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工作場所的生殖危害：職業化學性暴露對生殖健康的影響

Reproductive hazards in the workplace: effects of occupational chemical exposure on the reproductive system

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中文摘要

於 2006 年，在《職業醫學》雜誌上有一系列的深度文獻回顧被發表，以全面呈現工作場所中的危害暴露對生殖健康的影響。經過 16 年的時間，有許多關於生殖健康和職業危害之間關係的研究背發表了。

本次研究回顧了自 2006 年至 2021 年間國際科學文獻中相關的文章，這些文章是透過搜尋 MEDLINE 資料庫。本次文獻回顧僅收錄人類流行病學的研究，包括病例對照研究、病例世代研究與世代研究，且僅收錄討論化學性危害暴露與生殖健康的文獻。

在關鍵字搜尋後共有 5,441 篇文章，再經過篩選後，本次文獻分析共 105 篇人類的流行病學研究。除了過去大量討論過的化學物質，例如重金屬、有機溶劑或農藥外，過去 15 年中還新興了許多的化學物質，包含非金屬元素、雙酚類、環氧乙烷、多環芳香烃、揮發性有機化合物和粒子粉塵等。

接續 2006 年的深度文獻回顧報告，本次文獻回顧將過去十六年的研究收錄後並整理，顯示出有許多新興的化學物質與生殖健康有關，且呈現的負面影響不僅僅是早產、流產等傳統的生殖危害，而是包含從親代生育力、胚胎生長、子代發育等生殖健康的影響。雖然目前仍然只有有限的流行病學證據且結果不一定一致，但基於預防原則，我們仍建議積極採取預防措施，以保護職場中的父母與其子代的健康。同時我們也建議仍需要更多的相關研究，以提供不論是學術上的知識發展或實務上的改進措施。

關鍵字：生殖危害、化學暴露、職業健康、父母、孩童、勞工

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Abstract

In 2006, a series of in-depth reviews was published in the Occupational Medicine to present a comprehensive picture of the role of occupational risk factors in reproductive health. After 16 years, there are lots of updating studies about the relationship between reproductive health and occupational hazards.

The studies examined relevant articles published in the international scientific literature during 2006 to 2021, which were identified through the search of MEDLINE database. Among these articles, we only include human epidemiologic studies, including case-control, case-cohort, and cohort studies, which address occupational chemical exposures

Among 5,441 searched articles, 105 articles were included. In addition to previously discussed chemical agents, including metals, solvents, and pesticides and other chemicals used in the workplace, there are emerging chemical agents discussed in the past 15 years, all of the were about non-metal element, bisphenols, ethylene oxide, PAH, VOC, and particles.

Based on the prior review in 2006, we conducted an updated review showing that there are new emerging chemical agents linking to reproductive health more than pregnancy outcomes. Although there are only limited epidemiological evidence with mixed results, preventive interventions are suggested for precautious protection of reproductive health of both women and men, and more evidence is needed to be concluded.

Keywords: Reproductive hazard, Chemical exposure, Occupational health, Parents, Child, Labor

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Chapter 1 Introduction

1.1 Background

In 2006, a series of in-depth reviews had been made to present a comprehensive picture of the role of occupational risk factors in reproductive health (1-5). The authors have conducted a comprehensive review of literature on occupational hazards associated with reproductive health before 2005. They have produced an overview article along with three in-depth articles focused on women, fetuses, and men, respectively, to provide a thorough synthesis of the existing research.

Occupational risk factors were classified as physical factors, physical load, chemical agents, and psycho-social factors. Maternal exposure before or during pregnancy in all four exposure categories has been shown to be associated with an increased risk of spontaneous abortion and, to a lesser degree, preterm birth and low birth weight (1).

Exposure to various chemical agents such as heavy metals, pesticides, and organic solvents may result in spontaneous abortion and low birth weight. Birth defects are primarily related to exposure to lead, glycol ethers, organic solvents, and pesticides, but the specific chemicals that cause adverse pregnancy outcomes are often difficult to identify. Furthermore, these same exposures have also been linked to reduced semen quality, characterized by reduced total sperm count, reduced motility, or abnormal morphology. (2).

After 15 years, there have been quantities of new chemicals and evidence, including inorganic and organic compounds, needed to be updated for updating. Besides novel chemical exposures, our

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understanding of the impact of reproductive system from the exogenous hazards is also deeper and clearer.

1.2 Objective

The aim of this literature review is to provide a comprehensive analysis of the epidemiological evidence pertaining to the potential impact of occupational chemical exposures on the reproductive health of both workers and their offspring, within the timeframe of 2006 to 2021.

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Chapter 2 Literature Review

Chemical workplace reproductive hazards involve various types of substances used in different occupations. However, based on previous research, the most documented types of chemical workplace reproductive hazards are heavy metals, organic solvents, and pesticides.

Long-term exposure to heavy metals such as lead, mercury, nickel, and manganese have been known to be hazardous to reproduction for many years. The previous in-depth series of review have shown that reproductive effects may be observed at exposure levels previously considered safe, including an increased risk of spontaneous abortion, developmental toxicity in offspring, stillbirth, and delay in conception. (2)

Male effects, particularly on spermatogenesis, have been the focus of most studies, as metal production employees are predominantly male.(6) However, a review of epidemiological studies found negative reproductive effects, specifically spontaneous abortion, among women exposed to metals, including lead, arsenic, mercury, and cadmium. Other studies have shown that prenatal lead exposure increases the risk of pre-term delivery and low birth weight, and that heavy metal exposure can cause menstrual disorders, delayed conception rates, and other reproductive effects such as low birth weight and neural tube defects. Exposure to mercury among female dental assistants preparing amalgams has also been associated with spontaneous abortion and reduced fertility, particularly among those without appropriate protective measures. The interference of heavy metals with the endocrine system might explain the observed reproductive effects.

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A registry-based follow-up study in Norway found possible risks of neural tube defects among women working in healthcare, agriculture, and cleaning industries and exposure to glycol ethers or lead, but the evidence is limited. Another study found no cases of CNS defects among women exposed to electromagnetic fields during pregnancy(4). Treatment to reduce heavy metal body burden has been shown to improve the chances of conception in clinical studies of infertile women. (Table 1)

Solvents are another major category of occupational chemical exposure. The use of solvents in occupational settings has been linked to various negative reproductive outcomes, including spontaneous abortion, delayed conception, and reduced fertility (7-9). Solvent exposure has also been associated with menstrual disorders, infertility, and reduced birth weight. Exposure to specific solvents, including tetrachloroethylene and glycol ethers, has been associated with prolonged menstrual cycles and an increased risk of spontaneous abortion (10, 11), while working with petrochemicals has been linked to cytogenetic alterations and mutagenic effects.

In particular, women working in dry cleaning have been found to be at risk for various reproductive disorders, including spontaneous abortion and delayed conception. The risk of negative reproductive outcomes has been found to increase with exposure levels to certain solvents, such as toluene and aliphatic hydrocarbons (7-9).

New chemical risks associated with recombinant DNA techniques in laboratory settings, which have been linked to an increased risk of pre-term births, was also note (12). Given the continued use

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of solvents in various industries and new chemical risks, the potential for negative reproductive outcomes associated with solvent exposure is an ongoing concern for women of reproductive age.

Several studies have investigated the potential association between occupational exposure to organic solvents, including glycol ethers, during pregnancy and the risk of birth defects such as neural tube defects, cleft lip or cleft palate, and heart defects. While some studies have reported an increased risk of birth defects associated with maternal occupational exposure to organic solvents, others have found inconclusive or no evidence of such associations. The risk of giving birth to an infant with heart defects was increased when the mother was exposed to organic solvents during pregnancy compared with no exposure, and recent investigations suggest that genetic polymorphism may play a key role in solvent metabolism. However, the few studies addressing maternal occupational risk for cryptorchidism in boys are insufficient to draw conclusions, and the majority of findings are reassuring, with no clear indication that occupational exposure during pregnancy imposes a risk for hypospadias(4). (Table 2)

Occupational exposure to pesticides may have negative effects on human reproductive function, including spontaneous abortions, infertility and delay in conception. Congenital defects, and pre-maturity have also been observed in women exposed to pesticides. Greenhouse workers are more likely to suffer adverse reproductive effects because of higher and more continuous exposure to pesticides. Pesticide exposure in residential settings has also been linked to reproductive effects, particularly spontaneous abortion when exposure occurs during the early stages of gestation.

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Two studies had found an association between maternal serum concentration of DDE and pre-term and small for gestational age babies at birth, and DDT with spontaneous abortion, respectively. Although some of these studies were not specifically designed to evaluate occupational exposures, they reinforce the epidemiological literature on the role of occupational pesticide exposure in women and negative reproductive outcomes.

A study have found that maternal occupation in agriculture or fishing is associated with an increased risk of congenital heart defects (13). Another study in Finland found that professional applications of pesticide among pregnant women were associated with a 2-fold increased risk of cleft lip or cleft palate (14).

Different studies have reported inconsistent findings when it comes to the link between pesticide exposure and congenital defects. Some studies found an increased risk of birth defects in the musculoskeletal system among infants born to mothers working in the agricultural field. However, another study found limited relationship between pesticide exposure and limbs defects. While some studies suggest an association between pesticide exposure during early pregnancy and an increased risk of congenital heart defects, others have not been able to confirm these findings. Overall, the evidence linking pesticide exposure and congenital defects is limited, and further research is needed to better understand the possible effects of pesticide exposure on different types of congenital defects(4). (Table 3)

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According to previous research, we know that there are many well-known occupational chemical exposures related to adverse reproductive outcome, and as a result, relevant workplace regulations and protective laws have been established. However, despite the regulations, when we look at the various chemical exposures in the workplace, there are still many sources of hazards that we cannot accurately identify, and there are also emerging chemical hazards that have appeared in the workplace over the past decade. The review aims to synthesize and interpret the latest epidemiological research on this topic in order to contribute to the existing body of knowledge regarding the relationship between occupational chemical exposures and adverse reproductive outcomes.

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Chapter 3 Material and Methods

A computer-based literature search was conducted to identify studies on the impact of occupational hazards on human reproductive health. The search was conducted in the MEDLINE database from 2006 to 2021 using a combination of free text terms and the hierarchical controlled vocabulary. The keywords used for the search were "Reproduction"[MeSH Terms]) AND ("occupation*" OR "Occupational Exposure"[MeSH Terms]).

Three reviewers independently screened the titles and abstracts against the inclusion criteria, which were focused on human epidemiological studies, including case-control, case-cohort, and cohort studies, that addressed the impact of occupational chemical exposure on human reproductive health. Articles that did not meet the inclusion criteria, such as non-occupational exposure and non-epidemiological studies, were excluded, resulting in 461 eligible articles. Articles that dealt with non-chemical hazard exposure were also excluded, resulting in a final sample size of 105 studies for inclusion in the review. The inclusion process was presented in a flowchart (Figure 1).

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Chapter 4 Results

4.1 The classification of chemical risk factor

All articles included in the review were classified into different groups according to the target chemical risk factors examined in each study. In cases where some articles investigated multiple chemical risk factors, we classified them based on the major hazard specified in the study design. The most frequently occurring categories were pesticides, heavy metals, and solvents, with 35, 20, and 17 articles, respectively. Additional categories included endocrine-disrupting chemicals (EDCs), particles, polycyclic aromatic hydrocarbons (PAHs), and medicines. Categories that contained fewer than 5 articles were bisphenol A, disinfectants, ethylene oxide, oil mist, polychlorinated biphenyls, and volatile organic compounds (VOCs). (Figure 2)

4.2 **Metals**

We included a total of 20 articles about the potential health effects of exposure to heavy metals in our review, which encompassed various study designs such as cross-sectional, case-control, retrospective and prospective cohort studies. Exposure assessment in these studies was primarily conducted through interviews and registry data, although some studies also collected biomarkers such as blood lead, urine nickel, and urine mercury. Our analysis revealed that mercury was a key chemical of interest in these studies, followed by lead, arsenic, and boron. Additionally, some studies mentioned aluminum and nickel as potentially harmful metals. In addition to these specific metals, we also included studies that investigated the health effects of welding fume and metal dust.

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Due to significant differences in the chemical properties and pathophysiology of different heavy metals, we discussed each metal separately, with the exception of welding fumes or non-specific metal dust. (Table 4)

Mercury

In total, six studies examined the association between mercury exposure and reproductive health, including four prospective cohort studies, one retrospective cohort study from Finland, and one case-control study. Similar to previous research, exposure to mercury was found to be associated with adverse pregnancy outcomes such as miscarriage, stillbirth, and adverse birth outcomes(15, 16). However, there was no consistent association between mercury exposure and other outcomes such as conception difficulties, low birth weight, neural tube defects, developmental delay, learning difficulties, or epilepsy(15, 17-19).

Arsenic

Four studies were about arsenic exposure, two of them were conducted in the United States and focused on congenital abnormalities(17, 20), with positive association between arsenic (including organic and inorganic) exposure and cleft lip and palate, but the relationship between arsenic exposure and neural tube defects was not found to be significant. While the other two studies were from a prospective cohort in a Tanzanian mining area, which found that increased urine arsenic levels were associated with adverse birth outcomes, spontaneous abortion, and stillbirth.(16, 21)

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Lead

In regards to lead exposure and reproductive health, there were a total of three studies that were reviewed. The first study was a cross-sectional study that measured blood lead levels(22), while the second study was a case-control study conducted in Nordic countries that focused on offspring's testicular germ cell tumors (23). The third study was a retrospective cohort study conducted in Taiwan that investigated adverse reproductive outcomes such as small-for-gestational-age (SGA), low birth weight, and preterm delivery(24). They revealed a positive association between lead exposure and blood lead level, SGA and low birth weight, but no association with preterm birth and testicular germ cell tumors.

Boron

There were three studies related to boron exposure, including two case-control studies from the same Chinese cohort, which showed that boron exposure was associated with delay in pregnancy and decreased semen Y:X ratio(25, 26). However, a retrospective cohort study from Turkey, conducted 10 years later, showed no association between boron exposure and semen Y:X ratio or sex ratio at birth (27).

Nickle

Four studies related to nickel exposure were conducted by the same Russian team analysing the same cohort of more than 20,000 individuals. Their research showed that occupational nickel exposure was not significantly associated with genital malformation, undescended testes,

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spontaneous abortion, and congenital musculoskeletal defects, but was protective against SGA.(28-31)

Other metal exposure

One case-control study on aluminum exposure showed inconsistent results with a positive association observed between occupational aluminum exposure and preterm delivery, miscarriage, and congenital anomaly. For welding fume and metal dust, two retrospective cohort studies reported inconsistent findings with respect to their association with SGA, preterm birth, and low birth weight(32, 33). However, a case-control study in 2020 from the Netherlands revealed that metal fume exposure had adverse effects on the occurrence of offspring's septal defects(34).

4.3 Solvents

There are a total of 17 articles related to solvents, with more than half being case-control studies, and the rest being retrospective and prospective cohort studies. With the exception of one prospective cohort study from China in 2008 and one from Iran in 2012, exposure assessments were based on questionnaires, interviews, or registries. Organic solvents can be further divided into oxygenated, chlorinated, aromatic, and petrolic. (Table 5)

Similar to the previous review, studies found that occupational exposure to organic solvents is associated with adverse maternal and pregnancy outcomes, such as prolonged time to pregnancy (TTP), spontaneous abortion, and decreased gestational age(35-37). Additionally, a Finnish study in 2007 also observed that organic solvents increase the risk of SGA(38). In addition to maternal and

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pregnancy outcomes, this review showed more studies related to congenital anomalies, including anorectal malformation, circulatory anomaly, genital anomaly, cleft lip and palate, and neural tube defect(35, 39-44). Especially exposed to chlorinated solvents, or both parents' exposure (although maternal exposure is more impactful than paternal) is associated with stronger adverse effects.

Pediatric malignancies were another adverse outcome associated with solvent exposure. The most significant correlation was with pediatric leukemia and lymphoma(45, 46), while testicular germ cell tumors only showed an association in groups where both parents were exposed to organic solvents(47), and a 2006 US case-control study showed no association between solvents exposure and Wilms tumor(48).

Finally, there were two studies on children's behavioral development. In 2018, Costet showed that parents' occasional exposure to organic solvents has a negative impact on children's behavior development(49), while McCanlies found in 2019 that occupational exposures to organic solvents are associated with autism spectrum disorder (ASD).(50)

4.4 Pesticide

Our review included 35 relevant studies on the association between pesticides and reproductive health.(Table 6) Although retrospective exposure evaluation limits the identification of specific pesticide types in most studies, certain occupations such as farmers and veterinarians have been extensively studied (discussed separately in another related review). Few studies have focused on maternal and pregnancy outcomes, with adverse outcomes such as preterm birth, decreased birth

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weight, small for gestational age (SGA), and infertility (such as time to pregnancy or fecundability) being examined. Positive associations were found with SGA, decreased birth weight and sex ratio, but the results for other adverse outcomes were inconsistent(51-57). Similarly, there was no significant association found between pesticide exposure and male reproductive function(58).

In terms of adverse birth outcomes, some of the studies examined congenital anomalies, especially those related to the male genital system, such as cryptorchidism and hypospadism. However, no significant increase in the risk of major malformations such as holoprosencephaly, orchiopexy, or nonsyndromic orofacial clefts were observed due to occupational pesticide exposure.(59-65)

In contrast, more studies have focused on the impact of pesticide exposure on the neurobehavioral development of children. Retrospective cohort studies conducted in Ecuador showed a negative impact of pesticide exposure in floriculture on neurobehavioral development at different ages(66-68). Similar results were observed among female pesticide sprayers working in tomato farms whom exposed to pesticide 1 year before conception in Tanzania(69). In 2021, Chiu analyzed a birth cohort in Taiwan and found that parental chlorpyrifos exposure had a negative impact on the language and cognition development of children(70). In 2017, Schmidt reported that both indoor and agricultural pesticide exposure increased the risk of autism spectrum disorder (ASD), especially within the group of low folic acid supplement (71). Other negative health effects on offspring, such as blood pressure and asthma, and even long-term metabolic impacts on body

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weight, BMI, body fat during adultescent, and semen quality in male offspring, have also been observed. Some studies have even discussed gene-environment interactions among long-term metabolic impacts.(66, 72-74)

Over the past decade, there has been broad discussion about the correlation between pesticide exposure and pediatric malignancies, such as leukemia, lymphoma, retinoblastoma, and other solid tumors. Several studies have reported a positive association between pesticide exposure, including maternal and paternal exposure, and childhood leukemia and lymphoma(75-79). In 2013, Abdolahi reported that pesticide exposure 1 year before conception increased the risk of retinoblastoma(80). While the occurrence of childhood non-CNS tumors seemed to be associated with parental pesticide exposure, the association between pesticide exposure and mostly solid tumors, including CNS and non-CNS tumors, is still relatively uncertain.(77, 79)

4.5 Polycyclic Aromatic Hydrocarbons, PAH

All six articles on polycyclic aromatic hydrocarbon (PAH) are case-control studies using questionnaire and interview methods. (Table 7) Among the four articles related to congenital anomalies, Lupo in 2012 found a positive correlation between PAH exposure and gastroschisis, while another study in the same year found no correlation between PAH and congenital heart defects(81, 82). In 2020, Patel confirmed the positive correlation between PAH exposure at work and congenital heart defects, particularly with tetralogy of Fallot (ToF), but less so with other types

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of cardiological defects(83). PAH exposure was also associated with an increased probability of craniosynostosis(84).

Langlois investigating the correlation between PAH and small for gestational age (SGA) found a positive correlation, but no dose-response effect was observed in the subgroup analysis(85). In 2018, Omidakhsh's study showed a positive correlation between PAH and sporadic retinoblastoma, as well as exposure to dyes and other chemicals.(84)

4.6 Particles

6 articles were included in our review which investigated the effects of different types of particle exposure. (Table 8) Most of the studies are in the form of cohort studies, and the assessment method predominantly includes interview and registry. In 2009, Wong reported that maternal exposure to synthetic fibers in the textile industry increased the risk of miscarriage(86). In terms of the relationship between particle exposure and adverse pregnancy outcomes such as intrauterine growth restriction (IUGR), association between SGA and both organic and inorganic particles were broadly assessed. The results indicated that organic dusts such as wood dust, textile dust, and flour dust, inorganic dusts including iron, stone/concrete, and carbonaceous particles, and even nanoparticles, all increased the risk of SGA. Furthermore, the studies showed that exposure to organic dust and metal dust increased the risks of low birth weight and preterm birth(33, 87-89). Besides maternal reproductive outcomes, one study in 2020 found a positive association between

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exposure to organic dust and pediatric blood cancers (ALL and AML) or some types of CNS tumors (CNST), possibly related to organic dust or its combustion products.(90)

4.7 Medicine

As in previous studies, antineoplastics and anaesthetic gases are the two most commonly discussed types of occupational chemical exposure in the medical industry. Antineoplastics have been found to increase the risk of infertility and may also be associated with spontaneous abortion, stillbirth, premature delivery, and low birth weight, but statistical significance was not reached(91, 92). Anesthetics, on the other hand, have been found to be positively associated with spontaneous abortion, preterm delivery, and even congenital anomalies(93-95) . (Table 9)

4.8 Disinfectants

There were 3 studies that examined the relationship between occupational disinfectant use and maternal outcomes. These studies found that exposure to disinfectants may be associated with an increased risk of miscarriage and prolonged time to pregnancy.(96-98) (Table 10)

4.9 Endocrine-Disrupting Chemicals, EDC

While previous paragraphs have covered most categories of endocrine-disrupting chemicals (EDCs), such as heavy metals, pesticides, solvents, and polycyclic aromatic hydrocarbons (PAHs), some studies have focused specifically on occupational exposure to EDCs as a major risk factor. All of these studies were published before 2011 and demonstrated a strong positive association between parental occupational EDC exposure and urogenital malformations in their offspring(99-104).

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Additionally, a study conducted in the Netherlands suggested that exposure to metals may be related to infertility.(105) (Table 11)

4.10 Other chemicals

Only three studies have investigated the link between occupational exposure to bisphenol A (BPA) and adverse reproductive health outcomes. One study suggest that male sexual function may be decreased by occupational BPA exposure.(106). As for birth outcomes, maternal BPA exposure appears to be associated with a shorter anogenital distance in male offspring and a higher risk of low birth weight.(107, 108)

One study suggested that ethylene oxide exposure may increase the risk of spontaneous abortion, stillbirth, and pregnancy loss(109). Another study showed that polychlorinated biphenyls (PCBs) may increase the risk of asthma, eczema, and frequent ear infections in offspring(110). Siegel attempted to analyze the association between oil mist exposure and congenital anomalies, but except for a weak significant correlation with septal heart disease, no significant correlation was found for other birth defects(111). Finally, a large Japanese prospective cohort study in 2021 attempted to analyze the effects of parental occupational exposure to various types of organic chemicals, including VOCs, on the neurobehavioral development of offspring, but the results were mostly not significant.(112) (Table 12)

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Chapter 5 Discussion

5.1 Comparing Current Research to the Previous Review

The previous research had established certain associations between specific chemical exposures and adverse reproductive and developmental outcomes. For instance, lead and mercury had been linked to spontaneous abortion and infertility, while organic solvents had been linked to advanced pregnancy outcomes and some birth effects. Additionally, pesticides had been found to be associated with spontaneous abortion and birth effects.

After more than a decade, our review added to this knowledge by identifying further associations between chemical exposures and adverse reproductive and developmental outcomes. For example, the review highlights the diverse effects of heavy metals on both maternal and child health, including heterogenous outcomes such as preterm birth and developmental delays. Moreover, the review emphasizes the strong links between organic solvent exposure and advanced birth outcomes, as well as pediatric malignancies. The review also identifies additional adverse effects associated with pesticide exposure, including maternal outcomes such as small for gestational age and delayed pregnancy, as well as a range of child outcomes including malignancy, congenital anomaly, and even second-generation long-term effects. Furthermore, other chemicals, such as medicine, polycyclic aromatic hydrocarbons (PAHs), particles, disinfectants, and more, that have been linked to adverse reproductive and developmental outcomes were identified now. In addition to identifying more new chemicals associated with reproductive and developmental harm,

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studies included now also revealed new reproductive outcomes that were not covered by previous research, including long-term effects on the second generation.

5.2 Limitation and Challenges of Current Research

Despite the availability of large cohort studies, registry data, and national surveys over time, it remains difficult to identify specific chemical exposures in occupational exposure analysis based on questionnaire, registry data, or interviews, compared to direct on-site measurements or biomarker assessments of workers. Although some studies have focused on specific chemicals, there are still insufficient studies to determine the agents that cause adverse reproductive outcomes.

Similar to the previous in-depth review, most hazard assessments cannot provide actual quantitative impact of certain chemical hazards, making it difficult for most studies to present clear dose-response relationships. Even for well-known chemical hazards, such as certain pesticides or specific solvents, the available evidence presented in this updated review still does not allow us to derive clear exposure-response relationships.

As occupational hazard control, industrial technology, and occupational safety regulations continue to advance, the level of chemical exposure in the workplace has been decreasing in past decades, and it has become increasingly difficult to measure. Only a few of the epidemiological studies included in this review have shown long-term relationships of certain exposures, and there is still limited research to answer questions about the reproductive health effects of long-term low-dose exposure of chemical hazards.

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Finally, with the innovation and improvement of industry, more and more emerging chemicals are being used in factories, farms, or other workplaces. These newly developed materials and exposure situations may be completely new chemicals such as PFOS and its dozens of analogs, or they may be substitutes for previously extensively used but harmful substances that have been discovered through research. However, these new exposure situations and chemicals still lack epidemiological studies to fully understand their potential impact on reproductive and developmental health.

5.3 Occupational reproductive health real-world applications

Occupational health professionals face a number of key questions in protecting workers from reproductive health hazards. Firstly, it is important to identify the specific chemicals to which workers may be exposed, in order to develop appropriate protective measures. The timing of these measures is also critical, as it is necessary to determine whether protections should be put in place before or after workers begin trying to conceive or become pregnant, and how long these protections should be maintained. Finally, the strength of these interventions is a key consideration, with the need to balance protection against potential risks with the ability of workers to continue to perform their job duties.

While it is essential to base recommendations and regulations on relevant evidence, the limitations of existing evidence mean that a precautionary approach should be taken when revising protective measures and regulations for occupational reproductive health hazards. This approach

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can help to ensure that protections are in place to safeguard workers' reproductive health, even in cases where the full extent of potential risks is not yet fully understood.

Based on the in-depth review, we found that there is an increasing association between adverse reproductive outcomes before pregnancy and after birth, and occupational chemical exposure, such as prolonged time to pregnancy, newborn malformations, pediatric malignancies, and developmental delays in offspring. Currently, our occupational reproductive health protections mainly focus on traditional adverse maternal reproductive outcomes such as miscarriage, preterm birth, and low birth weight. However, reproduction is a continuous process that involves the production of gametes, fertilization, implantation, embryonic development, delivery, and postnatal development. Therefore, this study suggests that workplace chemical exposures with significant adverse reproductive outcomes in our review warrant protection for both women and men workers. Moreover, tracking mechanisms for adverse reproductive outcomes that have occurred in the workplace, including both parents and offspring, should be established to identify and monitor potential workplace hazards..

In addition to intervention of workplace protections, to safeguard the reproductive health of workers, it is essential to implement effective protections and exposure assessments in the workplace. One of the primary challenges in implementing effective exposure assessments is the difficulty in obtaining accurate exposure data. Workplace hazard monitoring data often faces biases and conflicts of interest, which can result in a lack of accuracy in reflecting the true situation. As a

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result, it can be challenging to identify and mitigate potential risks, highlighting the need for updated and revised protective measures and regulations in response to new hazards and their adverse effects.

To address these challenges, it is recommended to change the current situation of workplace environment monitoring by adjusting the structure of payment systems. This can help to decreased potential conflicts of interest and biases that can affect the accuracy of exposure data. In addition, providing open data sources of workplace hazard assessments can encourage more research on novel chemicals and exposures, leading to improved understanding of potential risks and the development of more effective protective measures.

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Chapter 6 Conclusion

Overall, the implementation of effective protections and exposure assessments in the workplace is essential for safeguarding the reproductive health of workers. By revising existing protective measures and regulations, improving exposure assessments, and providing more open data sources, we can better identify and mitigate potential risks and ensure a safer work environment for all workers. While existing epidemiological evidence may have limitations and inconsistent results, we should still keep mitigating the potential reproductive hazards in the workplace.

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Table 1. Selected occupational exposures of women to heavy metal with negative effects on reproductive health before 2005

Elements	**Effects observed**	**Reference**
Lead, Mercury, Cadmium, and Nickel (A review article, to 1994)	Spontaneous abortion	Anttila and Sallmen.
Lead	Menstrual disorders Spontaneous abortion Pre-term delivery Reduced fertility Low birth weight Neural tube defects Reduced sperm count	Herz-Picciotto, Andrews et al., Gerhard et al., Sallmen et al., Irgens et al., Irgens et al. Apostoli P et al. van Netten C et al.
Mercury	Spontaneous abortion Reduced fertility	Rowland et al.

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Table 2. Selected occupational exposures of women to solvents with negative effects on reproductive health before 2005

Chemical agents	**Effects observed**	**Reference**
Organic solvents (laboratories, industry, dry cleaning, etc.)	Spontaneous abortion Birth defect(cleft lip and palate)	Lindbohm (review)
Specific solvents (toluene, aromatic and aliphatic hydrocarbons, trichloroethylene, tetrachloroethylene)	Reduced fertility	Sallmen et al.
Tetrachloroethylene (dry cleaners)	Spontaneous abortion	Olsen et al., Doyle et al.
Glycol ethers (semiconductor industry)	Spontaneous abortion Reduced fertility Birth defect(neural tube, cleft lip and palate,)	Figa` -Talamanca et al. (review), Elliot et al., Chen et al
2-Bromopropane (electronics industry)	Haematological effect Menstrual disturbance Spontaneous abortion	Takeuchi et al. (review)
Petrochemicals (petrochemical industry)	Spontaneous abortion Reduce birth weight	Xu et al., Ha et al.
Solvents used in biochemical labs	Pre-term birth	Wennborg et al.

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Table 3. Selected occupational exposures of women to pesticides with negative effects on reproductive health before 2005

Effects observed	**Types of population and exposure**	**Reference**
Spontaneous abortion	Greenhouse workers Manual greenhouse workers Applying pesticides without PPE Husband work in DBCP factory	Restrepo et al., Taskinen et al. Goldsmith JR et al., Potashnik G et al., Sandifer SH et al.
Infertility Increased time to pregnancy	Working in agriculture Never using protective gloves Highly exposed Mixing and applying herbicides Using ethylene dibromide(EDB)	Fuortes et al., Curtis et al. Abell et al ., Greenlee et al. Wong O et al.
Cleft lip and cleft palate	Professional applications of pesticide	Nurminen (1995)
Congenital limb defect	Occupational exposure to pesticides Farming → Still limited evidence for adverse effects.	Garcia AM (1998) Hanke and Jurewicz (2004)
Decreased sperm count quality (not consistent)	Ethylene dibromide(EDB) Chlordecone chronic exposure Herbicides alachlor and atrazine Insecticide diazinon	Ratcliffe JM et al., Taylor JR et al., Guzelian PS et al., Cannon SB et al. etc.

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Table 4. Metals and reproductive outcome

Author,(Year)	Study design	Sample size (n)	Exposure assessment	Risk factors	Health Outcomes	Risk estimates
Brender et al., 2006 (17) USA	CC	184/225	interview biomarker(blood lead / urinary arsenic, cadmium, and mercury)	Arsenic(maternal) Cadmium(maternal) Lead(maternal) Mercury(maternal) Arsenic(paternal) Mercury(paternal)	neural tube defects	2.1 (0.5–8.8) 1.2 (0.1–19.7) 0.9 (0.2–4.2) 3.4 (0.9–12.9) 1.5 (0.7–3.0) 2.1 (0.8–5.5)
Chang et al., 2006 (25) China	CS	843/244	interview direct assesment(environmental)	Boron	Delay in pregnancy Spontaneous miscarriage Stillbirth More boys than girls	9.42%/4.62%, p=0.018 7.71%/4.02%, p=0.134 1.07%/2.05%, p=0.329 55.53%/60.31%, p=0.234
Chen et al., 2006 (24) Taiwan	RC	1,611	registry biomarker(blood lead)	lead	SGA Low birth weight Preterm delivery	2.15[1.15-3.83] 2.22[1.06-4.26] 1.97[0.92-3.86]
Vaktskjold et al., 2006 (28) Russia	RC	2942/20190	registry biomarker(urine Nickle)	Nickle	genital malformation Undescended testes(not hypospadias)	0.81[0.52-1.26] 0.76[0.40-1.47]
Jones et al., 2007 (18) NZ	PC	38/30	questionnaire	mercury	Conception difficulties Miscarriage Stillbirth Low birth-weight baby Child with birth defect	Non-significant but higher mean

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					Child with learning difficulties Child with developmental delay	
Vaktskjold et al., 2007 (29) Russia	RC	22836	registry biomarker(urine Nickle)	Nickle	SGA	0.84[0.75-0.93]
Robbins et al., 2008 (26) China	CS	63(worker),39(live nearby)/44	biomarker direct assesment	boron	Semen Y:X ratios	0.96 [0.93- 0.99]
Vaktskjold et al., 2008 (30) Russia	RC	474/4571	registry biomarker(urine Nickle)	Nickle	Spontaneous abortion	1.14 (0.95-1.37)
Vaktskjold et al., 2008 (31) Russia	RC	22,965	registry biomarker(urine Nickle)	Nickle	congenital musculoskeletal defects	0.96 (95% CI: 0.76-1.21)
Quansah et al., 2009 (32) Finland	RC	1,670	questionnaire	SGA-Welding fume(maternal) SGA-Metal dust(maternal) SGA-Welding fume and Metal dust(maternal) Preterm-Welding fume(maternal) Preterm-Metal dust(maternal) Low birth weight-	SGA Preterm delivery Low birth weight	1.78[0.53–5.99] 1.77[0.38–8.35] 2.92[1.26–6.78] 2.66[0.32–22.08] 5.64[1.14–27.81] 3.79[1.09– 13.19] 1.85[0.56–6.14] 1.70[0.70–4.15]

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				Metal dust(maternal) Low birth weight- Metal dust(maternal) Low birth weight- Welding fume and Metal dust(maternal)		
Sakr et al., 2010 (113) USA	CS	730	questionnaire	Aluminum	Preterm delivery Miscarriage Congenital anomaly	7.89[1.16, 53.77](mother in Lab-Congenital anomaly) 2.85[1.25, 6.49](father in Production-preterm delivery)
La-Llave-León et al., 2016 (22) Mexico	CS	31/268	interview	lead	blood lead level(>5ug/dL)	[22.6%, 7.1%] $p < 0.01$
Togawa et al., 2016 (23) Finland, Norway, Sweden	CC	8112/26264	registry	Chromium Iron/welding fume Nickel Lead Cadmium	Testicular Germ Cell Tumors in Offspring	1.37[1.05–1.79] (Chromium,Paternal, proportion of workers exposed>50, mean level of exposure>median)
Vähäsarja et al., 2016 (19) Switzerland	RC	59701	registry	Mercury(dental personnel)	neurological disease epilepsy intellectual disability	No association(neutral OR)

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El-Badry et al., 2018 (15) Egypt	PC	64/60	Interview Biomarker	Mercury	Urine mercury level SGA Spontaneous abortion Pre-eclampsia congenital malformations Preterm delivery	42.2 (14.6) vs 6.2 (3.8) p<0.001 6.2[2.3-16.4] 3.52[1.29 -2.23] 3.67[1.25 -10.76] 0.94[0.13 -6.8] 0.67[0.22-2.07]
Suhl et al., 2018 (20) USA	CC	349/1028	Registry	Arsenic Inorganic Arsenic	Cleft lip and palate	4.8[1.6-14.5] 8.6[1.1-65.1]
Duydu et al., 2019 (27) Turkey	RC	304	questionnaire double plate method Biomarker	Boron	Semen Y:X ratios Sex ratio at birth	0.99[0.95–1.06] no difference
Nyanza et al., 2019 (21) Tanzania	PC	788/173	Biomarker	ASGM(artisanal and small-scale gold mining)	Urine Arsenic level Blood Mercury level	9.4, 6.28 (ug/dL) 1.2, 0.66(ug/dL)

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Nyanza et al., 2020 (16) Tanzania	PC	788/173	Biomarker	ASGM(artisanal and small-scale gold mining) Arsenic Mercury	ASGM :	54.7, 26.6%
					adverse birth outcome-	12.3, 8.7%
					Spontaneous abortion	11.0, 1.7%
					Stillbirth	24.4, 9.1%
					Preterm delivery	19.8, 12.3%
					Low birth weight	1.5, 0%
					Congenital anomalies	—
					---	1.26[1.17–1.35]
					adverse birth outcome-Arsenic	1.27[1.19–1.35]
					adverse birth outcome-Mercury	1.38[1.17–1.63]
					Spontaneous abortion-Arsenic	0.96[0.78–1.18]
					Spontaneous abortion-Mercury	2.08[1.60–2.69]
					Stillbirth-Arsenic	2.71[2.10–3.45]
					Stillbirth-Mercury	
Spinder et al., 2020 (34) Netherlands	CC	1174/5602	questionnaire registry(JEM)	metal fume	septal defects	3.23[1.14-9.11]

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Table 5. Solvents and reproductive outcomes

Author,(Year)	Study design	Sample size (n)	Exposure assessment	Risk factors	Health Outcomes	Risk estimates
Chevrier et al., 2006 (39) France	CC	164(CL),76(CL/P)/236	interview	oxygenated solvents chlorinated solvents petroleum	Cleft lip and palate	1.76[1.1-2.9] 9.45[2.5-35.3] 3.64[1.5-8.8]
Hooiveld et al., 2006 (35) Netherlands	RC	398/302	questionnaire estimate models	organic solvents(Paternal) (painters vs carpenters)	prolonged TTP spontaneous abortion preterm delivery low birth weight congenital malformation	1.1[0.7-1.9] 1.1[0.4-2.7] 1.2[0.7-2.2] 1.7[0.9-3.2] 6.2[1.4-27.9]
Tsai et al., 2006 (48) USA	CC	303/575	interview	Dry cleaning agents Fuel oil Hairdressing chemicals Ink dyes Motor oil Paint and paint strippers Solvents Standard solvents	Wilms' tumor	non significant
Ahmed et al., 2007 (38) Finland	RC	147/1523	questionnaire	organic solvent	SGA low birth weight	1.67[1.02-2.73] 1.17[0.71-1.93]

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McKinney et al., 2008 (45) England	CC	1881/3742	registry questionnaire	Solvents (pregnant) Solvents (post-natal) ---Self report--- Solvents(preconception) Petrols(preconception) Solvents(pregnant) Petrols(pregnant) Solvents(post-natal) Petrols(post-natal)	childhood leukaemia and lymphoma	2.7 (1.6 – 4.6) 1.9 (1.1 – 3.3) --- 1.2(1.0-1.5) 1.6(1.2-2.2) 1.5(1.1-2.0) 2.1(1.2-3.6) 1.5(1.1-1.9) 2.2(1.3-3.5)
Qin et al., 2008(36) China	PC	546/567	Direct assesment Estimate model	organic solvent	decreased gestational age	-1.2 weeks(-1.6 to -0.9)
Garlantézec et al., 2009 (40) France	PC	566(occational), 850(regular)/1402(Self-report) 514(medium), 90(high)/2234(JEM)	questionnaire registry(JEM)	Solvents	congenital malformations (oral clefts, urinary malformations and male genital malformations)	2.48[1.4 -4.4] (self-report) / 3.48[1.4 -8.4](JEM) (subgroups of major malformations were associated with maternal exposure to solvents)
van Rooij et al., 2010 (41) Netherlands	CC	85/650	questionnaire	industrial cleaning agents and solvents(Maternal) occupational exposure to exhaust fumes(Paternal)	Anorectal malformation	2.9[0.9- 9.3] 1.9[1.0-3.6]

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Castro-Jiménez et al., 2011 (46) Colombia	CC	85/85	interview JEM	Hydrocarbons	childhood ALL	Expose to hydrocarbons 24m before conception Father only: 1.66(0.64-4.28) Mother only: 6.33 (1.41-28.31) Both parents: 13.47(3.31-54.71)
Vaktskjold et al., 2011 (42) Russia	PC	712/10561	registry	organic solvents	Congenital anomalies(all circulatory digestive genital	1.24 (0.85, 1.82) 2.03 (0.85, 4.84) 1.65 (0.50, 5.46) 2.24 (0.95, 5.31)
Attarchi et al., 2012 (37) Iran	PC	205/201	interview Direct assesment(environmental)	organic solvents (mixture) -Low -High	time to pregnancy spontaneous abortion	1.65[1.15–4.21] 1.98[1.89–8.43] 5.21[1.95–14.12] 7.70[2.09–15.38]
Desrosiers et al., 2012 (43) USA	CC	521(NTD), 1249(OFC)/2997	interview	organic solvents (maternal early pregnancy) Any solvents Chlorinated solvents Stoddard solvent Aromatic solvents	neural tube defects orofacial clefts	1.96 (1.34, 2.87)(chlorinated-NTD) 0.63 (0.33, 1.23)(Stoddard-NTD) 0.75 (0.36, 1.55)(Aromatic-NTD) 0.96 (0.70, 1.33)(chlorinated-OFC) 1.25 (0.78, 1.99)(Stoddard-OFC) 0.88 (0.52, 1.49)(Aromatic-OFC)
Le Cornet et al., 2017 (47) Finland, Norway, Sweden	CC	8112/26264	registry	~Parental organic solvents~ Aromatic hydrocarbon solvents Chlorinated hydrocarbon solvents	Testicular Germ Cell Tumors	Parental organic solvents -No significant association Sensitivity analysis: testicular germ cell tumor risk when parents have been exposed to solvents within the year before childbirth

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						1:53[1.08-2.17] 1.17[0.83-1.66]
Costet et al., 2018 (49) France	PC	715	questionnaire	organic solvents -occational -regular	Children Behavior Child Behavior Checklist and the Preschool Social Behavior Questionnaire at age 2 Strength and Difficulties Questionnaire at age 6	0.34[0.11-0.57] 0.26[0.05-0.48] 0.22[− 0.02-0.47] 0.07[− 0.14-0.28]
McCanlies et al., 2019 (50) USA	CC	537/414	interview	Occupational exposures Any solvents(maternal) Solvent(maternal)(moderate)	autism spectrum disorder (ASD)	1.50[1.01-2.23] 1.85[1.09-3.15]
Spinder et al., 2020 (44) USA	CC	879/7817	interview	Any solvent Aromatic solvents Chlorinated solvents Stoddard solvents	Gastroschisis in offspring -Multiple defect	1.00[0.75-1.32] 1.15[0.69-1.92] 0.98[0.73-1.32] 0.84[0.51-1.39] ---multiple defect--- 2.11[1.10-4.06](Any solvent) 1.44[0.65- 3.17](Chlorinated solvent)

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Table 6. Pesticides and reproductive outcomes

Author,(Year)	Study design	Sample size (n)	Exposure assessment	Risk factors	Health Outcomes	Risk estimates
Grandjean et al., 2006 (66) Ecuador	RC	35/37	interview Biomarker	Pesticide(fluriculture) -prenatal exposure -current exposure	Neurobehavioral deficits Systolic BP	β=-1.01 (P=0.009) β=4.57(P=0.018)
Lauria et al., 2006 (51) Italy	CS	138/575	questionnaire	Pesticide (greenhouse)	Time to pregnancy	0.96[0.81-1.13]
Zhu et al., 2006 (52) Denmark	PC	226(gardners),214(farmers) / 62164	interview	Pesticide (gardner/farmer)	Fetal loss Multiple births Male infant Preterm birth Very preterm birth SGA All malformations Major malformations	Very preterm birth-gardners 2.6[1.1-5.9] Biological use – major malformations : 4.8[1.0-24.3]
Carbone et al., 2007 (99) Italy	CC	90/203	interview	pesticide(Mother)	cryptorchidism and hypospadias	2.74[0.72-10.42]

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Andersen et al., 2008 (59) Denmark	PC	113/982	questionnaire interview experts evaluation	pesticide	testicular position, volume, penile length urethral opening	Cryptorchidism RR 3.2[1.4-7.4]
Handal et al., 2008 (67) Ecuador	RC	53/68	questionnaire	pesticide	Neurobehavioral development	Pesticide fine motor score -13%[-21% to -5%] communication -6%[-15% to 2%] visual acuity 3.9[0.94-16]
Harley et al., 2008 (53) USA	PC	402	biomarker questionnaire	Pesticide(Serum DDT) Pesticide use	Fecundability odds ratio	pesticides in home 0.6[0.4-0.9] home located within 200ft of an agricultural field 0.7[0.5-1.0] No association of blood DDT/DDE to fecundability
Multigner et al., 2008 (58) Guadeloupe(France)	PC	42/45 (banana plantation worker/non-worker)	questionnaire	Pesticides (banana plantation)	Male reproductive function	mostly non-significant
Shirangi et al., 2009 (60) Australia	CS	412	questionnaire	pesticides	birth defects	1.18[0.61-2.28]

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Harari et al., 2010 (68) Ecuador	RC	84	interview(mother's exposure during pregnancy) Biomarker(blood/urine, for children current status)	Pesticide(fluriculture) -prenatal exposure -current exposure	Neurobehavioral deficits(8-9 y/o children)	Visual memory function (Stanford-Binet Copying Recall Test) -Paternal: 13.35 [1.75 to 101.93] -Maternal: 6.62 [1.02 to 42.93]
Tagiyeva et al., 2010 (72) England	PC	8131	questionnaire registry(JEM)	biocide/fungicide antenatal postnatal	Wheezing/asthma	1.23 (1.07–1.40) (median to high exp.)
Burdorf et al., 2011 (54) Netherlands	PC	6302	questionnaire registry(JEM)	Pesticide	Time to pregnancy Preterm birth Decreased birth weight	2.04 [0.73 - 5.76] 1.67[0.51 - 5.52] 2.40[1.14-5.05]
Gabel et al., 2011 (61) Denmark	RC	646/783817	questionnaire registry(JEM)	Pesticide(exposure in horticulture)	Cryptorchidism Orchiopexy	Cryptorchisim 1.34 [0.30-5.96] Orchiopexy 1.34[0.72-2.49] Cryptorchidism(Cohort2) 2.58[1.07-6.20]
Gaspari et al., 2011 (62) France	CC	39/76	questionnaire	pesticide(parents)	Male genital malformation	4.41[1.21-16.00]
Rocheleau et al., 2011 (63) USA	CC	646/1493	questionnaire registry(JEM)	Pesticide	hypospadias(urogenital malformation)	No association(even OR<1)

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Wohlfahrt-Veje et al., 2011 (55) Denmark	PC	112/65	questionnaire biomarkers(blood)	Pesticide	lower birth weight body fat at school age	-4.8% [-9.0 - -0.7] 13% [0.7 – 26.8]
Abdolahi et al., 2013 (80) USA	CC	198/245	questionnaire registry(JEM)	Pesticide(10 years prior) Pesticide(1 years prior)	sporadic bilateral retinoblastoma	1.64[1.08 - 2.50] 2.12[1.25 - 3.61]
Kumar et al., 2014 (75) India	CC	132/132	Interview	Pesticide (during pregnancy)	childhood leukemia and lymphoma	21.2% vs 9.1% (P=0.005)
Febvey et al., 2016 (114) Europe	CC	1361/5498	Registry(JEM)	pesticide	CNS tumor in children	0.76[0.41 - 1.41]
Handal et al, 2016 (115) Ecuador	PC	16/10	Interview biomarkers (Urine)	Pesticide (rose worker)	Pesticide concentration of urine sample in early pregnancy Total DAP Total DM DMTP TCPy PTU ETU	Elevated but non significant 95% CI P 0.86–2.23, 0.18 0.77–2.02, 0.37 0.69–2.10, 0.51 0.74–2.33, 0.35 0.73–2.16, 0.42 0.65–1.48, 0.92
Tinggaard et al, 2016(73) Denmark	PC	101/62	Questionnaire	Prenatal pesticide exposure	adolescent body fat (measured by DXA, β means difference) Total fat% Total fat%(adjusted)	Girls 6.18[1.82–10.54]** 0.73[0.20–1.27)** Boys 1.33[3.15–5.82] 0.39[0.11–0.89]

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Gunier et al, 2017 (76) USA	CC	669/1021	Task-based Job modules JEM	Parental pesticide exposure the year before pregnancy Paternal perinatal exposure Maternal perinatal exposure	Acute lymphoblastic leukemia(ALL)	1.7[1.2, 2.5] Not associated
Schmidt et al, 2017(71) USA	CC	466/340	Interview	Indoor pesticide with low-FA Indoor pesticide with FA Some pet flea/tick product with low-FA Regular pet flea/tick product with low-FA Argricultural/commercial pesticide exposure with low-FA	autism spectrum disorder (ASD)	--- 2.6 [1.3-5.2] 1.9 [1.1-3.3] 1.0 [0.3-2.9] 3.9 [1.4-11.5] 2.0 [0.9-4.2]
t Mannetje et al, 2017(56) New Zealand	PC	355 children (127 fathers /21 mothers)	Interview Biomarker (blood)	TCDD(phenoxy herbicide procudtion plant) Paternal exposed at time of conception	Sex ratio	Sex ratio 0.47, compared to overall ration of 0.55. A significant dose-response relationship between paternal serum TCDD and sex ratio decreasing
Suhl et al, 2018(64) USA	CC	1185/2832	Interview with IH review	pesticide	nonsyndromic orofacial clefts	No association(neutral OR)
Addissie et al, 2020 (65) USA	CC	85/54	questionnaire	Pesticide(prenatal) 3-month before pregnancy During pregnancy Paternal Living next to agricultural field	holoprosencephaly	1.95 (0.07, 52.19) 1.15 (0.11, 11.42) 2.39 (0.34, 20.58) 3.24 (0.94, 12.31)

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Coste et al, 2020 (77) Switzerland	RC	Maternal 1807902 Paternal 1700149	Registries	pesticide	any cancer leukaemia CNS tumours (CNST), lymphoma, non-CNS solid tumours.	almost no relationship, except for : non-CNS solid tumours - both parental exposure(but low number)
Mavoungou et al, 2020 (78) France	CC	328 H L, 305 nonH /2415	Interviews	Maternal prenatal pesticides	Hodgkin lymphoma and non-Hodgkin lymphoma	Occupational pesticide: - domestic use of insecticides:+
Patel et al, 2020 (79)	RC	329658	Registries and JEM	[Parental] pesticides, animals organic dust	leukaemia(ALL and AML) CNS tumours (CNST)	Parental pesticide exposure and AML: 2.38[1.12-5.07] Father pesticides exposure and AML: 3.07[1.03-9.10] Parental organic dust exposure and AML: 2.38[1.12-5.07] Others: negative
Shirangi et al, 2020(57)	PC	4142	Registries and JEM	Pesticide Phthalates	percentage of optimal birth weight(POBW)<85-Pesticide SGA-Pesticide percentage of optimal birth weight(POBW)<85-Phthalates SGA- Phthalates	3.72[1.40-9.91] 5.45[1.59-18.62] 3.71[1.62-8.51] 1.69[0.34-8.41]
Chilipweli et al, 2021 (69) Tanzania	CS	172/114	Questionnaire	Pesticides (Mother work in tomato sprayed farms)	neurodevelopmental effect	Associated to time of exposure(1 year), aOR 4.26[1.6-12]

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Chiu et al, 2021(70) Taiwan	RC	425 mother-infant pairs	Questionnaire Biomarker(cord blood)	Chlorpyrifos (one of a pesticides)	[PPARγ DNA methylation levels] [Neurodevelopmental] Whole test Cognitive Language Motor Gross-motor Fine-motor Social Self-help	DNA meth levels: 0.77 (0.07-1.46)* Neurodevelopment: 0.44 (-1.55, 0.66) -1.20 (-2.25, -0.15)* -1.14 (-2.25, -0.03)* 0.59 (-1.63, 0.46) 0.69 (-1.91, 0.54) 0.08 (-1.18, 1.03) 0.22 (-1.25, 1.69) 0.86 (-0.46, 2.18)
Istvan et al, 2021 (74) France	CS	1045	questionnaire	Maternal occupational exposure to EDC: Pesticide Phthalates Heavy metals Organic solvents Alkyl phenolic	Semen parameters of child in adulthood -Volume -Sperm concentration -Total sperm count -Sperm motility -Normal forms	Pesticide 2.07 (1.11, 3.86)* 1.56 (0.81, 2.99) 2.14 (1.05, 4.35)* 1.21 (0.68, 2.16) 1.50 (0.85, 2.64)
Kumar et al, 2021 (116) India	RC	102/73	Questionnaire Biomarker(blood) Placentae	Pesticides(in tea garden workers)	placental insufficiency fetal growth restriction - birth weight - Head circumference -Infant's length -Ponderal index -Placenta weight	association of AChE activity levels with the birth outcome and PW in TGW and HW.

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Table 7. Polycyclic Aromatic Hydrocarbons(PAH) and reproductive outcomes

Author,(Year)	Study design	Sample size (n)	Exposure assessment	Risk factors	Health Outcomes	Risk estimates
Lupo et al., 2012 (81) USA	CC	299/2993	interview	PAHs	Gastroschisis	1.75[1.05-2.92]
Lupo et al., 2012 (82) USA	CC	1907/2853	interview	PAHs	Congenital Heart Defects	non significant
Langlois et al., 2014 (85) USA	CC	221/2582	interview	PAHs-Y/N PAHs-Low PAHs-High	SGA	2.2[1.3-3.8] 2.5[1.2-5.3] 1.9[0.9-4.2]
O'Brien et al., 2016 (84) USA	CC	316/2993	interview	PAHs	Craniosynostosis	1.75[1.01-3.05]
Omidakhsh et al., 2018 (117) USA, Canada	CC	282/155	questionnaire interview	PAH Paint	sporadic retinoblastoma	Any chemicals(>30y/o) 4.56[1.44-14.5] Paint 8.76[1.32-58.09] Pesticides/paints/vocs/PAH/radiation 5.25[1.14-24.2]
Patel et al., 2020 (83) USA	CC	12584/11829	interview	PAHs	Congenital heart defects	Congenital heart defect 1.41[1.00-2.00] ToF 1.83[1.21-2.78] others: non-significant

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Table 8. Particles and reproductive outcomes

Author,(Year)	Study design	Sample size (n)	Exposure assessment	Risk factors	Health Outcomes	Risk estimates
Wong et al., 2009 (86) China	RC	1752	registry(JEM) questionnaire	[Textile industry] Wool Cotton Silk Synthetic fiber Solvents Resins Lubricants Metals	miscarriage	Synthetic fiber 1.89[1.20-3.00] Mixed fiber(synthetic/natural) 3.31[1.30-8.42] Others: non-significant
Manangama et al., 2019 (87) France	RC	9113/1542/569(unexposed/uncertain/exposed)	interview(JEM)	nanoscale particles -uncertain -exposed	SGA	uncertain 1.23[0.99-1.52] exposed 1.63[1.22-2.18]
Norlen et al., 2019 (33) Sweden	RC	995843 20445 SGA 28272 LBW 46044 preterm birth	interview registry	inorganic particles (Iron, stone/concrete, others) welding fume	SGA Low birth weight Preterm delivery	inorganic particles-SGA 1.20[1.04-1.39] inorganic particles-LBW 1.32[1.18-1.48] inorganic particles-preterm 1.18 [1.07-1.30] Welding -SGA 1.45[1.19 to 1.78] Welding -LBW 1.22[1.02-1.45] Welding -preterm 1.24[1.07-1.42]

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Norlen et al., 2019 (88) Sweden	RC	995843 20445 SGA 28272 LBW 46044 preterm birth	interview registry	[Organic particles] (wood dust, textile dust, flour dust …) [Combustion products] (PAH)	SGA LBW preterm delivery	Organic particles SGA 1.14[1.04-1.25] LBW 1.15[1.07-1.23] Preterm 1.16[1.10-1.23] PAH: SGA 1.40[1.15-1.71] LBW 1.49[1.27-1.75] Preterm 1.13 [0.98-1.30
Manangama et al., 2020 (89) France	PC	12073	interview JEM	Carbonaceous particles (Carbon + PAHs)	SGA	SGA exposed 1.8[1.29-2.46] exposed and stop during 1st trimester 1.71[0.71-4.12] exposed and stop during 2nd trimester 1.84[1.13-3.02] exposed and stop during 1st trimester 1.80[1.10-2.95]
Volk et al., 2020 (90) Denmark	CC	4268/25-1 control	registry	[organic particles] Wood Paper Textile	leukaemia(ALL and AML) CNS tumours (CNST)	[Maternal] Wood: leukemia 1.44[1.08-1.94] Wood: AML 2.14[1.13-4.03] Paper: CNS cancer 2.28 [1.22-4.26] Paper: all cancers 1.56[1.02-2.38] [Paternal] Wood: astrocytoma 1.43[1.05-1.96] Wood: prenatally initiated cancers 1.23[1.05-1.45]=>neuroblastoma Wood: all cancer 1.22[1.07-1.39]

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Table 9. Medicine and reproductive outcomes

Author,(Year)	Study design	Sample size (n)	Exposure assessment	Risk factors	Health Outcomes	Risk estimates
Fransman et al., 2007 (91) Netherlands	RC	663/(324+178+177+177) (background-low-medium-high)	questionnaires	antineoplastic drugs	Time to pregnancy Spontaneous abortion Stillbirth Premature delivery Low birth weight Congenital malformation	0.8 [0.6-0.9] 1.2 (0.6-2.7] 1.8 [0.2-21.0] 1.4 [0.7-2.9] 2.1 [0.9-4.7] 1.1 [0.7-1.7] 0.9 [0.3-3.3]
Shirangi et al., 2008 (93) Australia	CS	940	questionnaire	anesthetic gas	Spontaneous abortion	2.49[1.02-6.04]
Shirangi et al., 2009 (94) Australia	CS	744	questionnaire	anesthetic gas	preterm delivery	2.56[1.33-4.91]
Teschke et al., 2011 (95) Canada	RC	546/14771	interview registry	anesthetic gas	congenital anomalies	1.49[1.04-2.13]
Nassan et al., 2021 (92) USA, Canada	PC	680(prior to baseline), 284(at baseline)/1476	questionnaire	Antineoplastic Drugs	miscarriage	1.26 [0.97–1.64]

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Table 10. Disinfectants and reproductive outcomes

Author,(Year)	Study design	Sample size (n)	Exposure assessment	Risk factors	Health Outcomes	Risk estimates
Lindbohm et al., 2007 (96) Finland	CC	222/ 498	questionnaire	disinfectants	miscarriage	1.5[0.9 - 2.7]
Gaskins et al., 2017 (97) USA	RC	537/1202	questionnaire	disinfectant	fecundity(Time to pregnancy)	1.18[1.05-1.31]
Ding et al., 2021 (98) USA, Canada	PC	416(user), 262(past user)/1901	questionnaire	Disinfectant(high dose, within 12 months)	miscarriage	1.78[1.08 - 2.93]

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Table 11. Endocrine-Disrupting Chemicals(EDC) and reproductive outcomes

Author,(Year)	Study design	Sample size (n)	Exposure assessment	Risk factors	Health Outcomes	Risk estimates
Fernandez et al., 2007 (100) Spain	nested-CC	50/114(total cohort 702)	biomarker(placenta pesticide) questionnaire	total effective xenoestrogen burden organochlorine pesticides	cryptorchidism and hypospadias	2.19TEXB(2.82[1.10-7.24]º o,p'-DDT (2.25[1.03-4.89]) p,p'-DDT (2.63[1.21-5.72]) lindane(3.38[1.36-8.38]) mirex (2.85[1.22-6.66]) endosulfan alpha (2.19[0.99-4.82])
Ormond et al., 2009 (101) England	CC	471/490	interview registry	EDC(JEM) -hair spray -phthalate	hypospadias	2.39[1.40-4.17] 3.12[1.04-11.46]
Giordano et al., 2010 (102) Italy	CC	80/80	questionnaire registry(JEM) biomarker(serum EDC)	EDC(one) EDC(more than one) hexachlorobenzene	hypospadias	2.44[1.06–5.61] 4.11[1.34–12.59] 5.50[1.24–24.31]
Nassar et al., 2010 (103) Australia	CC	1202/2583	registry(JEM)	EDC Metals(maternal) phthalates(maternal) polychlorinated organic(paternal) biphenolic(paternal)	hypospadias	2.6[1.3-5.2] 1.2[0.8-1.7] 1.3[1.0-1.8] 1.6[1.0-2.6]

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Morales-Suárez-Varela et al., 2011 (104) Denmark	RC	2,867/42,474	interview registry(JEM)	Mather EDC(probably)-cryptorchidism EDC(possible)-cryptorchidism EDC(probably)-hypospadias EDC(possible)-hypospadias	hypospadias cryptorchidism	1.8[1.0-2.6] 2.6[1.8-3.4] 1.6[0.4-2.8] 0.8[0.4-1.2]
Snijder et al., 2011 (105) Netherlands	CS	2,774	interview registry(JEM)	EDC(maternal) EDC(paternal) Metals(paternal)	Time to pregnancy	0.91[0.76-1.08] 0.83[0.71-0.97] 0.85[0.75-0.96]

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Table 12. Other chemicals and reproductive outcomes

Author,(Year)	Study design	Sample size (n)	Exposure assessment	Risk factors	Health Outcomes	Risk estimates
Gresie-Brusin, 2007 (109) South Africa	CS	19/7 9	questionnaire direct assessment (units or personal)	Ethylene oxide	spontaneous abortion still birth pregnancy loss	20.8[2.1-199] 3.5[0.6-25.3] 8.6[1.8-43.7]
Li et al., 2010 (106) China	CS	427	Biomarker(Urine)	BPA	Male sexual function	P<0.001
Miao et al., 2011(108) USA	RC	56/97	Registry Personal monitoring Biomarker	BPA -Father exposed only -Mother exposed	Anogenital Distance of Male Offspring	β = −2.87(p=0.15) −8.11(p=0.003)
Miao et al., 2011(107) USA	RC	93(F), 50(M)/444	Registry Personal monitoring Biomarker	BPA	Birth weight -Father exposed only -Mother exposed	β = −90.75(p=0.10) −168.40(p=0.02)
Parker-Lalomio, 2018 (110) USA	RC	288	interview	PCBs(多氯聯苯）	Asthma Eczema Frequent ear infection	3.24[1.30–8.09] 3.29[1.54–7.04] 2.24[1.19–4.22]

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Siegel, 2019 (111) USA	CC	8140/22011	registry	Oil mist	[Birth defect] septal heart defects Other birth defect	1.8[1.0–3.3] Other birth defect: non-significant
Nakaoka, 2021 (112) Japan	PC	71585	questionnaire	Occupational VOCs Kerosene, petroleum, benzene, gasoline Permanent marker Water-based paint or inkjet printer Organic solvents Engine oil Formalin, formaldehyde	neurodevelopmental delay	mostly non-significant -Formalin/formaldehyde 1.76[0.99-3.12]

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Figure 1 Review of occupational chemical hazard with advance reproductive health effects

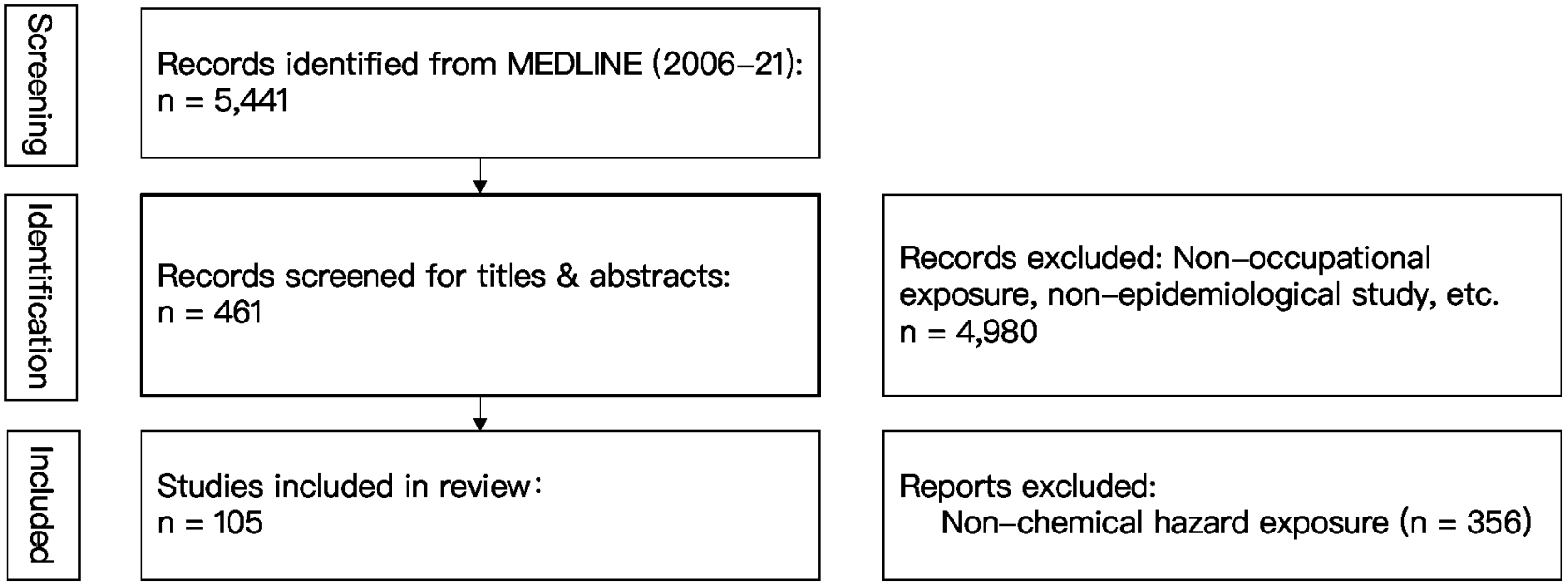

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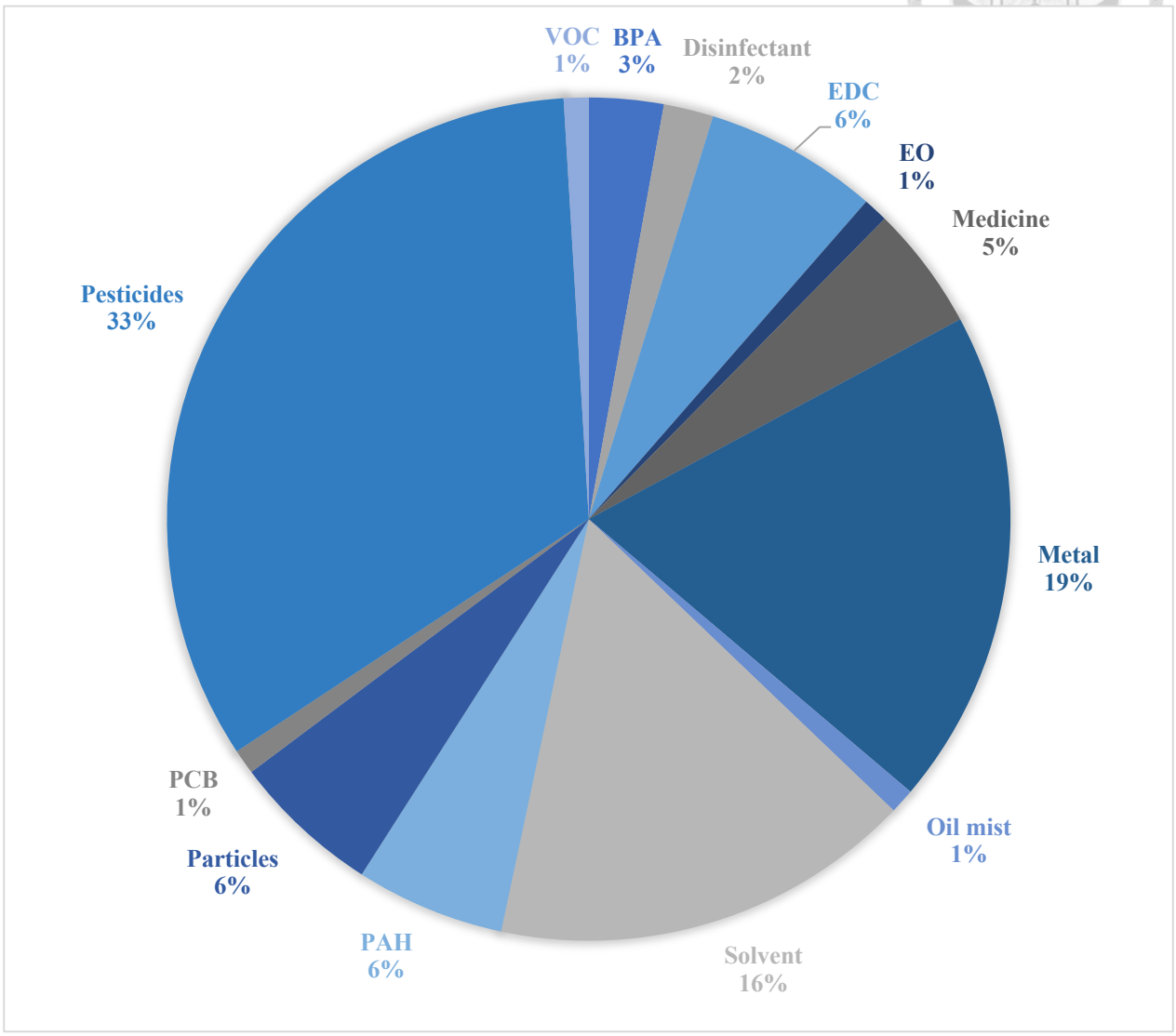
Figure 2 Proportion of chemical hazards by different categories



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