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## Review article

## Sudden deaths in infancy and pesticide exposure: A systematic review



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## ABSTRACT

Sudden unexpected deaths in infancy (SUDI) is defined as the unexpected death of an infant in the first year of life, including explained and unexplained death (SIDS). Risk factors, such as sleeping position and passive smoking, have been identified but few studies have addressed the influence of exposure to chemicals in the environment. Pesticides are ubiquitous but little is known about their impact on infant mortality.

We conducted a systematic review of studies on SUDI and pesticide exposure present in the MEDLINE database in March 2024. We included epidemiological and toxicological studies on humans. We identified 92 studies in total, 17 of which were included in the analysis. Biases were assessed qualitatively and with the NTP/OHAT evaluation process.

Epidemiological studies reported various results. Three studies found an association between SIDS and parental occupational exposure. Conflicting results were obtained in studies of domestic exposure, with half the studies showing no association. One accidental massive exposure to insecticides was associated with an increase in infant mortality. Several studies detected pesticides in brain samples from cases of SIDS, demonstrating exposure to organochlorine and organophosphate, and passage across the blood-brain barrier.

Many of these studies were quite old and may therefore not be representative of current exposure levels. Case-control studies may be associated with recall bias or measurement errors.

It is not possible to establish a clear association between SUDI and pesticide exposure from our findings. Further epidemiological studies are required. Studies on sudden perinatal deaths with universal definitions would be helpful.

## 1. Introduction

Sudden unexpected deaths in infancy (SUDI) is defined as the unexpected death of an infant before the age of one year (Blair et al., 2012; Krous et al., 2004). Deaths that remain unexplained after post-mortem investigations meet the definition of sudden infant death syndrome (SIDS) (Krous et al., 2004). The principal risk factors for SIDS identified to date are sleeping environment, exposure to tobacco smoke in utero or the environment, and preterm birth (Carlin and Moon, 2017; Vincent et al., 2023). Little is known about the etiology and mechanisms leading

to SIDS other than the involvement of these factors, but the sudden and unexpected nature of the death, and temporal and geographic variations point to environmental factors (Mitchell et al., 2020; de Visme et al., 2020; Shapiro-Mendoza et al., 2023).

A “triple-risk model” for SIDS has been hypothesized, with 1) a critical period of development (most cases of SIDS occur in the first six months), 2) intrinsic factors rendering the infant susceptible to SIDS, such as prenatal exposure to tobacco smoke, preterm birth, intrauterine growth retardation and genetic factors, and 3) exogenous factors triggering SIDS, such as a prone sleeping position, soft bedding, the

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presence of tobacco smoke in the environment and respiratory infections (Filiano and Kinney, 1994; Goldberg et al., 2018).

Exposure to environmental chemicals was not explicitly mentioned in the original version of the triple-risk model, but such exposure could potentially act as both a source of vulnerability and as a trigger for SIDS. There is growing evidence to suggest a possible association between exposure to environmental factors and SIDS, including studies on air pollution and ambient heat (Auger et al., 2015; Chen et al., 2021; Son et al., 2017).

Pesticides are of particular interest, as they are widely used and present everywhere, with many sources of exposure in the home (food, air, dust, etc.), workplace (agriculture, industry, etc.), and in public areas (ANSES. Exposition de la population, 2010; ANSES, 2020; Inserm, 2021). Pesticides are a major public health issue and are a matter of great concern to governments and the general public alike (Inserm, 2021). Studies on pesticides and their effects on health have revealed a specific risk during the perinatal period. Several pesticides have been associated with miscarriage, spontaneous abortion, perinatal death, preterm birth, intrauterine growth restriction, congenital malformations, and early childhood cancers (Pascale and Laborde, 2020). Pesticide exposure can also lead to adverse neurodevelopmental outcomes, including pervasive development disorder, attention problems, attention deficit hyperactivity disorder, altered behavioral development, and autism spectrum disorders (Muñoz-Quezada et al., 2013; Viel et al., 2017; Roberts et al., 2019; Vrijheid et al., 2016). However, there have been few studies on the potential contribution of pesticides to infant deaths. In this review, we provide an overview of the studies that have focused on the relationship between pesticide exposure and SUDI/SIDS.

## 2. Methods

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). We queried the Medline database in March 2024, with the following search algorithm: *("Sudden Infant Death"[MESH] OR "Sudden Infant Death"[TIAB] OR "SIDS"[TIAB] OR ("neonatal"[TIAB] OR "newborn"[TIAB] OR "perinatal"[TIAB]) AND "death"[TIAB]) AND ("Pesticides"[MESH] OR "pesticide"[TIAB])*.

We also tested the inclusion of the following terms in the algorithm, but none of these terms identified any additional publications: "insecticide", "herbicide", "fungicide", "organochlorine", "neonicotinoid", "organophosphate", "pyrethroid" and "carbamate".

We restricted the selection of studies to toxicological and epidemiological studies on humans. We excluded studies performed on animals or *in vitro*, reviews and meta-analyses, studies in languages other than English or French, and inaccessible or out-of-scope studies. Due to a lack of published articles on SUDI/SIDS and pesticides, we included studies on perinatal death and stillbirth that also addressed the death of liveborn infants (often identified as neonatal deaths).

The characteristics and results of the studies were extracted and summarized by EB (Table 1). RB and DB were consulted if arbitration was required in the synthetic analysis and interpretation of results. Bias was first assessed with a qualitative method without a specific score, to increase exhaustively. We then used the NTP/OHAT bias assessment process to identify risks of bias that appeared to be adapted to environmental health (supplementary materials)(Cano-Sancho and Antignac, 2023; National Toxicology Program, 2019). This assessment makes it possible to identify risk levels, and to classify studies into three tiers. The tier 1 corresponds to definitely low or probably low risk of bias. Tier 3 corresponds to definitely high or probably high risk of bias. Tier 2 includes studies which meet neither criterion for tier 1 or 3. Biases were assessed by EB and RB.

## 3. Results

The algorithm identified 92 studies, 68 of which were excluded on

the basis of their title or abstract: 33 studies performed in animals or *in vitro* studies, 14 reviews, 1 article published in a language other than French or English, and 20 articles that were out of scope. Another seven studies were excluded because the full-text analyses showed that they were out of scope. We therefore retained 17 studies for the final literature review. The flowchart for study selection is shown in Fig. 1. The characteristics and principal findings of the studies are presented in Table 1.

### 3.1. Characteristics of the studies

Only five of the 17 studies analyzed were published less than 10 years before the writing of this review (Roncati et al., 2016; Termopoli et al., 2015; Lavezzi et al., 2015a, 2015b; Capiello et al., 2014). One study was published between 2004 and 2014 (Mytton et al., 2007), and 11 studies were published before 2004 (Kleemann et al., 1991; Kristensen et al., 1997; Dimich-Ward et al., 1996; Zhang et al., 1992; Rupa et al., 1991; Schreinemachers, 2003; Wasley et al., 2002; Rylander and Hagmar, 1999; Taha and Gray, 1993; Pastore et al., 1997; Varma, 1987).

The studies were conducted principally in Italy ( $n = 5$ ) (Roncati et al., 2016; Termopoli et al., 2015; Lavezzi et al., 2015a, 2015b; Capiello et al., 2014), the USA ( $n = 3$ ) (Schreinemachers, 2003; Wasley et al., 2002; Pastore et al., 1997), and India ( $n = 2$ ) (Rupa et al., 1991; Varma, 1987). Most of the Italian studies were based on data from post-mortem investigations of cases of SUDI. The remaining seven studies were conducted in Germany (Kleemann et al., 1991), Canada (Dimich-Ward et al., 1996), China (Zhang et al., 1992), Norway (Kristensen et al., 1997), Sudan (Taha and Gray, 1993), Sweden (Rylander and Hagmar, 1999), and Thailand (Mytton et al., 2007).

Six of the studies were case-control studies based principally on perinatal mortality data (Lavezzi et al., 2015a; Kleemann et al., 1991; Zhang et al., 1992; Wasley et al., 2002; Taha and Gray, 1993; Pastore et al., 1997); five were cohort studies, including one case-control-nested-in-cohort study (Mytton et al., 2007; Kristensen et al., 1997; Dimich-Ward et al., 1996; Rupa et al., 1991; Rylander and Hagmar, 1999); three of the studies were case series including bio-monitoring data (Roncati et al., 2016; Termopoli et al., 2015; Capiello et al., 2014); one was a cross-sectional study comparing perinatal mortality in a population before and after accidental exposure to insecticides (Varma, 1987); one study was an ecological study comparing perinatal deaths linked to congenital abnormalities and pesticide exposure between counties (Schreinemachers, 2003); and one study was a case report including a post-mortem investigation of SIDS with analyses of pesticide levels in brain tissue (Lavezzi et al., 2015b).

Six studies directly measured pesticide levels in biological samples collected during post-mortem investigations of SIDS (Roncati et al., 2016; Termopoli et al., 2015; Lavezzi et al., 2015a, 2015b; Capiello et al., 2014; Kleemann et al., 1991). Most studies used indirect methods to assess pesticide exposure. The authors assigned levels of exposure based on agricultural practices in the area or residence, including the amount of money spent on pesticides and pesticide spraying equipment (Kristensen et al., 1997), workstations (Rupa et al., 1991), the duration of daily occupational exposure (Dimich-Ward et al., 1996), the consumption of specific foods (Rylander and Hagmar, 1999), and the density of crops (Schreinemachers, 2003). Four studies estimated the pesticide exposure of a sample of the population (professional or domestic) based on questionnaires, interviews or healthcare records (Mytton et al., 2007; Zhang et al., 1992; Taha and Gray, 1993; Pastore et al., 1997). One study focused on a sample exposed to a massive accidental release of insecticides into the environment, comparing health problems before and after this accidental exposure (Varma, 1987). One study estimated indoor exposure by measuring pesticides in house dust collected with wipes (Wasley et al., 2002).

**Table 1**  
Description of the studies included.

Author, year (study location)	Study design	Inclusion period	Pollutants studied	Outcome	Size of study population	Exposure assessment	Findings	Exposure period
Varma, 1987 (India)	Cross-sectional	1985	Methyl isocyanate	Pregnancy outcomes, perinatal death	865 women pregnant at the time of the accident, resulting in 486 live births	Everyone was exposed to methyl isocyanate (Bhopal accident)	More perinatal deaths after the accident than 2 years before	Prenatal
Kleemann et al., 1991 (Germany)	Case-control	1986–1988	Persistent chlorohydrocarbons (OCP and PCB)	SIDS	46 SIDS fatty tissue and 17 control fatty tissue samples	Biomonitoring in subcutaneous samples (OC and PCB)	No difference between the rural and urban SIDS groups or between the urban and control groups. Concentrations of HCB, alpha and beta HCH and dieldrin were lower in the rural group than in the control group	Prenatal and postnatal
Rupa et al., 1991 (India)	Cohort	Not reported	OC, OP and PYR	Abortion, stillbirth, neonatal death, congenital defects and infertility	1016 exposed 1020 non-exposed	Directly exposed to pesticides at workstation	More neonatal deaths in the pesticide-exposed group	Prenatal
Zhang et al., 1992 (China)	Case-control	1986–1987	Radiation, chemicals, occupational noise and pesticides	Perinatal death and birth defects	1875 cases with birth defects or perinatal death and 187 controls	Interviews	Greater risk of early neonatal death, antepartum fetal death and birth defects in cases of chemical exposure. No association with pesticides	Prenatal
Taha and Gray, 1993 (Sudan)	Case-control	1989–1990	Pesticides	Stillbirth, early neonatal death	197 cases and 812 hospital controls. 36 cases and 1505 community controls.	Questionnaires and interviews about occupational and domestic exposure to pesticides	More use of pesticide (domestic and agricultural) declared by parents of infants who died (stillbirth/early neonatal death)	Prenatal
Dimich-Ward et al., 1996 (Canada)	Cohort	1952–1988	Chlorophenate	Late-term abortion, stillbirth, early neonatal death	19,675 births to sawmill workers	Estimated number of hours spent at an exposed workstation	No association between pesticide exposure and neonatal death	Prenatal
Kristensen et al., 1997 (Norway)	Cohort	1967–1991	Pesticides	Gestational age, perinatal death, and birth weight	192,417 births to farmers and 61,351 to nonfarmers	Exposed: farmers Non-exposed: other parents Exposure estimated by money spent on pesticide and spraying equipment	No difference in perinatal death rates between farmers and non-farmers. More late-term abortions in farmers	Prenatal
Pastore et al., 1997 (USA)	Case-control	1984	Pesticides	Stillbirth, neonatal death	332 cases and 357 controls	Questionnaires about proximity to crops, domestic and occupational exposure to pesticides	Association between occupational exposure of the mother to pesticide and stillbirth and between domestic exposure of the mother and stillbirth due to congenital abnormalities	Prenatal
Rylander and Hagmar, 1999 (Sweden)	Cohort	1973–1991	OC	Stillbirth, early neonatal death, malformations	5054 infants from two cohorts of fishermen	Exposed: fishermen's families	No association between exposure and neonatal death	Prenatal
Wasley et al., 2002 (USA)	Case-control	1990–1994	Methyl parathion (MP)	SIDS	34 cases and 73 controls	Environmental samples collected from homes	No association found between MP concentration and SIDS	Prenatal and postnatal

(continued on next page)

Table 1 (continued)

Author, year (study location)	Study design	Inclusion period	Pollutants studied	Outcome	Size of study population	Exposure assessment	Findings	Exposure period
Schreinemachers, 2003 (USA)	Ecological	1995–1997	Chlorophenoxy herbicides	Malformations, small for gestational age, infant death from congenital malformations	74 exposed counties and 73 non-exposed counties	Exposed: counties with high proportions of land under wheat	Increase in the risk of death from congenital malformation for exposed infants	Prenatal and postnatal
Mytton et al., 2007 (Thailand)	Case-control nested in cohort	1993–2006	Benzyl benzoate lotion (BBL), permethrin	Stillbirth, neonatal death	445 exposed to BBL, 200 exposed to permethrin, 2618 control	Medical register of treatment with BBL or permethrin	No association between exposure to BBL and stillbirth/neonatal death. Insufficient data for permethrin	Prenatal
Cappiello et al., 2014 (Italy)	Case series	2011–2013	OC, OP, carbamates and phenols	SIUDS and SIDS	5 liver samples (3 SIDS and 2 SIUDS) and 5 brain samples (3 SIDS and 2 SIUDS)	Biomonitoring in brain and liver samples	Presence of OC in 2 SIDS brain samples, 1 SIUDS brain sample and 1 SIUDS liver sample	Prenatal and postnatal
Lavezzi et al., 2015a (Italy)	Case-control	Not specified	OC, OP, carbamates and phenols	Cases: SIDS, SIUDS. Controls: chorioamnionitis and congenital heart diseases (for SIUDS), bronchopneumonia, congenital heart diseases and pericarditis (for SIDS)	14 SIUDS, 9 fetuses control, 14 SIDS, 8 infant control	Biomonitoring in brain samples	Presence of pesticide in brain samples of 9 SIUDS, 1 fetus control, 3 SIDS	Prenatal and postnatal
Lavezzi et al., 2015b (Italy)	Case report	Not reported	2,6-ditert-butyl-4-nitrophenol (DBNP)	SIDS	1 7-month-old infant who died in her sleep	Biomonitoring in brain sample	Concentration of DBNP in brain sample and use of insecticide during the 2 weeks before death. Death not identified as SIDS after investigation	Prenatal and postnatal
Termopoli et al., 2015 (Italy)	Case series	2012–2014	OC and OP	SIUDS and SIDS	10 SIUDS and 4 SIDS	Biomonitoring in brain samples	Concentration of OC and OP in 2 SIDS and 6 SIUDS samples	Prenatal and postnatal
Roncati et al., 2016 (Italy)	Case series	2015	OC and OP	SIUDS and SIDS	27 SIUDS and 8 SIDS	Biomonitoring in brain samples	Concentration of OC and OP in 3 SIDS and 7 SIUDS samples	Prenatal and postnatal

SIDS: sudden infant death syndrome.

SIUDS: sudden intrauterine unexpected death syndrome.

OC: organochlorine; OP: organophosphate; OCP: organochlorine pesticide; PCB: polychlorinated biphenyls; PYR: pyrethroid.

### 3.2. Internal exposure (biomonitoring)

Two case-control studies compared pesticide concentrations in biological samples from infants who died from SIDS and control infants (Lavezzi et al., 2015a; Kleemann et al., 1991). The first study detected pesticides in three of the 14 brains in the SIDS group, including chlorpyrifos in two cases, and heptachlor,  $\gamma$ -chlordane,  $\alpha$ -chlordane, and p,p-DDE in one case each. No pesticides were detected in any of the eight control brains. This difference was statistically significant ( $p < 0.05$ ) (Lavezzi et al., 2015a). The second study analyzed subcutaneous fatty tissue from SIDS subjects and control who died from other causes. This study focused on several organochlorine pesticides (hexachlorobenzene,  $\alpha$ -HCH,  $\beta$ -HCH,  $\gamma$ -HCH, HepE, dieldrin, DDT) and PCB concentrations. The concentrations of HCB, dieldrin,  $\alpha$ -HCH and  $\beta$ -HCH were lower ( $p = 0.05$ ) in the rural SIDS group ( $n = 21$ ) than in the control group ( $n = 17$ ). However, there was no significant difference between urban ( $n = 23$ ) and rural SIDS or between the urban SIDS group and the control group (Kleemann et al., 1991). Nevertheless, the control group may not reflect a representative general population. Using a control group to compare to a dead group without significant knowledge on mechanisms makes it difficult to select appropriate control and may limit the ability to detect associations.

Three descriptive studies found pesticides in brain tissues from SIDS cases (Roncati et al., 2016; Termopoli et al., 2015; Cappiello et al., 2014). One study detected  $\alpha$ -chlordane,  $\gamma$ -chlordane, heptachlor, p,p'-dichlorodiphenyldichloroethylene (DDE), p,p'-dichlorodiphenyltri chloroethane (DDT), chlorfenvinfos, and chlorpyrifos in seven of 27 cases of sudden intrauterine unexplained death syndrome (SIUDS) and three of eight cortex samples from SIDS cases (Roncati et al., 2016). Termopoli et al. detected pesticides in six of ten brain samples from SIUDS cases and two of four brain samples from SIDS cases. The pesticides detected included DDE, chlorpyrifos, chlorfenvinfos, methoxychlor and  $\beta$ -endosulfan. The principal pesticides present in SIDS samples were  $\beta$ -endosulfan and chlorpyrifos (Termopoli et al., 2015). One study detected endrin and p,p'-DDE in one of two liver samples from SIUDS cases and  $\gamma$ -chlordane and  $\alpha$ -chlordane in one of two brain samples from SIUDS cases. Pesticides were also detected in two of the three SIDS brain samples:  $\alpha$ -chlordane and  $\gamma$ -chlordane in two cases, and heptachlor in one case (Cappiello et al., 2014). The principal pesticides present in the brain sample of a male newborn that died within 1 h of birth were  $\gamma$ -chlordane and  $\alpha$ -chlordane (Cappiello et al., 2014). However, these pesticides — particularly organochlorines — are ubiquitous, and these studies did not include controls. It is not possible to conclude from these results whether organochlorine compounds were found specifically in

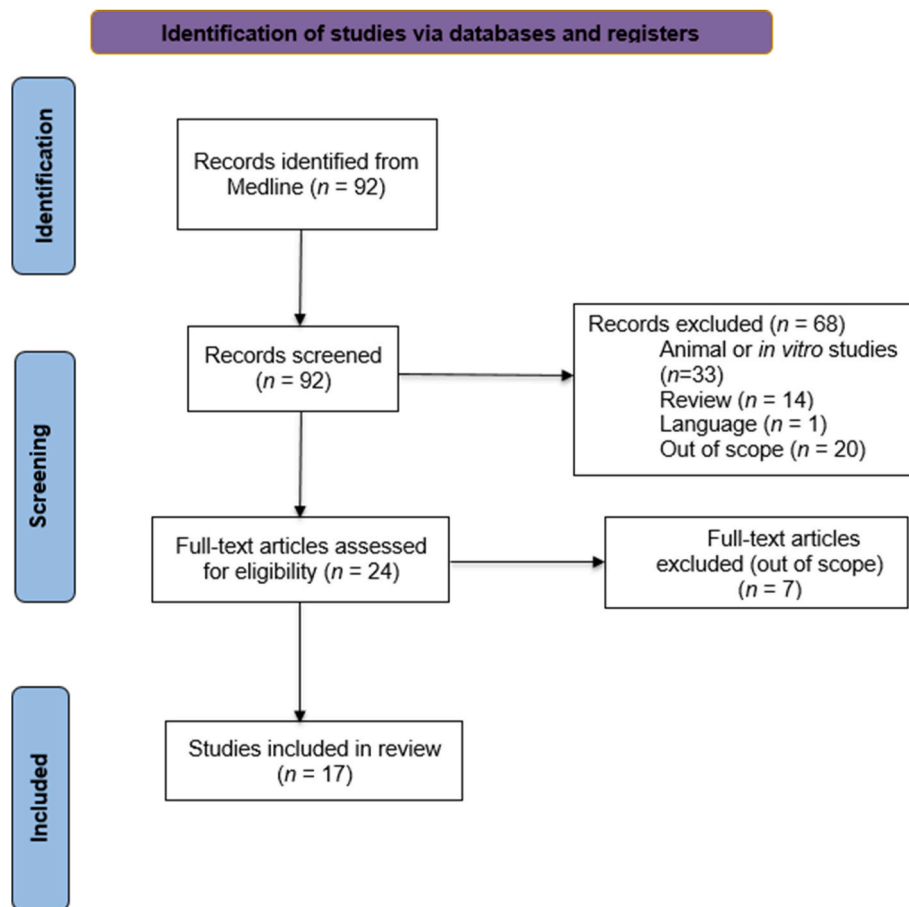


Fig. 1. Flowchart of study inclusions (PRISMA (Page et al., 2021)), records identified in March 2024.

SIDS cases or whether the concentrations detected correspond to the level of exposure of the general population.

### 3.3. Occupational exposure

Four studies focused on occupational exposure to pesticides (Dimich-Ward et al., 1996; Zhang et al., 1992; Rupa et al., 1991; Pastore et al., 1997). One of these studies found no association between occupational exposure to pesticides and perinatal death (Dimich-Ward et al., 1996). However, the authors focused on the father's exposure — defined as the duration of exposure per working day — without providing details of the active ingredient or pesticide class. The strategies used to assess exposure may have led to non-differential misclassification and a dilution of the effect.

One study found an association between self-reported (questionnaire) parental occupational exposure to chemical products in general and early neonatal death. Pesticides were included in the definition of exposure, but the authors did not present specific associations with pesticides (Zhang et al., 1992). Two studies reported an association between parental occupational exposure to pesticides and perinatal death, with the father's exposure taken into account in one study and the mother's exposure in the other (Rupa et al., 1991; Pastore et al., 1997). The first study found more neonatal deaths and stillbirths in the exposed group than in the control group ( $p < 0.05$ ); levels of exposure to specific pesticides were not detailed, but the authors assumed that workers were exposed to different organochlorine, organophosphate and pyrethroid pesticides (Rupa et al., 1991). The second study found a higher risk of stillbirth for mothers occupationally exposed during pregnancy, with risk ratios of 1.4 and 1.3 ( $p < 0.05$ ) for one month of exposure during the first and second trimesters, respectively, and risk ratios of 2.7 and 2.4 ( $p$

$< 0.05$ ) for three months of exposure during the first and second trimesters, respectively (Pastore et al., 1997). However, these two studies did not specifically focus on SIDS. The first defined neonatal death as infant death within the first 28 days (Rupa et al., 1991), and the second included all deaths between 20 weeks of amenorrhea and 24 h of life (Pastore et al., 1997).

Regarding these three studies (Zhang et al., 1992; Rupa et al., 1991; Pastore et al., 1997), it is not possible to exclude the presence of a recall bias that might lead to the overestimation of exposure in the case groups.

### 3.4. Domestic exposure

Eight studies have considered the effect of domestic pesticide exposure (Lavezzi et al., 2015b; Mytton et al., 2007; Kristensen et al., 1997; Schreinemachers, 2003; Wasley et al., 2002; Rylander and Hagmar, 1999; Taha and Gray, 1993; Pastore et al., 1997). Three studies used proximity to crops as a proxy for pesticide exposure (Kristensen et al., 1997; Schreinemachers, 2003; Pastore et al., 1997). One study found that the risk of infant death from congenital malformations was highest in the areas with the highest proportion of land under wheat cultivation (Schreinemachers, 2003). The authors assumed that wheat cultivation was associated with the use of chlorophenoxy herbicides, but the real levels of pesticide use were unknown, and many other pesticides may also have been used on the cereal crops. Other important data, such as socio-economic status, were not considered. Another study used the presence of crops close to homes (within 0.25 miles, or between 0.25 miles and 1 mile) to assess exposure to agricultural pesticides. No significant difference was found between the 332 cases (stillbirths or neonatal deaths) and the 357 controls (living children) in terms of the presence or absence of crops close to the family home (Pastore et al.,



1997). Only the presence or absence of crops in the neighborhood was considered. Crop type, acreage and pesticide use were not analyzed, probably resulting in exposure misclassification. Furthermore, the study lacked statistical power. The third study found no association between pesticide exposure in Norwegian farmers and perinatal mortality. The authors defined exposure based on agricultural practices in the area of residence, including the amount of money spent on pesticides and pesticide spraying equipment, but did not consider pesticide use practices or changes in agricultural practices over the three decades studied (Kristensen et al., 1997).

One study found no association between the concentration of methyl parathion on surfaces in the home and SIDS (OR 13.0; 95% CI: 0.2–2685). This study may have lacked statistical power (only 39 cases), and samples were collected a few years after the death of the infant, so misclassification was possible (Wasley et al., 2002). A Swedish study found no increase in the risk of neonatal death due to dietary exposure to organochlorine compounds (including pesticides). Exposure assessments were based on the father's occupation. The authors assumed that the families of fishermen consumed a lot of fish and that fish consumption was associated with exposure to organochlorines, but performed no biological analyses or questionnaires to confirm that this was the case (Rylander and Hagmar, 1999). Another study found no increase in the risk of stillbirth or neonatal death associated with domestic pesticide use during pregnancy. Exposure assessment was based on a questionnaire completed for 332 cases and 357 controls that did not specify the type of pesticide (Pastore et al., 1997). A study conducted in Sudan revealed an association between stillbirth and pesticide exposure in a hospital population (OR 1.9; 95% CI 1.3–2.8) (Taha and Gray, 1993). A similar association between perinatal deaths and pesticide exposure was also found in the non-hospitalized population (OR 2.7; 95% CI 1.1–6.4). Exposures were estimated retrospectively and there may, therefore, have been a recall bias. Furthermore, the quantity, period of application, and types of pesticide were not known (Taha and Gray, 1993).

Some pesticides also have clinical uses to treat various diseases. One study in Thailand focused on the use of benzyl benzoate to treat scabies but found no association with stillbirths or neonatal mortality (Mytton et al., 2007).

In one case report, 2,6-ditert-butyl-4-nitrophenol (DBNP) was detected in the brain tissues of an infant presenting lesions of the postrema area who died at the age of seven months. A post-mortem investigation was performed, during which the parents reported having used an insecticide for two weeks prior to the death of the infant. However, the authors did not specify whether the insecticide used effectively contained DBNP (Lavezzi et al., 2015b).

### 3.5. Other exposures

An increase in perinatal mortality during the first month of life was observed after the Bhopal incident in India, which resulted in massive exposure to methyl isocyanate (an insecticide). The proportion of deaths occurring during the first 30 days after birth was 14.2% after exposure, whereas it had been only 2.6–3% two years earlier (Varma, 1987).

## 4. Discussion

It is not possible, based on the data considered in this review, to conclude with confidence that there is a link between pesticide exposure and SIDS, due to the lack of robust studies of sufficient size. Nevertheless, the detection of organochlorine and organophosphate pesticides in the brains of infants dying from SIDS and the associations reported in certain studies between parental occupational exposure and infant death raise questions. We used only the MEDLINE database for this review. The inclusion of other databases might lead to the inclusion of extra studies.

Based on the available evidence of the broad effects of pesticide

exposure on development, we considered the potential neurotoxic effects of pesticides that might contribute to SIDS. Pesticide exposure may be associated with several perinatal outcomes. Studies have shown a higher risk of fetal death in cases of pesticide exposure (Inserm, 2013). Adverse birth outcomes, such as preterm birth and low birth weights and heights, have also been observed in cases of pesticide exposure (Pascale and Laborde, 2020; Inserm, 2013; Chevrier and Béranger, 2018; Roberts et al., 2012). Pesticide exposure has also been reported to be associated with a higher risk of congenital malformations, spontaneous abortion and intrauterine growth restriction (Pascale and Laborde, 2020; Inserm, 2013; Chevrier and Béranger, 2018; Roberts et al., 2012). These associations demonstrate the developmental toxicity of pesticides and support the hypothesis of an impact on neonatal mortality.

The concentrations of pesticides found in brain samples from SIDS victims highlight the passage of pesticides across the blood-brain barrier, raising questions about their possible neurotoxicity (Roncati et al., 2016; Termopoli et al., 2015; Lavezzi et al., 2015a, 2015b; Capiello et al., 2014). Studies focusing on SIDS have reported decreases in the levels of key enzymes, such as acetylcholinesterase, butyrylcholinesterase and choline-acetyltransferase, together with an increase in oxidative stress levels (Dick and Ford, 1992; Harrington et al., 2022; Joda et al., 2023; Aldridge et al., 2024). These biochemical alterations might impair the regulatory control of the brainstem over vital functions (Harrington et al., 2022; Mehboob et al., 2017). The brainstem plays a key role in respiratory rhythm and the sleep-wake cycle. Alterations to brainstem activity may, therefore, decrease the ability to respond to asphyxia, resulting in a particular vulnerability in infants (Mehboob et al., 2017). In addition, Wasley et al. hypothesis that baseline levels of acetylcholinesterase and plasma pseudocholinesterase activity are lower in infants, based on Ecobichon and Stephens study from 1973, suggesting a greater vulnerability of infants than of adults (Wasley et al., 2002; Ecobichon and Stephens, 1973). Lavezzi et al. found that organophosphate and organochlorine compounds had similar effects on  $\alpha 7$ -nAChRs to nicotine that were associated with developmental changes to the brainstem in SIUDS and SIDS cases (Lavezzi et al., 2015a). For example, exposure to organophosphate is known to inhibit acetylcholinesterase (Martin-Romera et al., 2024), leading to the stimulation of muscarinic and nicotinic receptors. This stimulation can manifest as central apnea, excessive salivation, rhinorrhoea, bradycardia, bronchoconstriction and alveolar edema (Aroniadou-Anderjaska et al., 2023). Pesticides, such as organochlorines, pyrethroids and neonicotinoids, may also be associated with central nervous system damage, an increase in oxidative stress, dopaminergic dysfunction, mitochondrial dysfunction or acetylcholinesterase inhibition (Kimura-Kuroda et al., 2012; Richardson et al., 2019; Mohammadi et al., 2019). Associations have been established between pesticide exposure and several neuropsychological development disorders in children, including impaired motor and cognitive abilities, internalized behavioral disorders, and behavioral traits related to autism spectrum disorders (Inserm, 2021).

Given the complex nature of the toxic mechanisms discussed above, accurate assessments of exposure are crucial for the validation of these findings. Differences in exposure assessment strategies and precision between studies make it impossible to draw definitive conclusions. Some exposure assessments were based on agricultural practice in the area around the family home (including sales data for pesticides and spraying equipment), parental job title, or raw questionnaire data, resulting in a low precision for the exposure variable. These estimates were not suitable for use in dose-response analysis, and could not be used to identify specific pesticide molecules or families associated with a higher risk of SIDS. The use of questionnaires in case-control studies might induce a recall bias leading to spurious associations. Such bias is very likely in cases of SIDS, which have a strong psychological impact on the parents and the unexplained nature of which can lead to the parents asking themselves many questions. It could involve both dilution effects and spurious associations. Bias was assessed in the NTP/OHAT process.

Mainly due to the imprecision of the exposure assessment, all the studies were classified in the second tier, indicating a risk of bias limiting the possibility of drawing conclusions (supplementary materials).

Most of the studies included in this review were conducted over two decades ago. Changes in agricultural practices, pesticide use and legislation over the intervening period may restrict the applicability of these results to current conditions. Some compounds, such as organochlorine compounds, persist in the environment for at least a dozen years or so, or even longer if still on the market, whereas others are no longer present in the environment and are, therefore, not among the chemicals to which children are currently exposed.

The different definitions of SIDS and related terms used complicate efforts to summarize and compare research findings, particularly in studies assessing the impact of environmental factors such as pesticides. SIDS should be considered as a syndrome and not as a specific and unique cause of death. SIDS probably includes several diseases and cause of death, sometimes identified as SUDI. We assume that environmental exposure might involve different types of SUDI: it would be more appropriate to consider SIDS as a syndrome sharing environmental mechanisms with SUDI. Several of the studies included in this review grouped together stillbirth and neonatal death under the umbrella term "perinatal death". In addition, these studies defined neonatal death as death within the first few days or weeks of life, which does not correspond to the most widely used definition of SIDS. Indeed, the definition of SIDS or equivalent conditions differs between countries and between studies. Some of the definitions used include neonatal deaths with identified causes, whereas other studies have focused on idiopathic deaths without specifying SIDS. The definitions used in recent studies have been more standardized. For example, the USA and Italy seem to use the same definition — unexpected death in the first year of life — whereas France uses a definition covering deaths within the first two years of life. This heterogeneity is also probably related to differences in perception between research and clinical teams. SUDI includes both SIDS and cases of death for which possible explanations (malformations, infections, etc.) were found during the postmortem investigation. For the same etiology, depending on the quality and promptness of the diagnosis, a specific case might therefore be attributed to explained infant death (pre-mortem identification of the cause), SUDI (post-mortem identification) or SIDS (no identification). The classification of a case as SUDI or SIDS therefore depends on the protocol used for post-mortem investigations, and differences in analysis and technical practices. The use of a common international definition, classification and protocol would facilitate reflections and future etiological analyses. Nevertheless, with or without a common definition, the number of SIDS cases remains small, limiting statistical power. SIUDS, stillbirth and SIDS may involve similar pathophysiological mechanisms and may differ in timing by only a few hours or weeks. We recommend to consider of stillbirths, SIUDS, and SIDS together, under the umbrella term "sudden perinatal death" to generate new hypotheses on environmental factors (Mehboob et al., 2017).

## 5. Conclusion

This review highlights the need to refine investigations into SUDI and SIDS by exploring environmental etiologies. Some progress has been made towards harmonizing the definitions of SIUD and SIDS, but the establishment of an international standard definition would greatly facilitate the interpretation of future studies and enhance global research collaborations. The development of registries including medical and socioeconomic data alongside samples from autopsies and reliable exposure data would markedly improve studies focusing on environmental exposures. Various initiatives have made it possible to study SUDI and SIDS. For example, the French *Observatoire de la mort inattendue du nourrisson (OMIN)* has been collecting data and samples from cases of SUDI in France since 2015 (Ducloyer et al., 2024). The [International Society for the Study and Prevention of Perinatal and](#)

[Infant Death \(ISPID\)](#) is also working towards the development and promotion of measures for preventing stillbirth and SUDI ([International Society for the Study and Prevention of Perinatal and Infant Death](#)). Registries with a common definition and classification could be used to compare studies and to pool them together to increase statistical power. Moreover, it is essential to integrate the systematic collection of both occupational and domestic exposure data into postmortem investigations, and to do so in such a way that the parents do not feel stigmatized. Given the relatively low incidence of SIDS and the likelihood of its mechanisms being common to SIUDS and stillbirth, the consideration of these three conditions together in studies would greatly enhance statistical power and analytical depth.

Given the current scarcity of research linking SUDI/SIDS to pesticide exposure, it is not possible to use the available evidence to draw definitive conclusions regarding specific associations. There is a pressing need for larger, more comprehensive toxicological and epidemiological studies using recent data and more precise exposure assessment strategies. Research should focus on pesticides known to interfere with acetylcholinesterase, to stimulate nicotinic acetylcholine receptors, or to induce oxidative stress, due to their potential neurotoxic effects. Such focused studies will play a key role to improving our understanding of these conditions and developing effective strategies for preventing these tragic losses.

## CRedit authorship contribution statement

**Emmanuel Bourdet:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Christèle Gras-Le Guen:** Writing – review & editing, Conceptualization. **Karine Levieux:** Writing – review & editing, Conceptualization. **David Boels:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Rémi Béranger:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2024.120741>.

## Data availability

No data was used for the research described in the article.

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