cardiovascular disease and cancers. The meagre health resources are rather focused on malnutrition and communicable diseases such as malaria, tuberculosis and Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV/AIDS) [4]. Hopefully, a shift of health priorities will result from the impetus given by the High Level Meeting of the United Nations for the prevention and control of NCDs [5].

In SSA, there is a trend for an increasing use of pesticides in agriculture and in other fields, for instance to fight against malaria. Low level of education, greed and corruption that often affect low-income countries, coupled with little concern for health, lead to suboptimal management and inadequate use of pesticides. Therefore, populations and their environment are at high risk of contamination [6, 7]. Current data support an association between exposure to certain environmental pollutants and diabetes. Could the high levels of pesticides exposure contribute to the ever increasing prevalence of diabetes in African populations? The aim of this review is to examine various factors that might influence the burden of diabetes in SSA and highlight the potential contribution of pesticides.

GENERAL METHODOLOGY FOR THIS REVIEW

In this review, we expose the features of diabetes prevalence and its contributing factors in SSA. We also examine the level of exposure to pesticides of African populations on the basis of available data. A summary of the existing evidence for the association between pesticide exposure and diabetes is then summarized to assess the potential contribution of pesticides to the rapid progression of diabetes in SSA.

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Databases such as Pubmed, Medline, Embase, Cab abstract, Cinhal, Toxline and 'Banque de Données en Santé Publique' (BDSP) were explored. Relevant publications cited by other authors were found using Web of Science. Additional information was sought on the official websites of governments, scientific associations and regulatory bodies. The main keywords used were: diabetes, pesticides, Africa*. The words organochlorin*, organophosphor*, pyrethrin*, carbamat*, Pollutants and POPs (Persistent organic pollutants) were also used as substitutes for "pesticides". Similarly, "health" and "disease" also replaced "diabetes".

Relevant documents of the last 20 years were given priority but less recent papers were also used as appropriate. Article selection focused on diabetes and the factors that explain its increasing prevalence. The retained articles focused on pesticide levels in biological tissues and environment, and health effects. Publications on the relationship between pesticide exposure and diabetes were exploited.

EPIDEMIOLOGY OF DIABETES IN SSA

In SSA, the three classical types of diabetes are observed: type I diabetes, type II diabetes and gestational diabetes [8, 9]. In addition, intermediate forms between type I and type II have been described such as type 1B diabetes [10-20], malnutrition related diabetes and fibro-calculous pancreatic diabetes [12, 21-25]. These atypical forms of diabetes observed specifically in SSA are not formally recognized due to lack of evidence to clarify their pathogenesis. They are therefore not taken into account in official classifications of the World Health Organisation (WHO) and the International Federation of Diabetes (IDF) although recent studies confirm their presence in SSA [16].

The estimated prevalence of diabetes among African adults aged 20 to 79 years increased from nearly null to the epidemic stage within a generation [26]. Epidemiological data on diabetes in SSA are few and inconsistent due to the variability in data collection methodology and definition criteria. The existing prevalence data come primarily from STEPwise (STEPS) surveys as recommended by WHO for chronic diseases monitoring [27, 28], hospital studies [29, 30] and a few population based studies [31-33]. From 3% over the last ten years, the prevalence of type II diabetes rose to 4.5% in 2011 and will reach 4.9% by 2030 according to the IDF [1, 34, 35]. The prevalence varies from 1 to 12% depending on the country [36]. Although the observed prevalence in SSA is low compared to other continents, the growth rate of 90% by 2030 is the highest in world. Type I diabetes and gestational diabetes also increase rapidly but the increase is lower than in developed countries [1]. The prevalence rates of type I diabetes and gestational diabetes were respectively estimated at 4-12 for 100 000 and 0- 9% in 2011 [36]. According to IFD 5th atlas, 36.1 thousands of African children under 14 years old were affected with type 1 diabetes and 5.9 thousands were detected every year. These prevalence figures could be underestimated due to lack of detection and high mortality associated with poor access to treatment, particularly for type 1 diabetes [37-40].

The burden of diabetes in SSA is also characterized by the high rate of complications, as these are generally the mode of detection of the disease. Indeed, SSA has the highest estimated proportion of undiagnosed diabetes (78%) while the overall worldwide rate is estimated at 50% [1-3]. Microvascular complications are the most common. Retinopathy affects 15-55% of patients and kidney complications 5-28% in the first year of diagnosis. Peripheral neuropathy accounts for approximately 10-36% of complications [26, 41-43]. In SSA, 6.1% of deaths are attributable to diabetes and two-thirds of affected subjects die of cardiovascular complications [1, 44]. The high complication and death rates of diabetes are due to late diagnosis and poor access to healthcare, but the determining factors of the rapid increase in the prevalence of the diseases need to be better understood. Ketoacidosis is the most frequent complication observed in Type 1 diabetes [39].

FACTORS ASSOCIATED WITH INCREASED PREVALENCE OF DIABETES IN SSA

Transitional Context and Intergenerational Impact of 'Dysnutrition'

In SSA, economic transition and increasing urbanization lead to a demographic transition characterized by aging of the population due to improved life expectancy. This translates into a widening of the upper part of the age pyramid. It is estimated that SSA's urban population will have increased by 98% in 2050 [45]. This rise in the urban population will contribute to the increase in the number of persons living with diabetes in the order of two-fifths [26]. Indeed, changes from traditional to urban lifestyles and eating patterns foster obesity and the development of diabetes as a consequence. Living in an urban area has been shown to be conducive to the adoption of an obesogenic lifestyle characterized by a high caloric diet rich in sugar and fat as well as by sedentary behaviors [46]. Thus, economic, demographic and nutrition transitions appear to usher the emergence of new epidemiological paradigms such as obesity, diabetes and cardiovascular disease [46-48]. While diabetes is usually more prevalent in urban areas [32], an increasing trend is also observed in rural areas [49]. Diabetes has been documented to occur more frequently in individuals of lower than higher socioeconomic status, but this varies according to the context. At least in developed countries, it has been reported that food choices of the poor and food insecure are oriented primarily towards energy-dense foods but low in micronutrients [50-52]. This adaptation strategy might contribute to explain the obesity of poverty paradox [53-55]. Hence, obesity is a threat at both ends of the socioeconomic spectrum. This pattern may explain the observed increase in obesity in SSA [56-59], while underweight also prevails. Hence both forms of 'dysnutrition' [60], that is, undernutrition and overnutrition, coexist.

While it is generally stated that 80% of persons with diabetes are obese, less than half the individuals with diabetes in SSA are obese [30]. Obesity is far more common in women than men [44, 58]. This can be explained by the fact that in several African cultures, overweight and obesity are regarded as socially desirable. A beauty feature in women, overweight is a sign of wealth in their spouses [61-63]. Meanwhile, 27-51% of women of childbearing age in SSA are undernourished and 21% of newborns have a low birth weight [64]. According to the established theory on the de-

velopmental origins of chronic diseases, children with low birth weight are more likely to develop chronic diseases later in life when exposed to an obesogenic environment [65-71].

Type 1 diabetes seems to be more prevalent in girls and is usually associated with undernutrition or low socioeconomic status as reported in several countries [15, 40, 72]. Type 1 diabetes is also consistently associated with environmental factors that interact with gene susceptibility [15].

Diabetes and Infections in SSA

Some infectious diseases such as tuberculosis and HIV are suspected to contribute to the development of diabetes. Current data show that tuberculosis is associated with diabetes [73, 74] and increases the risk of metabolic syndrome and cardiovascular diseases [75-77]. However, the relationship between the two diseases seems to be bidirectional [78]. Additionally, some drugs such as Isoniazid used in the treatment of tuberculosis could lead to hyperglycemia [75]. Antiretroviral drugs for HIV such as Zidovudine and Stavudine are also associated with an increased risk of developing diabetes by promoting dyslipidemia and insulin resistance [77-79]. Since tuberculosis and HIV infections are highly prevalent in SSA and since medicines are becoming more accessible, these diseases may be involved in the increasing prevalence of diabetes. This was suggested in a recent study showing a concomitant increase in the prevalence of diabetes, tuberculosis and HIV [80].

In summary, diabetes in SSA has been associated with factors related to demographic and nutrition transitions, with the intergenerational effect of undernutrition, as well as with some infectious diseases, particularly in genetically predisposed individuals. Data on Africans are scarce [81], but several studies in African-Americans have revealed a genetic predisposition to diabetes among people of African descent [82]. The weakness of African healthcare systems for the screening and prevention of diabetes is another factor. Environmental pollutants such as pesticides could also be an additional factor related to the burden of diabetes in SSA, as summarized by (Fig. **1**).

EXPOSURE TO PESTICIDES AND DIABETES IN SSA

Factors that contribute to pesticide exposure in African populations are reviewed first. We then discuss the potential contribution of pesticides to diabetes risk, particularly in SSA.

Level of Exposure to Pesticides in SSA

Pesticide Utilization

Economic challenges, the need to reduce postharvest food losses, and the fight against human disease vectors foster the increasing use of pesticides in SSA. Pesticides represent one group of chemical pollutants within the larger family of environmental pollutants. According to the nomenclature used in this review, the major groups of pesticides are insecticides, herbicides, fungicides, rodenticides [83]. A subgroup of insecticides, that of organochlorines, organophosphophates, carbamates and pyrethroids, is in general of more concern because they are documented as being the most harmful. Other chemical pollutants have also been associated with the development of diabetes, such as polychlorinated biphenyls (PCBs) and dioxins, but the present review focuses on pesticides as these are an issue in SSA.

Existing data provided by governmental agencies show that the amounts of pesticides used in SSA for crop protection and public health purposes have increased considerably over the years [7], although the amounts of pesticides officially available in SSA seem to be low (3% of world consumption) compared to other continents [84]. Persistent pesticides such as organochlorines are usually intended for cotton production for export. Pyrethroids are used for production and preservation of certain foods and also for public health purposes. Unfortunately, it is not uncommon to observe that dangerous pesticides are used in food production, processing and preservation. Numerous pesticides are also used by individuals for domestic purposes, and these are not registered in national reports.

Inadequate Management and Practices

Pesticides are often used inappropriately, with increased risk of human exposure. Persistent and harmful pesticides
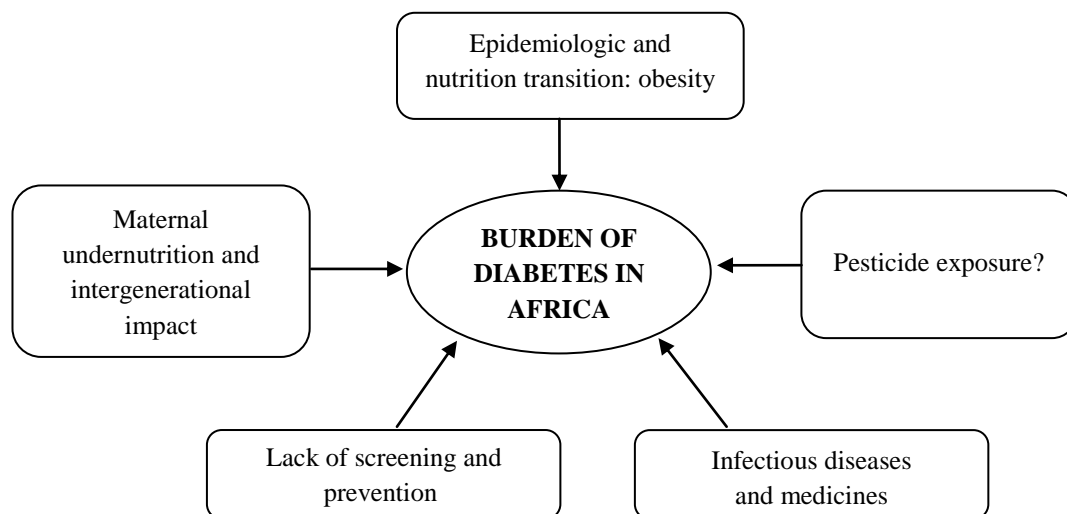

Fig. (1). Contributing factors to the burden of diabetes in SSA.

such as DDT (dichlorodiphenyltrichloroethane) are still being imported in SSA and might contribute to increased release in the environment and exposure of individuals [6, 7]. Even if they are excluded from the official lists of authorized chemicals in many countries in line with Stockholm and Rotterdam conventions [85-87], some of these harmful pesticides are still available on the informal market. Pesticides are sold in local shops, often near food products and restaurants, with high risk of contamination [88, 89]. Unfortunately, very little information is available on the nature of active ingredients, on the instructions to users and on the toxicity of pesticides imported fraudulently. Furthermore, since 2006, WHO has authorized DDT utilization in SSA to control malaria, despite its high persistence, because this chemical is still considered safe when sprayed into human and animal habitats according to guidelines [90]. However, these pesticides once sprayed on the walls are inhaled and absorbed by the exposed individuals even if the doses are extremely low.

Similarly, long-lasting bed nets that release pyrethroids slowly and gradually expose African people for many years to such pesticides. It is now suspected that long term exposure to low doses of these pesticides may contribute to their bioaccumulation in the human body and contribute to various chronic diseases including diabetes [91, 92].

Large amounts of obsolete pesticides are not destroyed and are often stored in inappropriate places. Containers are damaged over time and pesticides migrate into the environment, as observed in Ethiopia, Benin and elsewhere [93, 94]. Fortunately, a strategy for the destruction of obsolete stocks is underway in these countries. Empty pesticide containers and contaminated materials are often discarded in the environment or reutilized for various household needs [94]. The inadequate management of pesticide wastes is a common source of contamination of the environment as observed in Tanzania [95], and it is often responsible for fatal acute poisoning [96, 97]. Several cases of acute poisoning reported in African countries have been attributed to organochlorine or organophosphate pesticides, including more recently Endosulfan, which is now banned [96-98]. Protective equipments for pesticide users are not often available [94] and the instructions for individual and collective protection given to farmers are not followed for a variety of reasons [99, 100]. Despite the efforts of several institutions to provide coaching and training, the majority of pesticide users are still not well trained. Even when trained, due to the low levels of education, farmers may not be able to read or understand pictograms and instructions on containers [94, 100]. The inadequate protection was reflected in the high concentrations of pesticides on the pesticide users' skin, in a Gambian study [101]. Other inappropriate uses of pesticides have been observed, such as the utilization of pesticides in preparation of baits for fishing and hunting [95], overdosage during spraying, the cultivation of crops near pesticide-treated cotton fields and pesticide use for the preservation of food crops. These practices fueled by the pursuit of profit and poor education lead to significant contamination of the environment and individuals [102, 103].

Pesticide Levels in the Environment and Biological Fluids

High levels of the most persistent pesticides were detected in water, soil, air, plants, fish and other animals in SSA countries [104-110]. Persistent organochlorine pesticides (POCs) were also found in dairy products and various other foods [95, 99, 111-116]. The concentrations of POCs found in food and drinking water were often higher than regulated maximum residue levels (MRLs) [110, 117], although the levels of organophosphates and pyrethroids found in food samples in Cameroon and Nigeria were reportedly lower than the prescribed limits [118, 119]. The wide variation may be ascribed to different analytical methods which could vary from spectrophotometric assays to chromatographic techniques.

Available human biomonitoring data are quite limited. Blood levels of various pesticides among exposed farmers were shown to be beyond acceptable limits [120-123]. Pesticide levels found in breast milk of African women farmers in Ghana, Kenya and South Africa exceeded the tolerable daily limit for infants [120, 124-128]. High concentrations of organochlorine pesticides may well have adverse effects on infant growth and development, thereby contributing to chronic diseases in adulthood [128]. Furthermore, African children usually accompany their parents in fields treated with pesticides and frequently work in these fields [94]. In a Kenyan study, children aged 0-14 years were found to be the first victims of acute poisoning, representing 40% of cases of pesticide poisoning identified in a hospital.

Available data on concentrations of organochlorine pesticides in human blood and other body fluids in SSA and non African countries are summarized in (Tables **1** to **4**). The data show that pesticide concentrations in Africans were similar or higher than those observed in developed countries. For example, in a comparative study, pesticide concentrations in Tanzania were nine times higher than in Belgium [129]. Similarly, in Gambia, Ghana, Côte d'Ivoire and Tunisia, pesticide concentrations were approximately the same or higher than those in developed countries [130-134]. This high exposure in SSA may partly explain the occurrence of some cancers, reproductive disorders, respiratory diseases and metabolic disturbances leading to cardiovascular diseases. It thus appears relevant to ask the question whether pesticide exposure plays a role in the development of diabetes in SSA.

Pesticide Exposure and Risk of Diabetes

Scientific evidence on the relationship between diabetes and exposure to persistent organic pollutants including pesticides is now increasingly available [141-143]. Data linking diabetes and pesticide exposure primarily refer to type II diabetes. The relationship between persistent organic pollutants and diabetes was first suspected half a century ago [144]. This was further evidenced when symptoms were observed in veterans of the Vietnam War exposed to the defoliant herbicide known as 'Orange Agent'. Subsequent studies reported that one metabolite of that herbicide, 2,3,7,8-tetrachlorodibenzo-p-dioxine (TCDD), caused deleterious effects including diabetes. Available studies on the effects of organochlorine pesticide exposure showed a consistent association with diabetes [145-150]. A similar risk was found associated with other types of pesticides. For professional users, the risk of diabetes was twice as high when they were exposed to DDT [151]. The risk increased respectively by

Table 1. Blood Concentrations of DDT and its Metabolites in African and Non-African Countries.

Countries, Years	Authors (Reference)	N	p,p'-DDE	p,p'-DDD	p,p'-DDT	ΣDDTs
Ghana, 2001	N'tow [106]	20	380 ± 120	NA	NA	NA
Ghana, 2008	N'tow [120]	115	7.1± 1.2	<LOQ	0.5±0.1	9.1± 1.3
Gambia, 2002	Manirakiza [130]	100	M: 4020±3960 F: 3520±2720	M:560±700 F: 160±160	M: 1160±840 F: 900±920	M: 7920±5240 F: 5920±2640
Tanzania, 2006	Weiss [129]	46	M : 18.63 ±12.1[a] F : 12.77 ± 9.7	NA	NA	NA
Tunisia, 2010	Ennaceur [132]	82	1.69±10,7[b]	0.42±9.9	0.91±11.9	4.33±13.2
Tunisia, 2007	Ennaceur [131]	113	168.8±158	19.9±14.4	24.3±18.8	213.1±160
Belgium, 2006	Weiss [129]	42	M : 2.15 ±0.19[a] F : 1.15 ± 0.9	NA	NA	NA
Sweden, 2007	Rignell-Hydbom [135]	543	C: 240 (93-970)* T: 140 (49-500)	NA	NA	NA
Sweden, 2009	Rignell-Hydbom [136]	742	C: 4.11±4.46 [b] T: 3.76±3.55	NA	NA	NA
USA, 2007	Cox [137]	1303	9 (1.98-228.2)**	NA	3.22(2-71.9)	NA
Finland, 2011	Airaiksen [138]	1988	610±12	NA	NA	NA
Corea, 2010	Son [139]	80	C: 652.3±646.7 T : 376.0±290.7	C: 6.6±3.6 T: 5.7±3.7	C: 34.2±21.3 T: 23.8±12.1	NA
Belgium, 2011	Dirinck [140]	144	205 (30.2–1073.2)**	NA	NA	NA

Mean values ± % relative standard deviation are expressed in ng/g of total serum lipid weight; [a] Non adjusted values in µg/kg on this row; [b] Non adjusted values in µg/L on this row; * Median (95th CI); **Median (Range); M = Male and F = Female; C= Cases and T = Controls; NA: Not available; LOQ: limit of quantification.

Table 2. Blood Concentrations of other Organochlorine Pesticides in African and Non-African Countries.

Countries, Year	Authors (Reference)	N	βHCH	HCB	Aldrin	Dieldrin	Endrin	Hepta-chlore	ΣEndosulfan	Trans-nonachlore
Ghana, 2001	N'tow [106]	20	NA	30 ± 10	NA	NA	NA	NA	NA	NA
Gambia, 2002	Manirakiza [130]	100	M: 220±340 F: 240±440	M:540±620 F: 260 ±300	M:320±240 F: 260±260	M:440±640 F:80±100	M:1740±2300 F:260±180	M: 360±300 F: 220±240	M:2471±1307 F:872±749	NA
Tanzania, 2006	Weiss [129]	46	NA	NA	NA	0.5±0.07[a]	NA	NA	NA	NA
Ghana, 2008	N'tow [120]	115	0,2±0,1	5,3±1,9	NA	127±27,2	NA	NA	NA	NA
Tunisia, 2010	Ennaceur [132]	82	0.30±19.6[b]	0.42±15.4	NA	NA	NA	NA	NA	NA
Tunisia, 2007	Ennaceur [131]	87	26.4±34.7	49.1±29.6	NA	NA	NA	NA	NA	NA
Belgium, 2006	Weiss [129]	42	NA	NA	NA	0.02±0.01[a]	NA	NA	NA	NA
USA, 2007	Cox [137]	1303	1.70 (1-13.68)*	1,34(1-3.92)	NA	1,50(1-9)	NA	NA	NA	1.52(1-17.6)

Table 2. Contd…..

Countries, Year	Authors (Reference)	N	βHCH	HCB	Aldrin	Dieldrin	Endrin	Hepta-chlore	ΣEndosulfan	Trans-nonachlore
Sweden, 2009	Rignell-Hydbom [136]	742	C: 240 (93-970)* T: 140 (40-500)	NA	NA	NA	NA	NA	NA	NA
Korea, 2010	Son [139]	80	C: 57.9±24.5 T: 44.0±28.3	C: 24.2±13.0 T: 18.3±9.5	NA	NA	NA	C:11.2±6.4 T: 7.9±7.1	NA	C: 31.3±28.1 T: 20.2±17.4
Finland, 2011	Airaiksen [138]	1988	NA	NA	NA	NA	NA	NA	NA	32±0.40
Belgium, 2011	Dirinck [140]	144	19 (2–200)**	NA	NA	NA	NA	NA	NA	NA

Mean values ± % relative standard deviations are expressed in ng/g of total serum lipid weight. Values on the same row are expressed in: [a] µg/kg, [b] µg/L; M = Male and F = Female; Values on the same row are: *mean (95th CI), **median (25th -75th); C= case, T = Control

Table 3. Concentrations of DDT and its Metabolites in Breast Milk in African Countries.

Countries, Year	Authors (Reference)	N	p,p'-DDE	p,p'-DDD	p,p'-DDT	ΣDDTs
Kenya, 1998	Kinyamu [127]	216	306± 41	29±10	152±26	473±59
Ghana, 2001	N'tow [106]	20	490± 230	NA	NA	NA
Zimbabwe, 2002	Chikuni [125]	116	735.6-13784.4♣	2.4-156.8	268.4-2636	1303.6 - 16838.6
Tunisia, 2007	Ennaceur [131]	87	2421±1370	279±1510	1015±1570	3863±1200
Ghana, 2008	N'tow [120]	115	44.8±4.2	8.0±1.0	31.4±4.5	78.3±7.0
South Africa, 2008	Okonkwo [124]	30	1.13-850*	LOD - 480	LOD - 730	NA
Ivory Coast, 2009	Alle [133]	40	NA	NA	NA	61(LOD-68.4)**
Tunisia, 2010	Hassine [134]	36	508,7±570.1	218.1±363.5	437.2±519,9	1163.9±1005

Values are expressed in ng/g of breast milk lipid weight, as mean ±% relative standard deviation; Values on the same row are expressed as: *Range; ** Mean (95th CI); ♣ Range of region's means. LOD: Limit of Detection.

Table 4. Concentrations of other Organochlorine Pesticides in Breast Milk in African Countries.

Countries Year	Authors (Reference)	N	βHCH	Lindane	ΣHCH	HCB	Dieldrine	Heptachlore Epoxide	Endosulfan
Kenya, 1998	Kinyamu [127]	216	83±26	18±5	NA	NA	19±3	NA	NA
Ghana, 2001	N'tow [106]	20	NA	NA	NA	40±20	NA	NA	NA
Zimbabwe, 2002	Chikuni [125]	28	45.7-952♣	5.1-514	6.6-1887	NA	NA	NA	NA
Tunisia, 2007	Ennaceur [131]	87	50±2210	NA	67±2090	260±1710	59±1920	NA	NA
Ghana, 2008	N'tow [120]	115	14± 2.3	NA	46.4±5.5	4.9±0.3	112.8±24.8	NA	NA
Ivory Coast, 2009	Alle [133]	40	NA	5 (LOD-68)*	19 (LOD-24.6)	NA	43 (LOD-20.4)	6 (LOD-11.4)	2 (LOD-4.4)
Tunisia, 2010	Hassine [134]	36	39,7±43	36,5±32	76,2±62,28	286,8±272,6	9,1±13,9	NA	NA

Values are expressed in ng/g of lipid weight, as mean ±%RSD relative standard deviation. Values on the same row are expressed as: *Mean (Range); ♣ Range of region's means; LOD: Limit of Detection.

51%, 63% and 94% for aldrin, chlordane and heptachlor when exposed for 100 days or longer [152]. In subjects who consumed contaminated fish in polluted rivers, the risk of diabetes increased by 2.37 times or more [153, 154]. In the general population, studies conducted in Sweden, Korea, USA and other countries showed that the risk of diabetes was also strongly associated with exposure to organochlorine pesticides [138, 139, 143, 155-157]. Moreover, quite low levels of exposure were found to be associated with diabetes [139, 157-159]. In subjects who did not develop diabetes, exposure to organochlorine pesticides was associated with metabolic disturbances such as overall or abdominal obesity, dyslipidemia, insulin resistance and the metabolic syndrome, which are well known risk factor for type II diabetes. These metabolic effects were also observed in subjects who developed diabetes [91, 140, 156-158, 160-164]. Such metabolic dysfunctions may not only lead to diabetes but also to hypertension and cardiovascular diseases [165, 166].

Although the mechanisms linking pesticide exposure to diabetes are not fully elucidated, it is known that organochlorine pesticides, at low doses, act as endocrine disruptors over time [139, 157, 167]. Persistent organochlorine pesticides and their metabolites accumulate in adipose tissue and are gradually released into the bloodstream where they mimic or block cellular receptors and hormones. They reduce insulin sensitivity by mimicking estrogen receptors present in insulin-sensitive tissues and β cells of the pancreas [168]. In addition, most individuals are generally exposed simultaneously to various pesticides. This multiple exposure may increase the risk of developing diabetes because the effects of these pesticides may be additive or synergistic, and sometimes conflicting. These findings were confirmed by *in vitro* and animal studies showing that pesticides were related to disturbances in carbohydrate and lipid metabolism [169, 170-171]. The pesticides alter adipocyte differentiation, the functioning of mitochondria and Langherhans β cells, inducing insulin resistance [160, 172, 173]. Although the causal mechanism is not yet identified, there are several lines of evidence for a relationship between pesticide exposure, particularly organochlorines, and diabetes. Few studies have focused on organophosphates, carbamates and herbicides, and available data show inconsistent associations with diabetes [152, 160].

A recent review has confirmed the strong positive association of pesticides, particularly organochlorines pesticides, with diabetes although more experimental data are needed to establish the causality [174]. For pyrethroids, data are also scanty but frequent and regular exposure to low doses of these pesticides seems to induce abnormal glucose tolerance [175]. Organophosphosphates are also associated with glucose intolerance and insulin resistance [174, 176]. For rodenticides, some studies showed an association between exposure to Vacor and type 1 diabetes [177-182]. Very little data currently exist on fungicides [183]. Even if they are scarce, organic pollutants are consistently linked to type 1 diabetes through exacerbating autoimmunity [141, 184-186].

In summary, exposure to pesticides such as organochlorines may increase the risk of diabetes. Although there are no published studies on the relationship between diabetes and pesticides in SSA, there is every reason to believe that this association observed elsewhere also holds in SSA where inappropriate use of pesticides has been widely documented.

DOES EXPOSURE TO PESTICIDES CONTRIBUTE TO THE INCREASED RISK OF DIABETES IN SSA?

The particularly rapid progression of diabetes in SSA when compared to other regions of the world could plausibly be associated with greater exposure to pesticides and other persistent organic pollutants (see Tables **1** to **6**), in addition to other known risk factors such as nutrition and demographic transitions, malnutrition in early life, obesity and genetic predisposition. More importantly, all these factors predisposing to an increased risk of diabetes may have an intergenerational impact through epigenetic phenomena and birth defects [187].

Contamination of mothers during pregnancy entails children's exposure to pesticides and their metabolites very early in life through the placenta [188]. Moreover, children's exposure may continue through breastfeeding, complementary feeding and interaction with the environment. This early exposure during perinatal and infant periods may increase the risk of obesity [189] and early diabetes [141].

On the one hand, the nutrition transition, which entails a shift from traditional diets to a more westernized diet, is an important contributor to chronic disease development. On the other hand, fetal programming resulting from maternal malnutrition as well as early childhood malnutrition in combination with the effect of pesticide exposure [188] may contribute to early onset of diabetes and the rapid progression of the disease in SSA [189, 190]. The effect of chemical pollutant exposure during the prenatal and perinatal periods has been found to be detrimental to the offspring of exposed mothers [191-193]. Exposition to chemical pollutants early in life is considered as a risk factor for obesity [187, 194] and for diabetes through their abnormal programming effects as endocrine disruptors [195-197]. During pregnancy, pesticides interfere with pregnancy hormones and increase the risk of gestational diabetes. Indeed, several studies have shown that women exposed to pesticides or other pollutants tend to develop gestational diabetes and their offspring to develop early obesity and diabetes [194, 195, 198, 199]. Children are also considered more vulnerable to pesticides than adults because there are still in the growing process [182]. They are at greater risk of exposure of their digestive tract than adults through contaminated food and various objects in their environment that they put in their mouth. They are also more likely to be exposed to pesticides in play grounds [200]. In addition, it is currently hypothesized that exposure early in life to neurotoxicant pesticides such as organophosphates could later contribute to subconscious preference for high fat diets that promote obesity and diabetes [201]. In short, the evidence for the contribution of pesticides to the developmental origins of chronic diseases such as diabetes is increasing due to the detrimental effects of these endocrine disruptors on the development and functioning of the organs during prenatal and perinatal life [195]. Under the unfavorable nutritional and environmental conditions commonly observed in SSA, it can be contented that the risk is higher than that reported in developed countries. An increasing burden of diabetes in SSA could be the result

of adverse developmental effects of pollutants, combined with those of malnutrition, as suggested by Heindel and al [175].

It is possible that the use of pesticides in SSA could be associated with lower micronutrient content or bioavailability in food, thereby contributing to malnutrition which may itself increase the vulnerability to pollutants [189]. Although controversial, several authors argue that food derived from organic agriculture contain higher amounts of some micronutrients such as vitamin C, iron, magnesium, phosphorus, polyphenols such as flavonol, and carotenoids such as lycopene, than foods derived from conventional agriculture with the use of pesticides [202]. While it has not yet been proven that organic foods have positive effects on health, foods from conventional agriculture contain secondary pesticide metabolites that may delay growth or else reduce the bioavailability of micronutrients [203]. Some authors contend that variations in food levels of certain antioxidants and minerals are ascribable to differences in methods of fertilization, protection and conservation [202, 204-206].

The African genotype appears prone to diabetes [207-209]. Additionally, gene variants that modulate insulin action (but not insulin secretion) are affected by obesity and hence type 2 diabetes susceptibility is increased [208, 209]. This risk may be exacerbated by pesticides and other environmental pollutants [210]. Exposure to pesticides during the perinatal period may exacerbate epigenetic changes that cause metabolic disturbances (obesity and insulin resistance), which might in turn lead to diabetes later in life [182, 211]. While these factors exist in other countries, they are not as critical as in SSA. Developing countries such as India and China roughly had a similar burden of diabetes as SSA [212, 213]. However, despite major prevention and management of diabetes in these countries, the progression of diabetes barely slowed because of the strong genetic predisposition, levels of pesticide exposure and susceptibility to these environmental insults [214].

CONCLUSION

In addition to transitional factors inducing obesogenic lifestyles, we must now consider malnutrition and exposure to environmental pollutants as factors that might impact on future generations' health and increase the burden of diabetes in SSA. The protection of mothers and children should be a key strategy to halt the progression of diabetes in this continent. The promotion of sustainable food production systems in a healthier environment may contribute to a lower risk for developing diabetes. The use of biological pesticides should be given more emphasis. The reduction of maternal and child malnutrition as well as the promotion of healthy lifestyles could also foster a better future for next generations. More research is needed in SSA on the environmental risk factors for chronic disease. In order to contribute to generating evidence, an original study was recently launched in West Africa to explore the relationship between exposure to organochlorine pesticides and the risk of type II diabetes.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ABBREVIATIONS

AIDS	=	Acquired Immunodeficiency Syndrome
BDSP	=	Banque de données de Santé Publique
DDT	=	Dichlorodiphenyltrichloroethane
IDF	=	International Diabetes Federation
HIV	=	Human Immunodeficiency Virus
MRL	=	Maximum Residue Limit
NCDs	=	Non communicable Diseases
ng/g	=	nanogram per gram
POCs	=	Pesticides Organochlorine
POPs	=	Persistent organic Pollutants
SSA	=	Sub-saharan Africa
STEPS	=	STEPwise approach to surveillance
TCDD	=	Tétrachlorodibenzo-p-dioxine
USA	=	United State of America
WHO	=	World Health Organisation

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