EXTERNAL SCIENTIFIC REPORT

Literature review on epidemiological studies linking exposure to pesticides and health effects[1]

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ABSTRACT

We performed a systematic and extensive literature review of epidemiological studies examining the association between pesticide exposure and any health outcome published after 2006. We searched 43,259 citations and identified 603 published articles examining a very wide variety of outcomes and presenting over 6,000 analyses between pesticide exposure and health outcomes. We divided the different outcomes into 23 major disease categories. The largest proportion of studies pertains to cancer outcomes (N=164) and outcomes related to child health (N=84). The majority of studies were case-control studies and cross-sectional studies (N=222) and examined occupational exposure to pesticides (N=329). A wide and diverse range of pesticides was studied with studies using various definitions of pesticides; it is very hard to harmonise between studies this information. Despite the large volume of available data and the large number (>6,000) of analyses available, firm conclusions cannot be made for the majority of the outcomes studied. This observation is disappointing especially when one accounts for the large volume of research in the area. However, this observation is in line with previous studies on environmental epidemiology and in particular on pesticides which all acknowledge that such epidemiological studies suffer from many limitations and that the heterogeneity of data is such that does not allow firm conclusions to de made. We also performed updated meta-analysis for major outcomes and for those where a relevant meta-analysis published after 2006 was identified. This has only been possible for childhood leukaemia and for Parkinson's disease. For both these outcomes we found significant associations between pesticide exposure and disease in line with previous evidence.

KEY WORDS

Pesticides; epidemiological studies; pesticide exposure; health outcomes; mortality; case control studies; cohort studies

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外部科学報告書

農薬ばく露と健康影響に関連する疫学研究に関する文献レビュー[1]

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概要

我々は、2006 年以降に発表された農薬ばく露と健康影響との関連を調査した疫学研究の系統的かつ広範な文献レビューを行った。43,259 件の引用文献を検索し、非常に多様な影響を調査した 603 件の論文を同定し、6,000 件以上の農薬ばく露と健康影響との間の分析結果を提示した。さまざまな影響を 23 の主要な疾患カテゴリーに分類した。研究の中で最も多いのは、発がん影響（N=164）と子どもの健康に関連した影響（N=84）であった。研究の大部分は症例対照研究と横断研究（N=222）で、農薬への職業ばく露（N=329）を調査したものであった。さまざまな農薬の定義を用いて研究が行われ、広範囲かつ多様な農薬が研究されていたため、これらの情報を研究間で調和させることは非常に難しい。利用可能なデータの量が多く、分析の数も多い（6,000 以上）にもかかわらず、研究された結果の大部分について確固たる結論を出すことはできなかった。これは、この分野の研究量の多さを考慮すると、特に残念な結果である。しかし、この結果は環境疫学、特に農薬に関するこれまでの研究と一致しており、疫学研究には多くの限界があり、データの不均一性があるために確固たる結論を出すことができないことを認めている。我々はまた、主要な影響及び 2006 年以降に発表された関連するメタアナリシスが確認されたものについて、更新されたメタアナリシスを実施した。これは小児白血病とパーキンソン病についてのみ可能である。これらの影響については、以前のエビデンスに沿って、農薬ばく露と疾患との間に有意な関連があることが分かった。

キーワード 農薬；疫学研究；農薬ばく露；健康影響；死亡率；症例対照研究；コホート研究

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BACKGROUND AND TERMS OF REFERENCE

Over the last years an abundance of epidemiological studies investigating possible associations of pesticide exposure with adverse health effects on humans have become available. In these studies exposure to pesticides e.g. via inhalation, ingestion, dermal contact or across the placenta has been established as being, or suggested to be, causative for instance for cancer in various organs and tissues, disturbed neurodevelopment of children, allergies, decreased fertility (male and female), birth defects and Parkinson's disease.

However, for many adverse health effects that are attributed to pesticide exposure contradictive or ambiguous studies also exist. Studies vary generally greatly in design (e.g. case control versus cohort studies), sample size and in many cases exposures are rather estimated or assumed than actually determined.

A comprehensive up-to-date literature collection and review covering relevant publications from 1st January 2006 to 31st March 2012 should be carried out in which also the quality of these studies is evaluated.

The objectives of the contract resulting from the present procurement procedure are as follows:

Objective 1: To collect and compile scientific publications in which possible links between pesticide exposure and adverse human health effects have been investigated.

Objective 2: To review and evaluate each collected study in regard to its qualitative aspects (e.g. the corner points of the investigations).

Objective 3: Provision of a database and a report of epidemiological studies.

This contract was awarded by EFSA to: The Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Grecce.

Contractor: The Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Grecce.

Contract title: Literature review on epidemiological studies linking exposure to pesticides and health effects.

Contract number: CFT/EFSA/PRAS/2012/04 – CT 01.

背景と参考文献

ここ数年の間に、農薬ばく露とヒトへの有害健康影響との関連を調査する疫学研究が豊富に行われるようになった。これらの研究では、例えば、吸入、経口、経皮及び経胎盤による農薬ばく露が、様々な臓器や組織のがん、小児の神経発達障害、アレルギー、生殖能力の低下（男性と女性）、先天異常、パーキンソン病などの原因となる、あるいはその可能性が示唆されていることが立証されている。

しかし、農薬ばく露に起因する多くの有害健康影響については、矛盾した、あるいは曖昧な研究も存在する。研究は一般的にデザイン（例：症例対照研究とコホート研究）、サンプルサイズ、そして多くの場合、ばく露量は実際の測定値ではなく、むしろ推定値または想定値である。

2006年1月1日から2012年3月31日までの関連出版物を網羅した包括的な最新の文献収集とレビューを実施し、これらの研究の質も評価すべきである。

今回の調達手続きによる契約の目的は以下の通りである。

目的１：農薬ばく露とヒトへの有害健康影響との関連が調査された科学的出版物を収集・集積する。

目的２：収集された各研究の質的側面（調査のコーナーポイントなど）をレビューし、評価する。

目的３：疫学研究のデータベースと報告書の提供。

本契約は、EFSAが次の者に授与した。イオアニナ大学医学部衛生・疫学部（Ioannina, Grecce）
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契約タイトル：農薬へのばく露と健康影響を関連付ける疫学研究の文献調査
契約番号：CFT/EFSA/PRAS/2012/04 - CT 01

INTRODUCTION AND OBJECTIVES

This project aims to systematically collect, review and appraise epidemiological studies carried out to investigate possible links of pesticide exposure to health-related outcomes in order to improve understanding of already established or suggested associations with adverse effects in humans. The review focuses on all exposure types either through occupation or in general population with a particular focus on investigating sources of heterogeneity. In particular, we have collected scientific publications in which possible links between pesticide exposure and adverse human health effects have been investigated. The available evidence is under review and evaluation with regard to its qualitative aspects. Finally, a database of studies, which examine adverse health effect of pesticides, was compiled.

The final report is structured around health outcome categories and is linked to a *data extraction database*. In the methods we provide a detailed documentation of the search criteria and search strategy used for the literature review and the study selection process. This section also describes the analytical framework with the detailed documentation on the selected exposure and indicators of exposure and the surrogate and clinical outcomes examined. We present the results of the literature search with the full list of eligible studies and the contents of the *data extraction database*. We also present the results of the outcomes and pesticides examined and conclusions based on the literature review findings.

BACKGROUND AND AIMS

Pesticides have been widely used against pests that can damage crops such as insects, fungi, rodents, noxious, weeds, in order to prevent or reduce losses and improve product quality, for many years. Their use is very popular; in 2006 and 2007, the world used approximately 5.2 billion pounds of pesticides. However, despite their extensive use, and the associated benefits from pesticide use, there have been concerns on adverse effects in human health as these chemicals are designed to have adverse biological effects on target organisms. Indeed, there is evidence between pesticide use and adverse health outcomes such as cancers, neurodegenerative disease and birth defects; however, results so far have been inconsistent and firm conclusions cannot be drawn for several pesticides.

The aim of this review is to systematically collect, review and appraise epidemiological studies carried out to investigate possible links of pesticide exposure to health-related outcomes. This review includes all exposure types either through occupation or in the general population with a particular focus on investigating sources of heterogeneity. In particular, we have collected and compiled scientific publications in which possible links between pesticide exposure and adverse human health effects have been investigated. The available evidence has been reviewed and evaluated with regard to its qualitative aspects and data from each eligible study has been extracted. Finally, a database of studies, which examine adverse health effects of pesticides, has been compiled with the aim to facilitate the continuous update of results.

The aforementioned aims constitute a stimulating task due to the methodological challenges of environmental epidemiology and pesticide exposure in particular and the vast volume of the peer-reviewed literature.

序文と目的

本プロジェクトは、すでに確立されている、あるいは示唆されているヒトにおける有害影響との関連についての理解を深めるために、農薬ばく露と健康関連影響との関連を調査するために実施された疫学研究を体系的に収集し、レビューし、評価することを目的としている。このレビューでは、特に食い違いの原因を調査することに焦点を当て、職業を通じた、あるいは一般集団におけるすべてのばく露タイプに焦点を当てている。特に、農薬ばく露とヒトへの有害健康影響との関連が調査された科学的出版物を収集した。利用可能なエビデンスは、その質的側面に関してレビューと評価が行われている。最後に、農薬の有害健康影響を調査した研究のデータベースを作成した。

最終報告書は、健康影響カテゴリーを中心に構成され、データ抽出データベースとリンクしている。方法のセクションでは、文献レビューと研究の選択プロセスで使用した検索基準と検索戦略の詳細な文書を提供している。このセクションでは、選択されたばく露とばく露指標及び検討された代用及び臨床影響に関する詳細な文書を用いた分析的枠組みについても記述している。対象となる研究の完全なリストとデータ抽出データベースの内容を含めた文献検索の結果を提示する。また、検討した影響と農薬の結果及び文献レビューの結果に基づく結論を提示する。

背景と目的

農薬は、昆虫、真菌、野鼠、不快生物、雑草などの作物にダメージを与えることができる有害生物に対して広く使用されており、長年にわたり、損失を防止または削減し、作物の品質を向上させるために使用されている。2006年と2007年には、世界で約52億ポンドの農薬が使用された。しかし、農薬は広範囲に使用されており、それに関連して農薬の使用による利益があるにもかかわらず、これらの化学物質は対象生物に有害影響を及ぼすように設計されているため、ヒトへの有害健康影響が懸念されている。実際、農薬の使用とがん、神経変性疾患、先天異常などの健康有害影響との間にはエビデンスがあるが、これまでのところ結果には一貫性がなく、いくつかの農薬について確固たる結論を出すことはできていない。

本レビューの目的は、農薬ばく露と健康関連影響との関連を調査するために実施された疫学研究を体系的に収集し、レビューし、評価することである。このレビューでは、特に食い違いの原因を調査することに重点を置いて、職業を通じた、または一般集団におけるすべてのばく露タイプを対象としている。特に、農薬ばく露とヒトへの有害健康影響との関連が調査された科学的出版物を収集し、まとめた。利用可能なエビデンスは質的側面に関してレビューされ評価され、妥当な研究からデータが抽出されている。最後に、結果の継続的な更新を容易にする目的で、農薬の有害健康影響を調査した研究のデータベースを作成した。

前述の目的は、特に環境疫学と農薬ばく露の方法論的課題と、膨大な量の査読付き文献のため、刺激的な課題を構成している。

MATERIALS AND METHODS

1. Search strategy

A comprehensive literature search was conducted of peer-reviewed original research pertaining to pesticide exposure and any health outcome. The search strategy was designed so as to identify observational epidemiologic studies published between 1st of January 2006 to 30th of September 2012 and examining the relationship between pesticide exposures during critical exposure time windows (preconception, pregnancy, childhood, adulthood) and any health-related outcome as discussed previously. The search strategy was developed to search primarily the MEDLINE (1950–to date), and EMBASE (Excerpta Medica Database; 1980 to-date) databases as well as TOXNET (Toxicology Data Network; U.S. National Library of Medicine 2012), OpenSigle (2012), and ProQuest Digital Dissertations and Theses (2012) as supplemental searches.

2. Search algorithm for original studies in MEDLINE and EMBASE

This systematic review aimed to identify studies examining any clinical outcome or valid biomarker acting as surrogate for a clinical outcome that has been associated with exposure to pesticides. In order to achieve maximum sensitivity, we did not include any outcome-related search terms in the search algorithm that we developed. For the formation of the search algorithm, we concentrated on pesticides related terms, identified through the MEDLINEMESH terms and EMBASE classification trees on pesticides. In MEDLINE, the MESH terms of pesticides and pesticides (pharmacological action) were examined. Similarly, we examined the pesticide term in the EMBASE Emtree index. We have looked for pesticide categories (i.e. insecticides, herbicides, fungicide etc.) and for specific pesticide names as described in the literature or as pharmacological terms (e.g. DDT or Dichlorodiphenyltrichloroethane) in order to be comprehensive. We have also examined the search terms used in published systematic reviews on pesticide exposure during the past 10 years and looked for any additional terms.

Our first constructed algorithm was long including all aforementioned terms. We piloted different searches and shortened the search to improve the sensitivity of the algorithm with modest impact on the precision. All searches were limited to Humans and to publication date after 1st of January 2006.

The long list of pesticide names provided from the MESH database for pesticides pharmacological names only provided 2,270 citations on top of the pesticides related words search (pesticid* OR pesticides"[MeSH Terms] OR "pesticides"[All Fields] OR "pesticide"[All Fields] OR "pesticides"[Pharmacological Action]) in MEDLINE. Examination of 200 from those 2,270 citations showed that these did not include epidemiological studies and referred to chemical studies on the substances and chemical formation of pesticides. We therefore adopted the search algorithm including the generic terms. The algorithm was constructed in EMBASE as the database provides a function to study MEDLINE and EMBASE simultaneously (see textbox below). The following algorithm was developed:

材料と方法

1. 検索戦略

包括的な文献検索を実施し、農薬ばく露と健康影響に関する査読付きの原著研究を対象とした。検索戦略は、2006年1月1日から2012年9月30日までに発表された観察疫学研究で、重要なばく露期間（妊娠前、妊娠期、小児期、成人期）における農薬ばく露と健康関連影響との関係を調査したものを特定するように設計された。検索戦略は、主にMEDLINE（1950年から現在まで）、EMBASE（Excerpta Medica Database、1980年から現在まで）データベースを使用し、TOXNET（Toxicology Data Network、U.S. National Library of Medicine 2012）、OpenSigle（2012）及びProQuest Digital Dissertations and Theseses（2012）を補足検索として使用した。

2. MEDLINE 及び EMBASE における原著論文の検索アルゴリズム

本システマティックレビューは、農薬へのばく露と関連した臨床影響または臨床影響の代用となる有効なバイオマーカーを調査した研究を特定することを目的とした。最大限の感度を得るために、我々が開発した検索アルゴリズムには影響に関連する検索用語は含まれていない。検索アルゴリズムの構築にあたっては、MEDLINEMESHの用語とEMBASEの農薬分類ツリーを用いて同定された農薬関連の用語に集中した。MEDLINEでは、農薬と農薬（薬理作用）のMESH用語を調べた。同様に、EMBASE Emtreeインデックスの農薬用語を調べた。農薬のカテゴリー（例えば、殺虫剤、除草剤、殺菌剤など）と、文献に記載されている特定の農薬名、または薬理学的用語（例えば、DDTまたはジクロロジフェニルトリクロロエタン）を網羅的に調べた。また、過去10年間の農薬ばく露に関する出版されたシステマティックレビューで使用された検索用語を調べ、追加の用語を調べた。

最初に構築したアルゴリズムは、前述のすべての用語を含む長いものであった。異なる検索を試験的に行い、精度への影響を最小限に抑えながらアルゴリズムの感度を向上させるために検索を短縮した。すべての検索はヒトに限定し、2006年1月1日以降の出版日に限定した。

農薬薬理学的名称のMESHデータベースから提供された農薬名の長いリストは、MEDLINEの農薬関連語検索（pesticid* OR pesticides"[MeSH Terms] OR "pesticides"[All Fields] OR "pesticide"[All Fields] OR "pesticides"[Pharmacological Action]）の上位2,270件の引用のみを提供していた。そのうち2,270件の引用のうち200件を調査したところ、疫学研究は含まれておらず、農薬の物性や化学構造に関する化学的研究を参照していることが判明した。そこで、一般用語を含む検索アルゴリズムを採用した。アルゴリズムは、データベースがMEDLINEとEMBASEを同時に検索する機能を提供しているため、EMBASEで構築した（下記のテキストボックスを参照）。以下のようなアルゴリズムを構築した。

Table 1: Search algorithm for EMBASE and MEDLINE

pesticid* OR 'pesticide'/exp OR 'chemical pest control'/exp OR fungicid* OR 'fungicide'/exp OR herbicid* OR 'herbicide'/exp OR insecticid* OR 'insecticide'/exp OR molluscacid* OR'molluscacide'/exp OR molluscicid* OR 'molluscicide'/exp OR rodenticid* OR 'rodenticide'/exp OR carbamat* OR 'carbamate'/exp OR pyrethroid* OR 'pyrethroid'/exp OR 'chlorinated hydrocarbon'/exp OR 'agricultural chemical'/exp AND [humans]/lim AND [2006-2013]/py

The algorithm resulted in 43,259 citations in EMBASE and MEDLINE combined. Of those, 14,539 were unique to EMBASE. The algorithm includes all pesticides related terms and subcategories used either as emtree entries with the explode option and also as text words. The explode option ensures that when a term has any more specific, or narrower, index terms within the Emtree thesaurus, they are also automatically retrieved as part of the search. Terms such as organochlorine, glyphosate, paraquat and maneb were excluded as they are part of the pesticide tree of the explode option and are searched. Inclusion of these terms would lead to the same set of results. Figure 1 below shows examples of the indexing trees in EMBASE for some of our search terms.

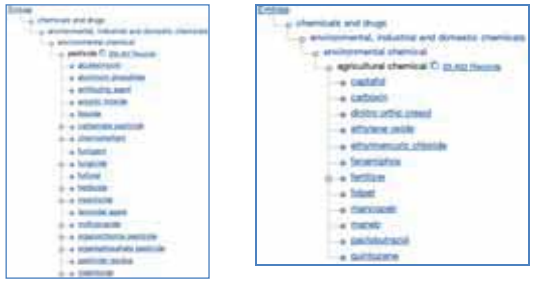


Figure 1: Examples of Emtree classification trees

3. Supplemental searches

The database of TOXNET, which lists databases on toxicology, hazardous chemicals, environmental health, and toxic releases, was also searched to identify any information missed from previous search in MEDLINE and EMBASE. We used only the Databases, which look for references in the biomedical literature (i.e. the Toxicology Literature Online (TOXLINE) and the Developmental Toxicology Literature (DART)). The remaining TOXNET databases provided summaries of Chemical, Toxicological, and Environmental Data per chemical substance and were not relevant to this search. For TOXLINE and DART, we used the generic terms “Pesticide OR Pesticides” as longer search algorithms with the inclusion of pesticides subcategories had only minor impact on the number of references identified. The searches were limited to publication dates after 2006, excluding references identified through MEDLINE. The function to identify chemical synonyms to the search term was enabled. Overall, 893 references were retrieved from TOXLINE and 34 from DART.

表 1：EMBASE 及び MEDLINE の検索アルゴリズム

pesticid* OR 'pesticide'/exp OR 'chemical pest control'/exp OR fungicid* OR 'fungicide'/exp OR herbicid* OR 'herbicide'/exp OR insecticid* OR 'insecticide'/exp OR molluscacid* OR'molluscacide'/exp OR molluscicid* OR 'molluscicide'/exp OR rodenticid* OR 'rodenticide'/exp OR carbamat* OR 'carbamate'/exp OR pyrethroid* OR 'pyrethroid'/exp OR 'chlorinated hydrocarbon'/exp OR 'agricultural chemical'/exp AND [humans]/lim AND [2006-2013]/py

このアルゴリズムにより、EMBASE と MEDLINE を合わせて 43,259 件の引用が行われた。そのうち 14,539 件は EMBASE に固有のものであった。このアルゴリズムには、分割オプションを使用して Emtree エントリとして、またテキストワードとして使用された農薬関連の用語とサブカテゴリがすべて含まれている。分割オプションを使用すると、用語が Emtree のシソーラス内でより具体的な、またはより狭いインデックス用語を持つ場合、それらも検索の一部として自動的に検索される。有機塩素、グリホサート、パラコート、マネブなどの用語は、分割オプションの農薬ツリーの一部であり、検索されるため、除外された。これらの用語を含めると、同じ結果が得られる。以下の図 1 は、EMBASE で検索された用語のインデックスツリーの例を示している。

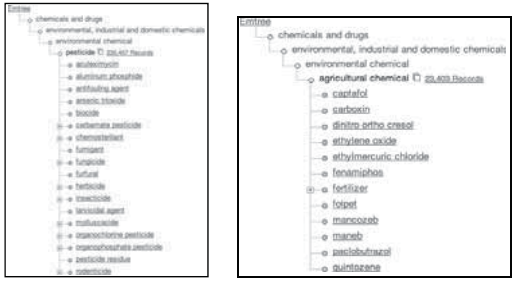


図 1：Emtree の分類ツリーの例

3. 補足検索

また、毒性学、有害化学物質、環境衛生、有害物質排出に関するデータベースを掲載しているTOXNETのデータベースを検索し、MEDLINEやEMBASEでの前回の検索で見逃した情報を特定した。生物医学文献（Toxicology Literature Online（TOXLINE)及びDevelopmental Toxicology Literature（DART））の文献を検索するデータベースのみを使用した。残りのTOXNETデータベースは、化学物質ごとの化学的データ、毒物学的データ、環境データのサマリーを提供しており、今回の検索には関係なかった。TOXLINEとDARTについては、「Pesticide OR Pesticides」という一般的な用語を使用したが、農薬のサブカテゴリを含む検索アルゴリズムが長くなっても、同定された参考文献の数にわずかな影響しかなかったためである。検索は2006年以降の出版日に限定し、MEDLINEで同定された文献は除外した。検索語の化学物質の同義語を特定する機能を有効にした。全体では、TOXLINEから893件、DARTから34件の文献が検索された。

また、ヨーロッパで出された灰色文献[非商業出版物]（論文）の書誌的参考文献700,000件を収録したSystem for Information on Grey Literature in Europe（OpenSigle）も調べた。2006年以降に出

We also looked into the System for Information on Grey Literature in Europe (OpenSigle), which includes 700.000 bibliographical references of grey literature (paper) produced in Europe. There were no bibliographical references on pesticides (search term pesticid*) published after 2006.

We have also constructed a search algorithm to search the ProQuest Digital Dissertations and Theses database. We excluded from our search articles published in scholarly journals as those will have been identified through MEDLINE and EMBASE. We used the search term "pesticide* AND health" and limited our search to specific subjects (environmental science OR public health OR environmental health OR epidemiology OR pesticides OR nutrition OR occupational health) and to publication dates between 2006 and 2012. This search strategy resulted in 1,713 results. Results were numerous when no subject limits were used (12,135) or when the term "health" was excluded from the initial algorithm (18,195).

Finally, the reference lists of all identified eligible studies and systematic reviews are scanned during data extraction for additional references.

4. Search for literature systematic reviews and meta-analysis

We also performed targeted searches for systematic reviews and meta-analysis in relation to specific outcomes. We restricted the search for reviews on those outcomes where more than 4 studies had been identified and we performed targeted searches in MEDLINE using the name of the outcome along with the keywords "systematic review OR meta-analysis" limited to the title or the abstract of the paper.

5. Structure of this report

This report is structured around health outcome categories and provides the results for each outcome group separately. A section on general conclusions is presented at the end. At the end of each section on outcomes and tables and figures are presented to allow ease of reading. Also, the ID numbers of each eligible article are referenced throughout the text. These correspond to the ID for each health outcome group in the *data extraction database* which has been provided as a separate file to this report. The ID is defined with an abbreviation for the specific health outcome and a study number.

版された農薬（検索語pesticid*）に関する書誌的文献はなかった。

また、ProQuest Digital Dissertations and Thesesデータベースを検索するための検索アルゴリズムを構築した。MEDLINEやEMBASEで検索した結果、学術雑誌に掲載された論文は検索対象から除外した。検索語を"pesticide* AND health "とし、特定の主題（環境科学 OR 公衆衛生 OR 環境保健 OR 疫学 OR 農薬 OR 栄養 OR 労働衛生）と、2006年から2012年までの出版日に限定して検索を行った。この検索戦略の結果、1,713件の検索結果が得られた。主題制限が行われていない場合（12,135）、または「健康」という用語が最初のアルゴリズムから除外されている場合（18,195）には、多くの検索結果が得られた。

最後に、特定されたすべての妥当な研究とシステマティックレビューの参考文献リストをデータ抽出の際にスキャンして追加の参考文献を探した。

4. 文献システマティックレビューとメタアナリシスの検索

また、特定の健康影響に関連したシステマティックレビューやメタアナリシスを対象とした検索を行った。MEDLINEでは、4件以上の研究が確認された健康影響を対象としたレビューに限定し、健康影響名と「システマティックレビュー OR メタアナリシス」というキーワードを用いて、論文のタイトルまたは要約に限定して検索を行った。

5. 本報告書の構成

本報告書は、健康影響のカテゴリーを中心に構成されており、各健康影響のグループの結果を個別に提供している。最後に一般的な結論のセクションが提示されている。また、各健康影響のセクションの最後には、読みやすいように表と図を掲載している。また、本文中では各対象論文の ID 番号を参照している。これらは、本報告書に別ファイルとして提供されているデータ抽出データベースの各健康影響グループの ID に対応している。IDは、特定の健康影響の略語と研究番号で定義されている。

Table 2: Summary of recourses searched, search terms and references identified

Database	Search terms	Limits	N references
MEDLINE	pesticid* OR 'pesticide'/exp OR 'chemical pest control'/exp OR fungicid* OR 'fungicide'/exp OR herbicid* OR 'herbicide'/exp OR insecticid* OR 'insecticide'/exp OR molluscacid* OR' molluscacide'/exp OR molluscicid* OR 'molluscicide'/exp OR rodenticid* OR 'rodenticide'/exp OR carbamat* OR 'carbamate'/exp OR pyrethroid* OR 'pyrethroid'/exp OR 'chlorinated hydrocarbon'/exp OR 'agricultural chemical'/exp	Humans, Publication date: 2006-2012	28,729
EMBASE	pesticid* OR 'pesticide'/exp OR 'chemical pest control'/exp OR fungicid* OR 'fungicide'/exp OR herbicid* OR 'herbicide'/exp OR insecticid* OR 'insecticide'/exp OR molluscacid* OR' molluscacide'/exp OR molluscicid* OR 'molluscicide'/exp OR rodenticid* OR 'rodenticide'/exp OR carbamat* OR 'carbamate'/exp OR pyrethroid* OR 'pyrethroid'/exp OR 'chlorinated hydrocarbon'/exp OR 'agricultural chemical'/exp	Humans, Publication date: 2006-2012, no references identified through MEDLINE	14,530
TOXLINE	Pesticide OR Pesticides	Publication date: 2006-2012, no references identified through MEDLINE	893
DART	Pesticide OR Pesticides	Publication date: 2006-2012, no references identified through MEDLINE	34
OpenSigle	Pesticide*	Publication date: 2006-2012	0
ProQuest	Pesticide* AND health	Publication date: 2006-2012, Subjects (environmental science, public health, environmental health, epidemiology, pesticides, nutrition, occupational health), no articles published in scholarly journals	1,713 Total: 45,899

表 2：検索されたリソース、検索語及び特定された参照先の概要

データベース	検索条件	Limits	文献数
MEDLINE	pesticid* OR 'pesticide'/exp OR 'chemical pest control'/exp OR fungicid* OR 'fungicide'/exp OR herbicid* OR 'herbicide'/exp OR insecticid* OR 'insecticide'/exp OR molluscacid* OR' molluscacide'/exp OR molluscicid* OR 'molluscicide'/exp OR rodenticid* OR 'rodenticide'/exp OR carbamat* OR 'carbamate'/exp OR pyrethroid* OR 'pyrethroid'/exp OR 'chlorinated hydrocarbon'/exp OR 'agricultural chemical'/exp	ヒト，公開日：2006～2012	28,729
EMBASE	pesticid* OR 'pesticide'/exp OR 'chemical pest control'/exp OR fungicid* OR 'fungicide'/exp OR herbicid* OR 'herbicide'/exp OR insecticid* OR 'insecticide'/exp OR molluscacid* OR' molluscacide'/exp OR molluscicid* OR 'molluscicide'/exp OR rodenticid* OR 'rodenticide'/exp OR carbamat* OR 'carbamate'/exp OR pyrethroid* OR 'pyrethroid'/exp OR 'chlorinated hydrocarbon'/exp OR 'agricultural chemical'/exp	ヒト， 公開日：2006～2012，MEDLINE で確認された文献は無い。	14,530
TOXLINE	Pesticide OR Pesticides	公開日:2006～2012 年､MEDLINE で確認された文献は無い。	893
DART	Pesticide OR Pesticides	公開日:2006～2012 年､MEDLINE で確認された文献は無い。	34
OpenSigle	Pesticide*	掲載時期：2006 年～2012 年	0
ProQuest	Pesticide* AND health	掲載時期：2006 年～2012 年、主題（環境科学、公衆衛生、環境保健、疫学、農薬、栄養、労働衛生）、専門的学術誌に掲載された論文は無い。	1,713 合計: 45,899

6. Selection of studies

All titles identified through the literature search of various databases were screened to identify studies, which evaluated the association between pesticides and health outcomes including any surrogate outcome. All abstracts of the selected titles are then screened in duplicate to identify epidemiological studies linking pesticide exposure to any health outcome including surrogate outcome. Both primary studies and systematic reviews or meta-analyses are selected. Articles that potentially meet eligibility criteria at the abstract screening stage have been retrieved and the full text articles have been reviewed in duplicate for eligibility. The reason for rejection of all full text articles has been recorded.

6.1. Eligibility criteria for full text articles

We included observational studies assessing the association between pesticide exposure and health-related outcomes. We included cohort, cross-sectional and case- control studies. We included studies performed in humans published from 1st of January 2006 to 30th of September 2012. Animal studies and studies performed in human cells have been excluded. We had no language, population or geographical restrictions. To enhance totality of the evidence, all types of pesticides have been considered. Exposure to pesticides was defined as reported use of pesticides by the study participant or by government registry data (self administrated questionnaires, interviewer administrated questionnaires, job exposure matrix (JEM)), by residential status (proximity to pesticide exposure), by detecting biomarkers associated with pesticide exposure or by any other means as defined by each study. Eligible health-related outcomes were “major” clinical outcomes, such as neoplasias or Parkinson’s disease, clinical surrogate outcomes such as neurocognitive scales, or laboratory surrogate outcomes with an established association with clinical outcomes, such as liver enzymes.

Narrative reviews, case-series and case-reports (studies without control populations) are excluded. We also excluded studies assessing the health-related effect of pesticide poisoning or accidental high-dose pesticide exposure. We have excluded studies with no availability of sufficient quantitative information reported in the article (e.g. effect estimates) so that effect sizes or measures of associations can be calculated. Whenever reports pertained to the same study at different follow-up periods and examining the same outcome, we retained the one with the longer follow-up to avoid data duplication. We also excluded studies that referred to fertilizers (exploded from the algorithm term “agricultural chemical”) as well as studies referred to the adverse effects of substances used as therapy for various medical conditions such as warfarin for anticoagulation or agents used in the treatment of scabies. Solvents and other non-active ingredients in pesticides/herbicides were not considered eligible. We excluded studies that investigate the various effects of Agent Orange on chemical warfare veterans as they represent cases of very high dose exposures. Finally, studies which examined the association between exposure and biomarkers of exposure were also not considered eligible as they do not examine health outcomes. Finally, following consultation with EFSA, we excluded studies/analyses investigating exposure to pesticides: arsenic, α, β, hexachlorocyclohexane (HCH), lead, dioxins and dioxin-like compounds including polychlorinated biphenyls (PCBs) as these chemicals were not considered relevant for the current project.
Regarding systematic reviews and meta-analyses, we considered all systematic reviews and meta-analyses that systematically assessed the effect of pesticide exposure to health-related outcomes, regardless of the pesticide, exposure window and outcome assessed. We included all publications where a systematic approach was endorsed (systematic literature search, assessment of methodological characteristics of the included studies and, if a meta-analysis was performed, the use of standard analytical tools including the use of a weighted summary estimate and a formal appraisal of heterogeneity). Narrative reviews are excluded.

6. 研究の選択

様々なデータベースの文献検索で特定されたすべてのタイトルをスクリーニングし、農薬と代替健康影響を含む健康影響との関連を評価した研究を特定した。次に、選択したタイトルのすべての要約を重複してスクリーニングし、農薬ばく露と代替健康影響を含むあらゆる健康影響との関連を評価する疫学研究を特定した。主要研究とシステマティックレビューまたはメタアナリシスの両方を選択する。要約審査の段階で妥当性基準を満たす可能性のある論文を検索し、全文論文を重複して審査して妥当性を確認した。すべての全文論文の却下理由は記録されている。

6. 1. 全文論文の妥当性基準

農薬ばく露と健康関連影響との関連を評価する観察研究を対象とした。コホート研究、横断研究、症例対照研究を対象とした。2006 年 1 月 1 日から 2012 年 9 月 30 日までに発表されたヒトを対象とした研究を対象とした。動物を対象とした研究及びヒトの細胞を対象とした研究は除外した。言語、集団、地理的制限はなかった。エビデンスの全体性を高めるために、すべての種類の農薬を考慮した。農薬へのばく露は、研究参加者による農薬の使用報告、または政府登録データ（自己管理質問紙、面接官管理質問紙、職業ばく露マトリックス（JEM））、居住状況（農薬ばく露への近接性）、農薬ばく露に関連するバイオマーカーの検出、または各研究で定義されたその他の手段によって定義されたものとした。妥当な健康関連影響は、腫瘍形成やパーキンソン病などの「主要な」臨床影響、神経認知スケールなどの臨床代替健康影響、肝酵素などの臨床影響との関連が確立されている代用実験的影響とした。

ナラティブレビュー、症例集積、症例報告（対照集団のない研究）は除外した。また、農薬中毒または不慮の高用量農薬ばく露による健康関連の影響を評価する研究も除外した。論文で報告された十分な量的情報（効果推定値など）が入手できない研究は除外し、効果量や関連の尺度を計算できるようにした。異なる追跡期間で同じ研究に関連する報告があり、同じ結果を調査している場合は、データの重複を避けるために、追跡期間が長い方の研究を保持した。また、肥料に言及した研究（アルゴリズム用語「農薬」から分解）や、抗凝固剤のワルファリンや疥癬の治療に用いられる薬剤など、様々な病状の治療に用いられる物質の副作用に言及した研究も除外した。農薬・除草剤に含まれる溶剤などの非有効成分は対象外とした。化学戦経験者に対するオレンジ剤の様々な影響を調査した研究は、極高用量ばく露の事例であるため除外した。最後に、ばく露とばく露のバイオマーカーとの関連を調査した研究も、健康への影響を調査していないため、対象外とした。最後に、EFSAとの協議により、ヒ素、アルファ及びベータヘキサクロロシクロヘキサン（HCH）、鉛、ポリ塩化ビフェニル（PCB）を含むダイオキシン類などの農薬へのばく露を調査した研究／分析は、本プロジェクトには関係がないと考えられるため除外した。

システマティックレビュー及びメタアナリシスについては、評価された農薬、ばく露域、影響にかかわらず、健康関連影響に対する農薬ばく露の影響をシステマティックに評価したすべてのシステマティックレビュー及びメタアナリシスを調査した。系統的アプローチ（系統的文献検索、対象とした研究の方法論的特徴の評価、メタアナリシスが実施された場合には重み付け要約推定値の使用や不均一性の形式的評価を含む標準的な分析ツールの使用）が承認されているすべての出版物を対象とした。ナラティブレビューは除外する。

6.2. Quality control measures

The pilot literature searches have all been performed in duplicate. In addition, the first 500 results of all title searches were performed in duplicate and results were compared between investigators, which displayed high levels of agreement. The kappa statistic for agreement was 0.78. Two independent research group members performed in duplicate the abstract screening, the full text screening and the data extraction. All discrepancies are resolved by consensus or by a third arbitrator.

6.3. Data extraction database

We have constructed and tested the *data extraction database* with data extraction items and quality assessment items that were implemented through the whole process. The *data extraction database* has been structured in 7 domains: Reference, Time period, Study characteristics, Exposure assessment, Outcomes, Statistical analysis and Quality assessment (separate database file). The first 6 domains pertain to information directly extracted from the full-texts of eligible studies and would be primarily used to select studies for quantitative synthesis and aid quantitative synthesis. Studies contribute one row in the database for each outcome examined and for each exposure examined. When studies present various definitions of exposure we select for data extraction the most comprehensive definition of exposure and subsequently the one with the largest sample size. However when studies include any type of quantitative information for different biomarkers used for the identification of the same chemical substance e.g. p,p'-DDT and p,p'-DDE for dichlorodiphenyltrichloroethane (DDT), they are all reported in separate rows. When studies present data in subgroups (e.g. males and females) we extract only their main analysis (whole group) unless the data is only presented in subgroups in which case multiple rows are presented. Analyses regarding different pesticide classes and different health outcomes are extracted individually. Appendix II explains all the items used in the *data extraction database*.

The data extraction form was validated through a robust and systematic procedure. Specifically, various versions of the form were validated after blinded loops of extracting information for studies randomly selected from the database. We opted for the maximum agreement while preserving the comprehensiveness of the database. Two investigators extract each item independently and discrepancies are resolved with discussion.

6.4. Quality appraisal

The last part of the *data extraction database*, concerns the methodological appraisal of each eligible paper. The areas that we have focused are the study design, the study population, the level of details in exposure definition and the methods of exposure measurement and the specificity of the measurement. These are crucial questions to be asked in exposure assessment epidemiology. We have also focused on the efforts undertaken to account for confounders through matching or multivariable models, blinded exposure assessment and well-defined and valid outcome assessment. We have also looked at whether the source of funding was acknowledged. The elements of the methodological appraisal were considered from the RTI item bank. The RTI item bank is a practical and validated item bank for evaluating the risk of bias and precision of observational studies of interventions or exposures included in systematic evidence reviews. The questions were adapted to reflect exposure assessment. Across the quality appraisal questions we consistently coloured the responses to qualitative assessment in green, orange and red with green representing low risk of bias and red high risk of bias. Table 3

6.2. 品質管理対策

パイロット文献検索はすべて重複して実施した。さらに、すべてのタイトル検索の最初の500件の結果は重複して行い、研究者間で結果を比較し、高いレベルの一致を示した。同意度のカッパ統計量は0.78であった。2人の独立した研究グループのメンバーが、要約スクリーニング、全文スクリーニング、データ抽出を重複して行った。すべての不一致は、合意または第三者の判定によって解決した。

6.3. データ抽出データベース

全工程を通じて実行されたデータ抽出項目と品質評価項目を用いて、データ抽出データベースの構築及び確認を行った。データ抽出データベースは7つのドメイン：参考文献、期間、試験特性、ばく露評価、影響、統計分析、品質評価（別々のファイル）で構成されている。最初の 6 つの領域は、対象となる研究の全文から直接抽出された情報に関連しており、主に定量的統合のための研究を選択し、定量的統合を支援するために使用される。研究は、調査された各影響と調査された各ばく露について、データベースの一行を提供している。研究が様々なばく露の定義を提示している場合には、最も包括的なばく露の定義をデータ抽出のために選択し、それに続いてサンプルサイズが最も大きいものを選択する。しかし、同じ化学物質の同定に使用される異なるバイオマーカーの定量的情報を含む研究、例えばジクロロジフェニルトリクロロエタン（DDT）の p,p'-DDT と p,p'-DDE のように、それらはすべて別々の行で報告されている。研究がサブグループでデータを提示している場合（例：男性と女性）は、データがサブグループでのみ提示されている場合は複合論争が提示されている場合を除き、主分析（グループ全体）のみを抽出している。異なる農薬クラスと異なる健康影響に関する分析は、個別に抽出されている。付録IIでは、データ抽出データベースで使用されたすべての項目を説明している。

データ抽出フォームは、妥当で体系的な手順を経て検証された。具体的には、データベースから無作為に選択された研究の情報を抽出するブラインドループの後、様々なバージョンのフォームを検証した。データベースの網羅性を維持しつつ、最大の一致度が得られるものを選択した。各項目については、2名の研究者がそれぞれ独立して抽出し、不一致は議論によって解決している。

6.4. 品質評価

データ抽出データベースの最後の部分は、対象となる各論文の方法論的評価に関するものである。ここでは、研究デザイン、研究集団、ばく露の定義の詳細度、ばく露測定の方法、測定の特異性などに焦点を当てている。これらはばく露評価の疫学において問われる重要な問題である。我々はまた、マッチングモデルや多変量モデル、盲検化されたばく露評価、十分に定義された有効な影響評価によって交絡因子を考慮するための努力にも焦点を当ててきた。また、資金源が認められているかどうかにも注目した。方法論的評価の要素は RTI 項目バンクから調査した。RTI 項目バンクは、システマティック・エビデンスレビューに含まれる介入またはばく露の観察研究のバイアスのリスクと精度を評価するための実用的で妥当性のある項目バンクである。質問はばく露評価を反映するように適応されている。質的評価の質問では、質的評価への回答を一貫して緑、オレンジ、赤で色分けし、緑はバイアスのリスクが低く、赤はバイアスのリスクが高いことを表している。以下の表 3 は、それぞれどの回答が低リスク、高リスクと考えられたかを説明したものである。しかし、品質評価の質問は、各研究に関連

below explains which answers were considered low and high risk respectively. However, the quality appraisal questions should be interpreted with caution, as they are only suggestive of the risk of bias associated with each study. There may be studies which score high in this quality assessment and still have a high risk of bias and vice versa. A final column was constructed to grade the overall quality of the studies in low, intermediate and high. This classification was based on the answers to the methodological assessment questions as explained in Table 3.

Table 3: Methodological assessment of eligible studies

Question	High risk	Low risk
Study design (prospective, retrospective, mixed, cross-sectional)	Retrospective, mixed, NA	Prospective
Inclusion/exclusion criteria clearly stated (yes, partially, no)	No	Yes
Authors mention power calculations (yes, no)		Yes
Level of detail in describing exposure (high, medium, low)	Low	High
Robust measurement of exposure. (biomarker (yes); small area ecological measures, job titles, questionnaire (partial); was based on large area ecological measures (no)	No	Yes
Were measures of exposure specific? yes; based on broader, chemically-related groups (partial); based on broad groupings of diverse chemical and toxicological properties (no)	No	Yes
Attempt to balance the allocation between the groups (e.g., through stratification, matching)	No	Yes
Adjustment performed for potential confounders (yes, some, no)	No	Yes
Assessors blinded to exposure status (for cohort studies)	No	Yes
Outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	No	Yes
Sample size	Low	Top
Rough quality assessment	>6 answers high risk	>6 asnwers low risk

6.5. Quantitative synthesis

Quantitative synthesis of the results was only attempted when there were more than 4 studies per examined outcome and when there was no substantial heterogeneity among the published evidence. The presence and extent of heterogeneity was assessed by the I^2 (ranging from 0% to 100%) (Ioannidis 2007). We have summarized the RR/OR estimates using fixed and random-effects models (Lau 1997). Fixed-effects models assume that there is a common underlying effect and the variability observed is attributed to chance alone; random effects models acknowledge that true between-study heterogeneity exists and take into account the presence of heterogeneity into their calculations. In the absence of heterogeneity, fixed-and random-effects models yield the same results. Publication bias was assessed using funnel plots and visual inspection of the results.

For each outcome with more than 5 eligible studies quantitative synthesis was attempted. We did not include data from the same cohort study; either presented in the same or in different publications in the same meta-analysis when the groups compared were not mutually exclusive. For each outcome with more than 4 studies, we also looked for previously published meta-analyses to compare results and to interpret our findings in the context of previous studies. Meta-analyses were found through a) systematic reviews and meta-analyses identified through our literature review and b) targeted searches in PUBMED to identify published meta-analyses for each outcome of interest. We attempted to update any previously published meta-analyses with our results when the meta-analysis a) included studies published by 2006 and b) when outcome and exposure definitions were comparable with the definitions used in this report. Finally, we also plotted funnel plots to visually inspect asymmetry when more than 10 studies were include in the meta-analysis.

するバイアスのリスクを示唆しているに過ぎないので、注意して解釈する必要がある。この品質評価のスコアが高くても、バイアスのリスクが高い研究もあれば、その逆もあるかもしれない。最後の列は、研究の全体的な質を低、中、高で評価するために作成された。この分類は、表３で説明した方法論的評価の質問に対する回答に基づいている。

表 3：対象研究の方法論的評価

質問	高リスク	低リスク
研究デザイン（有望、回顧的、混合、断面的）	回顧的、混合、該当なし	有望
除外基準が明確に記載されている（はい、部分的に、いいえ）	いいえ	はい
著者は電力計算について言及しています（はい、いいえ）		はい
暴露の記述の詳細レベル（高、中、低）	低	高
暴露のロバストな測定（バイオマーカー（有）；小面積生態学的尺度、職種、アンケート（部分的）；大面積生態学的尺度（無）に基づいている。）	いいえ	はい
曝露の尺度は特定のものだったか？（はい；より広範な化学的に関連したグループに基づいて（部分的）、多様な化学的および毒性学的特性の広範なグループに基づいて（いいえ）。	いいえ	はい
グループ間の配分のバランスを図る（層別化、マッチングなど）。	いいえ	はい
潜在的な交絡因子の調整を行った（はい、いくつか、いいえ）。	いいえ	はい
被ばく状態に盲検化された評価者（コホート研究の場合）	いいえ	はい
有効かつ信頼性の高い尺度を用いて評価された結果は、すべての研究参加者に一貫して実施されているか？	いいえ	はい
サンプルサイズ	低	最大
ラフな品質評価	6 以上の回答で高リスク	6 以上の回答で低リスク

6.5. 定量的な統合

結果の定量的な統合は、調査された影響ごとに4件以上の研究があり、発表されたエビデンス間に実質的な不均一性がない場合にのみ試みられた。不均一性の存在と程度は、I2（0%から100%の範囲）で評価した（Ioannidis 2007）。固定効果モデルとランダム効果モデルを用いて、RR/ORの推定値をまとめた（Lau 1997）。固定効果モデルでは、共通の基礎となる効果が存在し、観察された変動は偶然のみに起因すると想定している。不均一でない場合、固定効果モデルとランダム効果モデルでは同じ結果が得られる。出版バイアスは、ファンネルプロットと結果の視覚的精査を用いて評価した。

5件以上の妥当研究がある各影響について、定量的な統合を試みた。比較するグループが相互に排他的でない場合には、同じメタアナリシスにおいて、同じコホート研究からのデータはなかった。4件以上の研究がある各影響については、結果を比較し、以前の研究の背景の中で我々の知見を解釈するために、以前に発表されたメタアナリシスも探した。メタアナリシスは、a) 文献レビューで同定されたシステマティックレビュー及びメタアナリシス及びb) 調査対象の各影響について公表されているメタアナリシスを同定するために、PUBMDBDでの標的検索によって発見された。メタアナリシスのa) 2006年までに発表された研究が含まれており、b) 影響及びばく露の定義が本報告書で使用されている定義と同等である場合には、以前に発表されたメタアナリシスを我々の結果で更新するよう試みた。最後に、10件以上の研究がメタアナリシスに含まれている場合に非対称性を視覚的精査するためにファンネルプロットをプロットした。

RESULTS

7. Overall results

This section focuses on the literature review results including flowcharts with number of studies screened and deemed eligible as well as number of excluded studies and corresponding reasons. It also provides an overview of the studies identified and their main characteristics.

7.1. Selection process for individual studies

Of the 43,259 retrieved citations, 40,477 were excluded at the title screening level. Of the 2,782 remaining titles, a further 1,654 were excluded after the abstract screening. We thus deemed eligible, 1,128 citations to be scrutinized at the full-text level of which 1,101 were original research articles and 27 were systematic reviews or meta-analyses. Of the 1,101 original articles, 184 were excluded (Figure 2). For few (101) publications were the full text (or abstract for conference presentations) has not been found online, we sought the full text through letters to authors and investigations from our library. This has not been possible for 58 studies for which we extracted information from the abstract only.

Main reasons for exclusion at the full-text level pertained to: no quantitative information/ data (these were mainly abstract presentations or comments/ editorials which did not present any quantitative information for the association between pesticides and health outcomes, n=108); duplicate records (n=28), no implied use of pesticides (n=18), studies on poisoning or accidental very high doses (n=11), reviews with no primary data (n=11), no data on health outcomes (n=8). Supplemental searches did not succeed to provide additional references as they resulted in a large number of policy documents, grant applications documents and studies already retrieved. Supplemental searches through reference lists of identified studies and especially the reference lists of identified systematic reviews will continue during data extraction and any new identified studies will be added to the current list of eligible studies. During full text screening and data abstraction a further 301 studies were excluded. The main reason for exclusion was no eligible pesticide, such as Polychlorinated Biphenyls (PCBs) (Figure 2). Overall, 602 individual publications were eligible for inclusion in the present review. These 602 publications correspond to 6,479 different analyses, which are also present in the *data extraction database*.

Any enquiries related to this output should be addressed to pesticides.ppr@efsa.europa.eu

Suggested citation: Ntzani EE, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I, 2013. Literature review on epidemiological studies linking exposure to pesticides and health effects. EFSA supporting publication 2013:EN-497, 159 pp.

Available online: www.efsa.europa.eu/publications

結果

7. 全体の結果

このセクションでは、スクリーニングされ、妥当と判断された研究の数、除外された研究の数とそれに対応する理由を示すフローチャートを含む文献レビューの結果に焦点を当てている。また、同定された研究とその主な特徴の概要についても説明する。

7.1. 個々の研究の選択プロセス

検索された43,259件の引用のうち、40,477件がタイトルのスクリーニングレベルで除外された。残りの2,782タイトルのうち、さらに1,654タイトルが要約スクリーニングで除外された。その結果、1,128件の引用文献のうち、1,101件が原著論文であり、27件がシステマティックレビューまたはメタアナリシスであることが判明した。1,101 本の原著論文のうち 184 本が除外された（図 2）。また、全文（または学会発表のための要約）がオンラインで見つからない出版物（101 件）については、著者への手紙や蔵書からの調査により全文を検索したが、要約のみから情報を抽出した58研究については、これが不可能であった。

全文レベルで除外した主な理由は次の通りである：定量的な情報/データがない（これらは主に、農薬と健康影響との関連に関する定量的な情報を提示していない要約発表またはコメント/論説であった、n=108）；記録の重複（n=28）、農薬の使用が示唆されていない（n=18）、中毒または不慮の極高用量ばく露に関する研究（n=11）、主要データのないレビュー（n=11）、健康影響に関するデータがない（n=8）。補足検索では、大量の政策文書、助成金申請書、研究が既に検索されたため、追加の参考文献を提供することはできなかった。識別された研究の参照リスト、特に識別されたシステマティックレビューの参照リストからの補足検索は、データ抽出の間も継続され、新たに識別された研究は、現在の妥当な研究リストに追加される。全文スクリーニングとデータ抽出の際に、さらに301研究が除外された。除外の主な理由は、ポリ塩化ビフェニル（PCB）などの妥当な農薬がなかったことであった（図 2）。全体として、602 の個別の出版物が本レビューに含めることができた。これらの602の出版物は、6,479の異なる分析に対応しており、データ抽出データベースにも存在する。

このアウトプットに関連するお問い合わせは pesticides.ppr@efsa.europa.eu までお願いします。
提案された引用。Ntzani EE, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I, 2013. 農薬へのばく露と健康への影響を関連付ける疫学研究に関する文献レビュー。EFSA 支援出版物 2013:EN-497, 159 pp
Available online: www.efsa.europa.eu/publications

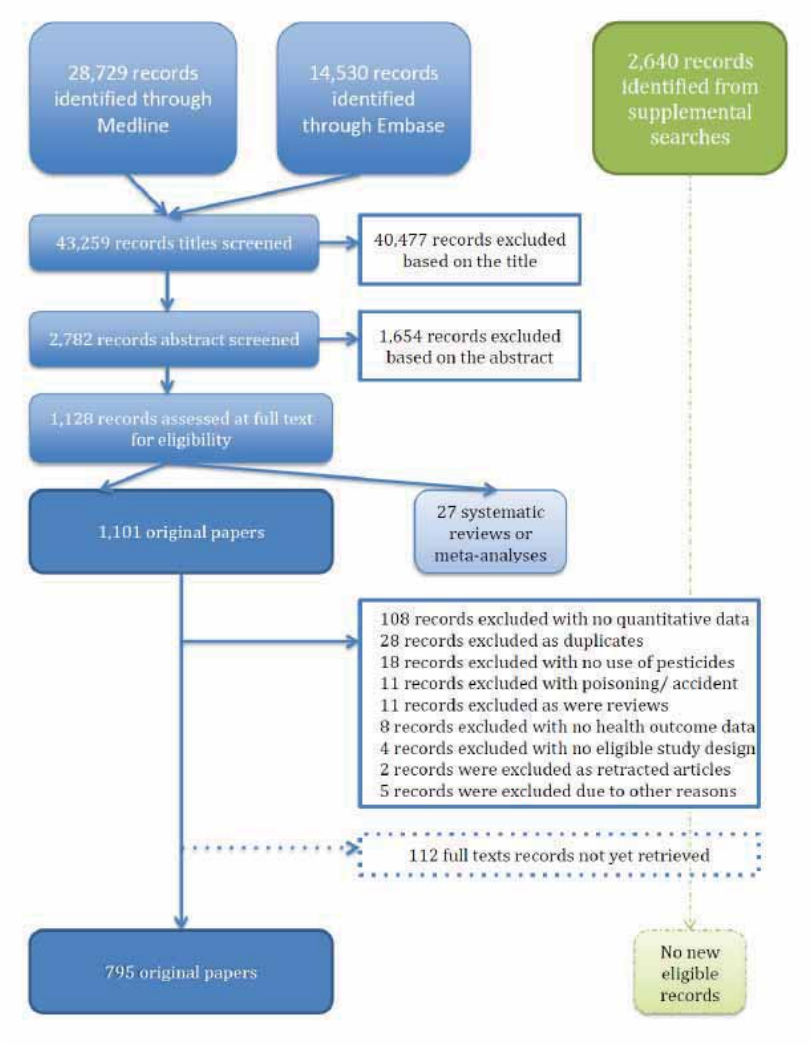


Figure 2: Flowchart of eligible studies

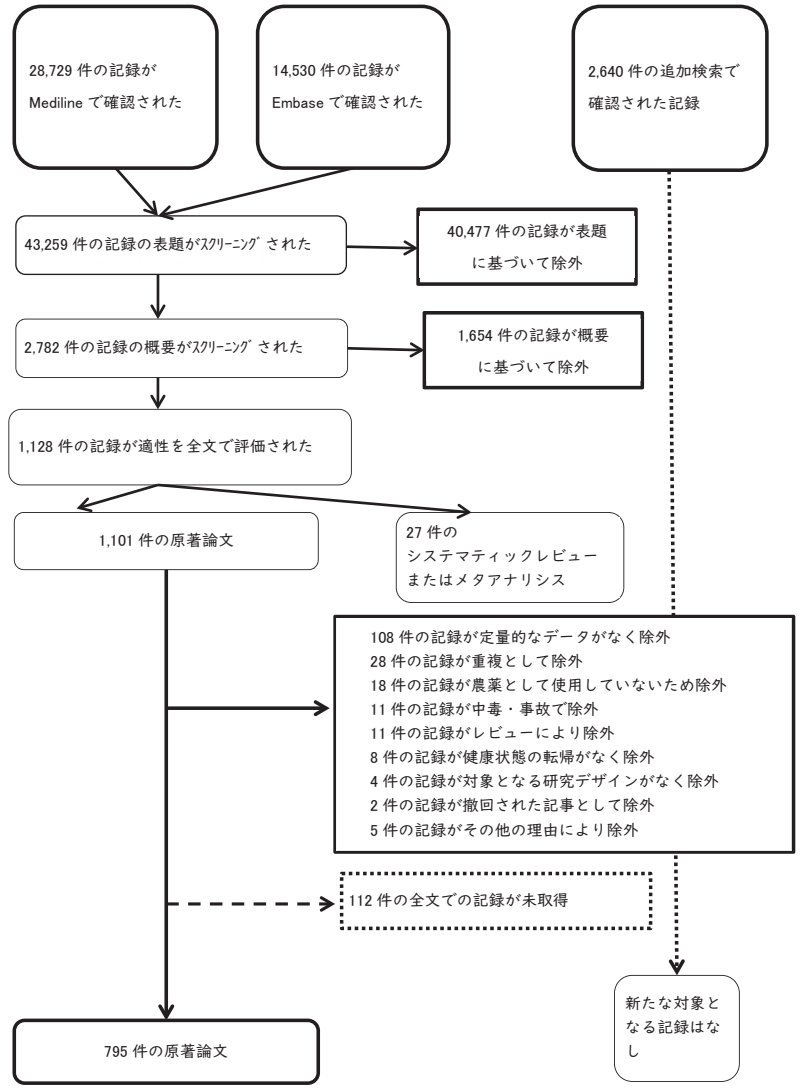


図 2：対象となる研究のフローチャート

7.2. Evidence map tables and outcomes examined

We observed a great variety of assessed outcomes covering a wide range of pathophysiologies. “Hard” clinical outcomes as well as many surrogate outcomes are present in the database reflecting the different methodologies endorsed to approach the assessed clinical research questions. We divided the different outcomes into 23 major disease categories (Table 4 and Figure 3). The largest proportion of studies pertains to cancer outcomes (N=164) and outcomes related to child health (N=84). Table 4 corresponds to the Evidence map Table and shows the outcome mapping of the project describing all outcomes that have been associated with pesticide exposure between 2006 and 2012 and their frequency.

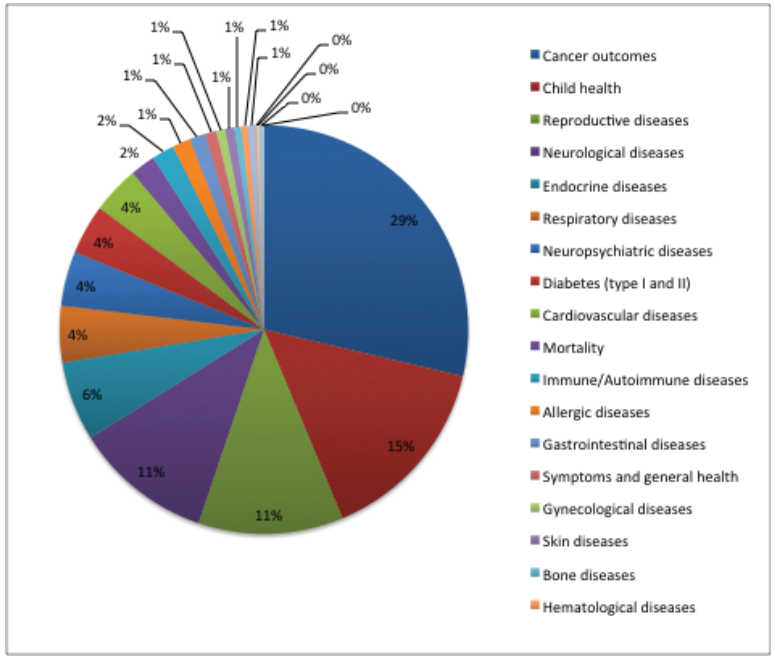


Figure 3: Major outcome categories and corresponding percentage of studies examining those outcomes among the eligible publications

7.2. エビデンスマップ表と調査した影響

我々は、幅広い病態生理をカバーする多種多様な評価された影響を調査した。このデータベースには、評価された臨床研究上の質問にアプローチするために承認された様々な方法論を反映して、「ハード」な臨床影響と多くの代替健康影響が存在している。我々は、異なる影響を23の主要な疾患カテゴリーに分類した（表4及び図3）。研究の中で最も多いのは、発がん（N=164）と小児の健康に関連する影響（N=84）である。表4はエビデンスマップ表に対応し、2006 年から 2012 年の間に農薬ばく露に関連したすべての影響とその頻度を記述したプロジェクトの影響マッピングを示したものである。

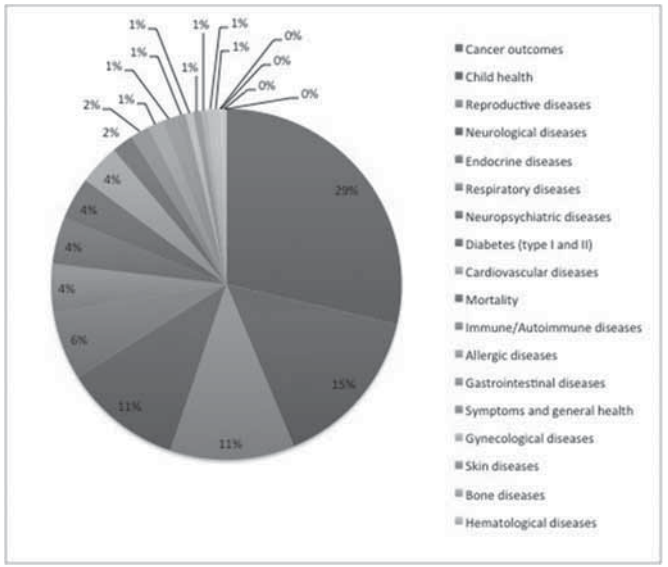


図 3：対象となる論文のうち、主要な影響カテゴリーとその影響を調査した研究の割合

Table 4: Evidence map table including all major outcome categories examined by eligible studies.

Major outcome	N studies
Cancer outcomes	164
Child health	84
Reproductive diseases	64
Neurological diseases	61
Endocrine diseases	35
Mental and psychomotor development	32
Respiratory diseases	25
Neuropsychiatric diseases	15
Diabetes (type I and II)	22
Cardiovascular diseases	31
Hematological diseases	15
Mortality	11
Immune/Autoimmune diseases	10
Allergic diseases	8
Gastrointestinal diseases	7
Symptoms and general health	5
Gynecological diseases	4
Skin diseases	4
Bone diseases	3
Kidney diseases	3
Benign tumors	1
Dental diseases	1
Men health	1
Metabolic diseases	1

7.3. Characteristics of eligible studies

The eligible studies were published from 2006 to 2012. The observed distribution of the publication year of the eligible studies indicates an approximately equal distribution of studies throughout the past 5 years (Figure 4). Of note, we expected a considerable presence of the results of the various reports of the Agricultural Health Study (AHS), the largest to-date observational study performed in the field. Indeed, the AHS publications (n=42) represent a recognizable proportion of the included studies (7%). Another 22 studies come form the cross-sectional National Health and Nutrition Examination Survey (NHANES) cohorts.

The majority of studies were case-control studies (N=222) and cross-sectional studies (Figure 5) and examined occupational exposure to pesticides (N=329). Almost half of the studies (N=285) were based in America (Figure 6). The most frequent method of pesticide assessment was measurement of biomarker or use of self reported questionnaire (Figure 7). Approximately half (N=261) studies were classified as 'high' in the methodological assessment.

表 4：対象となる研究で調査されたすべての主要な影響カテゴリーを含むエビデンスマップ表

主な影響	研究数
発がん	164
小児の健康	84
生殖器疾患	64
神経疾患	61
内分泌疾患	35
精神・精神運動発達	32
呼吸器系疾患	25
精神神経疾患	15
糖尿病（I 型・II 型）	22
循環器疾患	31
血液疾患	15
死亡率	11
免疫・自己免疫疾患	10
アレルギー性疾患	8
消化器疾患	7
症状と全身の健康	5
婦人科系の疾患	4
皮膚疾患	4
骨の疾患	3
腎臓の疾患	3
良性腫瘍	1
歯科疾患	1
男性の健康	1
代謝性疾患	1

7.3. 対象となる研究の特徴

対象となる研究は 2006 年から 2012 年までに発表されたものである。対象研究の発表年の分布を見ると、過去 5 年間でほぼ均等に分布していることがわかる（図 4）。特筆すべきは、現場で実施された今日までの観察研究の中で最大のものである Agricultural Health Study (AHS)の様々な報告書の結果がかなりの割合で存在することである。実際、AHSの出版物（n=42）は、含まれている研究の7%を占めている。その他の22件の研究は、国民健康・栄養調査（NHANES）コホートの横断研究である。

研究の大部分は症例対照研究（N=222）と横断研究（図5）であり、農薬への職業ばく露（N=329）を調査していた。研究のほぼ半数（N=285）はアメリカを拠点とした研究であった（図6）。農薬の評価方法は、バイオマーカーの測定、または自記式質問紙の使用が最も多かった（図7）。約半数（N=261）の研究が方法論的評価で「高」に分類された。

広範囲で多様な農薬が研究されており、様々な農薬の定義を用いた研究が行われている。また、公表されている文献のかなりの割合が、欧州連合（EU）や先進国のほとんどで使用が承認されていない農薬に焦点を当てていることも予想される。このような研究は、農薬の長期残留の根拠や、開発途上国での継続的な農薬使用の根拠に関わるものであることを認識している。例えば、DDTとその代謝物のみに焦点を当てた研究は、対象となる研究のほぼ10%を占めている。

A wide and diverse range of pesticides was studied with studies using various definitions of pesticides; it is very hard to harmonise between studies this information. We also anticipated a considerable proportion of the published literature to be focusing on pesticides no longer approved for use in the European Union and in most of the developed countries. We acknowledge that this research lies on the rational of pesticide long-term residuals, as well as of the continuing use of these pesticides in developing countries. For example, studies focusing solely on DDT and its metabolites constitute almost 10% of the eligible studies.

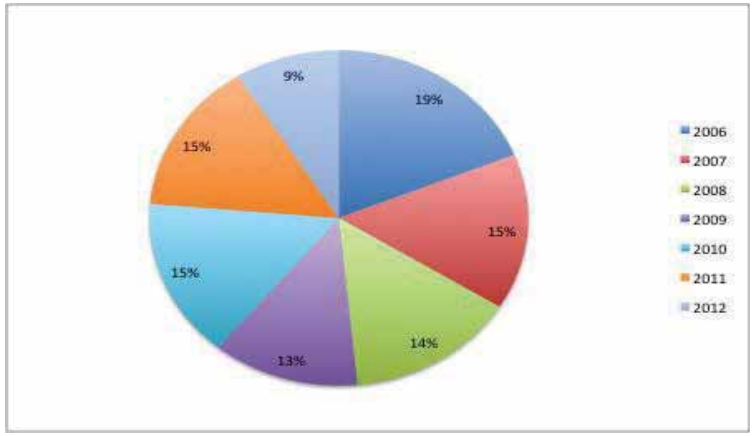
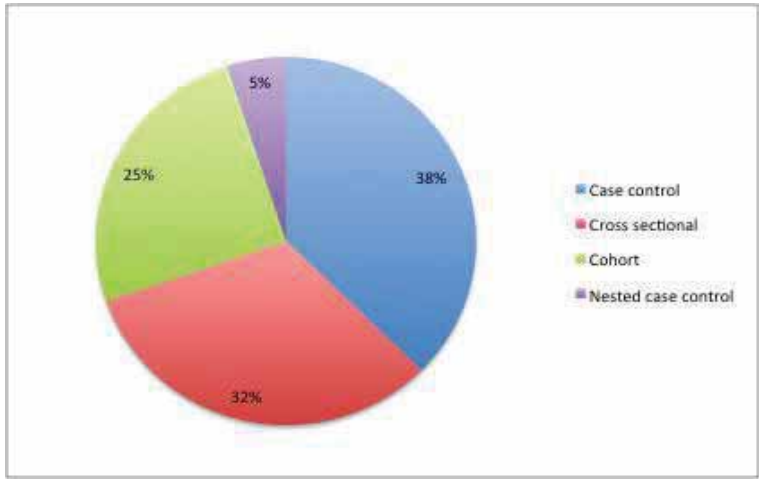


Figure 4: Percentage of eligible papers per publication year between 2006 and 2012



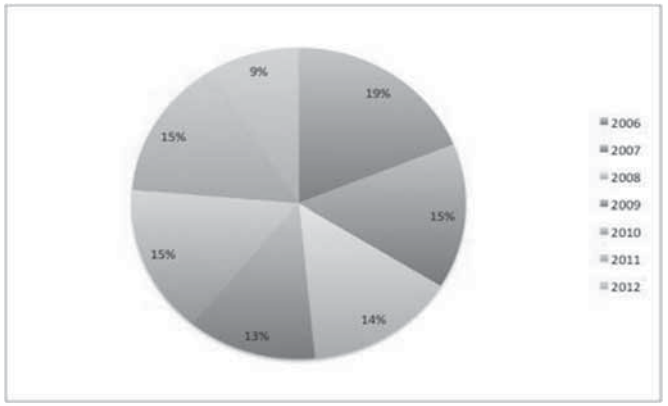


図 4：2006 年から 2012 年までの出版年度ごとの対象論文の割合

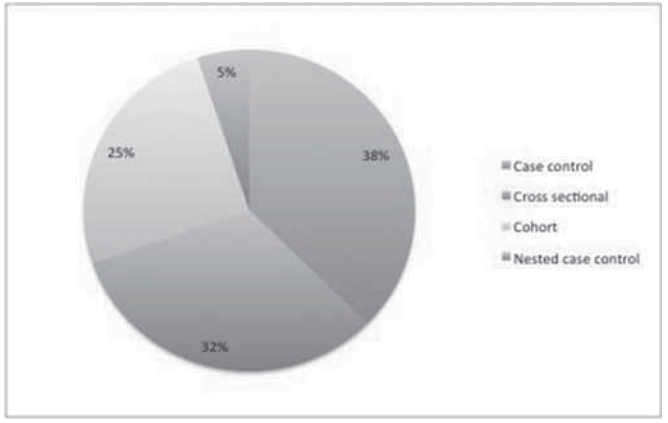


図 5：対象となる出版物の疫学研究デザイン

Figure 5: Epidemiological study designs of eligible publications

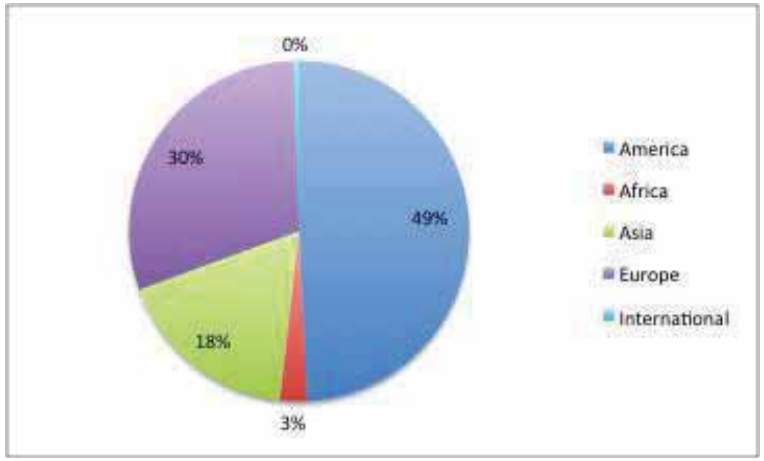


Figure 6: Location (continent) where eligible epidemiological studies were conducted

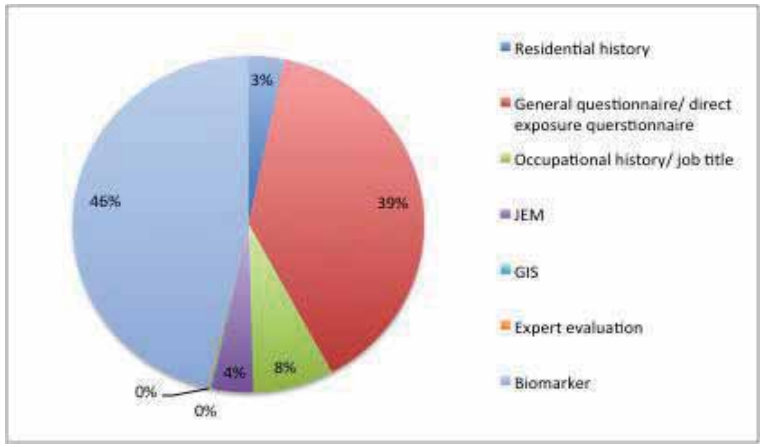


Figure 7: Method of exposure assessment in eligible epidemiological studies

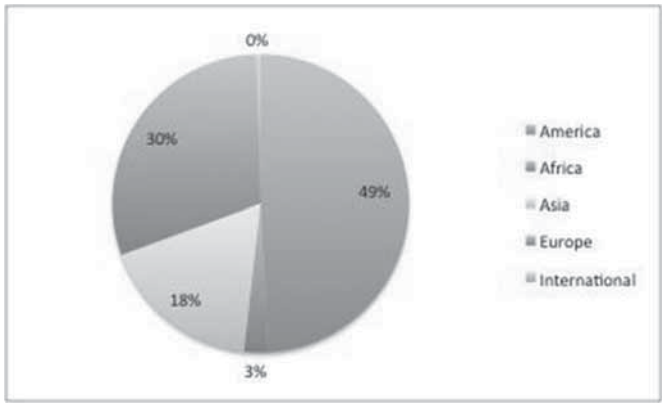


図 6：対象となる疫学研究が実施された地域（大陸）の状況

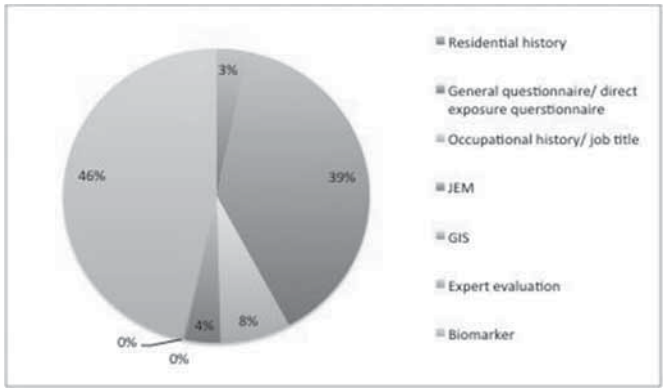


図 7：対象となる疫学研究におけるばく露評価の方法

7.4. Systematic literature review of systematic reviews and meta-analysis

Throughout our search strategy we also identified systematic reviews and meta-analyses. Overall, 21 different eligible reviews were identified published after 2006. The outcomes examined are shown in Table 5 below. Most reviews examined cancer related outcomes and some claimed positive associations between pesticides and examined outcome. The reviews are discussed in relevant outcome categories along with the individual studies.

Table 5: List of systematic reviews and meta-analyses identified in the literature review

Outcome	N studies	Authors claim association	Author, Journal, Publication year
Amyotrophic lateral sclerosis	3	No	Sutedja NA et al, 2009 Kamel F et al, 2012 Malek et al, 2012
Cancers	11		
Breast cancer	*1*	No	Khanjani N et al, 2007
Childhood cancer	*2*	Yes	Infante-Rivard C et al, 2007 Vinson F et al, 2011
Childhood Leukaemia	*6*	Yes	Wingle DT et al, 2009 Turner et al, 2010 Van Maele-Fabry G et al, 2010 Van Maele-Fabry G et al, 2011 Bailey HD et al, 2011 Turner MC et al, 2011
Multiple cancers	*1*	Yes	Cooper et al, 2008
Prostate cancer	*1*	Yes	Budnik LT et al, 2012
Multiple health outcomes	1	Yes	Koureas M et al, 2012
Neurobehavioral	2	No	Ismail AA et al, 2012 Li AA et al, 2012
Parkinson disease	2	Yes	Van der Mark M et al, 2012 Van Maele Fabry G et al, 2012
Reproductive	1	No	Shirangi A, 2011
Time to pregnancy	1	Yes	Snijder CA et al, 2012

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7.4. システマティックレビューとメタアナリシスのシステマティック文献レビュー

検索戦略を通じて、システマティックレビューとメタアナリシスも同定した。全体として、2006年以降に出版された21の異なる妥当なレビューが同定された。調査した影響を以下の表5に示す。ほとんどのレビューではがんに関連した影響を調査しており、いくつかのレビューでは農薬と調査した影響との間に明確な関連があると主張していた。これらのレビューは、個々の研究とともに、関連する影響カテゴリーで議論されている。

表 5：文献レビューで確認されたシステマティックレビューとメタアナリシスのリスト

影響	研究数	著者が主張する関連	著者・雑誌・出版年
筋萎縮性側索硬化症	3	No	Sutedja NA et al, 2009 Kamel F et al, 2012 Malek et al, 2012
がん	11		
乳がん	*1*	No	Khanjani N et al, 2007
小児がん	*2*	Yes	Infante-Rivard C et al, 2007 Vinson F et al, 2011
小児白血病	*6*	Yes	Wingle DT et al, 2009 Turner et al, 2010 Van Maele-Fabry G et al, 2010 Van Maele-Fabry G et al, 2011 Bailey HD et al, 2011 Turner MC et al, 2011
多発性がん	*1*	Yes	Cooper et al, 2008
前立腺がん	*1*	Yes	Budnik LT et al, 2012
複合的健康影響	1	Yes	Koureas M et al, 2012
神経行動学	2	No	Ismail AA et al, 2012 Li AA et al, 2012
パーキンソン病	2	Yes	Van der Mark M et al, 2012 Van Maele Fabry G et al, 2012
生殖性	1	No	Shirangi A, 2011
妊娠までの期間	1	Yes	Snijder CA et al, 2012

8. Cancer Outcomes

Overall, 164 publications examined the effect of pesticide exposure on cancer outcomes, contributing more than 2000 separate analyses. As seen with other outcomes, the diversity of exposure definition is remarkable and poses special challenges to data synthesis. Only 36 out of the 164 were prospective cohort studies and other 13 were nested case-controls; the overwhelming majority of evidence comes from retrospective case-control analyses, which are prone to recall bias in exposure measurement. Also, out of the 49 prospective analyses, 30 (61%) were from the same prospective study, the Agricultural Health Study (AHS) and evidence beyond this prospective cohort is limited. This is an important observation as it emphasizes the fact that 60% of the evidence for prospective associations comes from a single population. The sample size of the analyses was often small; it ranged between 24 and 82,596 participants (median 301). In addition, 33 studies had information on biomarkers of exposure and only 7 assessed occupational exposures through job exposure matrix (JEM). Common limitations in studies included small sample sizes, self-reported exposure, potential for high false positive rates due to multiple testing (studies test multiple hypothesis without adjusting for multiple testing and therefore results are likely to be false positives), and retrospective design. A wide variety or pesticides were assessed, with many studies examining organochlorine insecticides.

The different cancer categories examined are presented in Table 6 along with the number of studies contributing to each outcome category and a recommendation for quantitative synthesis. Due to heterogeneity of data and small number of studies identified, statistical synthesis of the data (meta-analysis) was only performed for some cancer subgroups.

8.1. Hematological neoplasms

8.1.1. Leukemias

Overall, 26 studies (and 2 abstracts) examined associations between pesticide exposure and various forms of leukaemia. Fourteen out of these 26 studies were reports from the AHS with some overlapping results and examination of different pesticide groups. Only 2 studies, both on DDE (ID CAN_063, ID CAN_064) examined residential exposure and all the remaining studies examined occupation exposure to pesticides. Twelve out of 99 different analyses were statistically significant with effect sizes across all studies ranging between 6.1 and 0.2. Statistically significant results come from 7 different studies; with the exception of the AHS all were of modest to low quality. Table 7 shows summarised results across studies that reported information on the same pesticide class. The vast majority of results are non-significant and of small effect sizes. Figure 8 shows random effect meta-analyses keeping analyses with largest sample size form each study. The meta-analysis resulted in a non-significant pooled effect (OR 1.26, 95% CI 0.93, 1.71) and had modest heterogeneity. Previous meta-analyses on occupational exposure to pesticides and leukaemia were published in 2008 and 2007 (Merhi 2007, Van Maele-Fabry 2008). The overall summary effect estimates from previous meta-analyses suggested that there is a significantly positive, albeit weak, association between occupational exposure to pesticides and all hematopoietic cancers. But both reports acknowledged a wide range of limitations including the lack of sufficient data about exposure information and other risk factors for hematopoietic cancer and unclear definition of exposure and of leukemia type.

8. 発がん

全体では164の出版物が農薬ばく露の発がんへの影響を調査し、2,000以上の個別の分析に貢献した。他の影響に見られるように、ばく露の定義の多様性は驚くべきものであり、データ統合に特別な問題をもたらしている。164件のうち36件のみが前向きコホート研究であり、他の13件はコホート内症例対照研究であった。エビデンスの圧倒的多数は後ろ向き症例対照分析から来ており、ばく露測定においてリコールバイアスがかかりやすい。また、49の前向き分析のうち、30（61%）は同じ前向き研究であるAgricultural Health Study（AHS）からのものであり、この前向きコホートを超えたエビデンスは限られている。これは重要な観察であり、前向きな関連のエビデンスの60%は単一の集団から得られているという事実を強調している。分析のサンプルサイズはしばしば小さく、参加者数は24～82,596人（中央値301人）であった。さらに、33の研究ではばく露のバイオマーカーに関する情報が得られており、職業ばく露マトリックス（JEM）を用いて職業ばく露を評価したのは7件のみであった。研究に共通する制限事項としては、サンプルサイズが小さいこと、ばく露が自己申告であること、多重検定による高い偽陽性率の可能性（多重検定を調整せずに複数の仮説を検定しているため、結果が偽陽性になる可能性がある）及び後ろ向きなデザインなどが挙げられる。多くの研究で有機塩素系殺虫剤を調査しており、多種多様な農薬が評価された。

調査されたさまざまながんのカテゴリーを、各影響カテゴリーに寄与した研究の数及び定量的統合の推奨事項とともに表6に示す。データの不均一性と同定された研究数が少ないため、データの統計的統合（メタアナリシス）は一部のがんサブグループについてのみ実施された。

8.1. 造血器新生物

8.1.1. 白血病

全体では、26件の研究（及び2件の要約）が農薬ばく露と様々な形態の白血病との関連を調査した。これら26件の研究のうち14件はAHSからの報告であり、結果が重複していたり、異なる農薬群の調査が行われていたりした。DDEに関する2件の研究（ID CAN_063、ID CAN_064）のみが住居ばく露を調査しており、残りの研究はすべて農薬への職業ばく露を調査したものである。99の異なる分析のうち12の研究は、6.1と0.2の間にあるすべての研究の効果量で統計的に有意であった。統計的に有意な結果が得られたのは7つの研究であり、AHSを除くすべての研究の品質は中等度から低度であった。表 7 は、同じ農薬クラスに関する情報を報告した研究の結果をまとめたものである。結果の大部分は、有意ではなく、効果量が小さいものであった。図8は、ランダム効果メタアナリシスを示しており、各研究で最大のサンプルサイズで分析を行っている。このメタアナリシスでは、有意ではない統合効果（OR 1.26、95% CI 0.93、1.71）が得られ、中等度の不均一性を有していた。農薬への職業ばく露と白血病に関する以前のメタアナリシスは、2008年と2007年に発表されている（Merhi 2007, Van Maele-Fabry 2008）。以前のメタアナリシスからの全体的な要約効果推定値は、農薬への職業ばく露とすべての造血器がんとの間には、弱いながらも有意に明確な関連があることを示唆していた。しかし、両報告とも、ばく露情報や造血器腫瘍の他のリスク因子に関する十分なデータが不足していること、ばく露の定義や白血病型の定義が不明確であることなど、幅広い限界があることを認めている。

8.1.2. Hodgkin lymphoma

Seven studies examined the associations between pesticide exposure and Hodgkin lymphoma. All studies assessed exposure through questionnaires, one studies had large sample size and all studies were retrospective. A wide range of pesticides classes was examined which did not allow any meaningful synthesis of the results. Twelve out of 75 separate analyses were statistically significant with effect sizes ranging from 8.4 to 0.4 across all analyses. We attempted random effects meta-analysis keeping only the Agricultural Health Study (AHS) analysis with the largest sample size. The result was not statistically significant and had high heterogeneity which can be attributed to the range of different pesticide classes examined by each study (Figure 9).

8.1.3. Other lymphomas

A very wide variety of definitions of lymphomas other than Hodgkin lymphoma were used in 44 studies of which 21 were reports from the Agricultural Health Study (AHS) and 2 from the BC (British Columbia) sawmill workers cohort study. Studies examined broad definitions of lymphomas and lymphoproliferative syndromes (ID CAN_047, ID CAN_049, ID CAN_074) and other examined more specific definitions of follicular lymphoma, diffuse large cell lymphoma and peripheral T-cell lymphoma. Twenty-one studies provided effect sizes between pesticide exposure and broad definitions of Non- Hodgkin lymphomas. Five of those studies were prospective (ID CAN_063, ID CAN_064, ID CAN_067, ID CAN_118, ID CAN_121) and seven examined associations with biomarkers of exposure (ID CAN_056, ID CAN_057, ID CAN_064, ID CAN_065, ID CAN_067, ID CAN_060, ID CAN_052). However, the later analyses were all on organochlorine pesticides with only few significant results (6 analyses among a total of 35 analyses) without any firm evidence for associations. In the AHS, large and significant effect size was observed between butylate use and Non-Hodgkin lymphomas (RR 2.94, 95% 1.49–5.96, p=0.002; high vs. no exposure). However, again the AHS in the same publication has examined ten different outcomes and results need adjustment for multiple testing.

8.1.4. Multiple myeloma

Also, 11 studies examined associations between pesticides and multiple myeloma, myelodysplastic syndromes and monoclonal gammopathy of undetermined significance. These studies were generally heterogeneous and no quantitative synthesis was suggested. Overall, some analyses were statistically significant, but those were mainly from the French case control study (ID CAN_049) which presented overall 147 separate analyses and results are prone to bias. The AHS also reported significant associations between permethrin, dieldrin, Carbon-tetrachloride/carbon disulfide mix and Chlorthalonil but again these were amongst 52 other analyses and require cautious interpretation. One study, reported very high significant effect size of 7.3 for myelodysplastic syndrome (ID CAN_070) but the quality of the study was poor and adjustment of covariates very limited and results were not replicated by other studies on the same phenotype.

8.2. Prostate cancer

Overall, 39 studies (in 260 analyses) examined the effects of pesticide exposure on prostate cancer. One study was a conference abstract which provided little data on methodology to allow meaningful appraisal of its results (ID CAN_107). Also, 25 of those 39 studies were studies from the AHS population with some overlapping results. For example, two studies (ID CAN_022, ID CAN_106) examined interactions between pesticide exposure and genetic variants in relation to prostate cancer. These AHS studies presented the same main effects for pesticide exposure; effects were largely null and, if anything, significant inverse effects were found e.g. for carbaryl, chlordane, metalachlor and

8.1.2. ホジキンリンパ腫

7件の研究が農薬ばく露とホジキンリンパ腫との関連を調査した。すべての研究は質問紙を用いてばく露を評価しており、1件の研究はサンプル数が多く、すべての研究は後ろ向きであった。広範囲の農薬クラスが調査されたが、結果の意味のある統合はできなかった。75の個別分析のうち12の分析が統計的に有意であり、すべての分析において効果量は8.4から0.4の範囲であった。我々は、最大のサンプルサイズを持つAgricultural Health Study（AHS）分析のみを残して、ランダム効果メタアナリシスを試みた。その結果は統計的に有意ではなく、各研究で調査された農薬クラスが異なることに起因する可能性がある高い不均一性を有していた（図9）。

8.1.3. その他のリンパ腫

ホジキンリンパ腫以外のリンパ腫については、非常に多様な定義が44件の研究で使用されており、そのうち21件は農業健康調査（Agricultural Health Study：AHS）からの報告で、2件はBC（ブリティッシュコロンビア州）製材所の労働者コホート研究からの報告であった。研究ではリンパ腫及びリンパ増殖性症候群（ID CAN_047、ID CAN_049、ID CAN_074）の広範な定義が調査され、他の研究では濾胞性リンパ腫、びまん性大細胞リンパ腫及び末梢性T細胞リンパ腫のより具体的な定義が調査された。21件の研究では、農薬ばく露と非ホジキンリンパ腫の幅広い定義との間の効果量が報告された。これらの研究のうち5件は前向き（ID CAN_063、ID CAN_064、ID CAN_067、ID CAN_118、ID CAN_121）であり、7件はばく露のバイオマーカーとの関連を調査した（ID CAN_056、ID CAN_057、ID CAN_064、ID CAN_065、ID CAN_067、ID CAN_060、ID CAN_052）。しかし、それ以降の分析はすべて有機塩素系農薬に関するものであり、関連を示す確固たるエビデンスがないまま、有意な結果が得られたのはわずかであった（全35 回の分析のうち 6 回の分析）。AHSでは、ブチル酸塩の使用と非ホジキンリンパ腫との間に大きな有意な効果量が観察された（RR 2.94、95% 1.49-5.96、p=0.002；高ばく露と非ばく露との間に有意な効果量が観察された）。しかし、同じ出版物のAHSは10種類の異なる影響を調査しており、結果は複数の試験のための調整が必要であることを繰り返している。

8.1.4. 多発性骨髄腫

また、11件の研究では、農薬と多発性骨髄腫、骨髄異形成症候群及び意義不明の単クローン性免疫グロブリン血症との関連が調査された。これらの研究は全般的に異質であり、定量的な統合は示唆されなかった。全体的に、いくつかの分析は統計的に有意であったが、それらは主にフランスの症例対照研究（ID CAN_049）からのものであり、147の個別の分析が行われており、結果にバイアスがかかりやすい。AHSはまた、ペルメトリン、ディルドリン、四塩化炭素/二硫化炭素の混合物、クロルタロニルとの間の有意な関連を報告しているが、これらは他の52分析の中に含まれており、慎重な解釈が必要である。ある研究では、骨髄異形成症候群（ID CAN_070）に対して7.3という非常に高い有意な効果量が報告されているが、研究の質が悪く、共変量の調整が非常に限られており、同じ表現型の他の研究で結果が再現されていなかった。

8.2. 前立腺がん

全体では、39件の研究（260件の分析）で農薬ばく露が前立腺がんに及ぼす影響が調査された。そのうちの1件は学会発表の要約であり、その結果を評価するための方法論に関するデータがほとんど提供されていなかった（ID CAN_107）。また、これら39件の研究のうち25件はAHS集団を対象とした研究であり、いくつかの結果が重複していた。例えば、2つの研究（ID CAN_022、ID CAN_106）では、農薬ばく露と前立腺がんとの関連における遺伝子変異との相互作用が調査されていた。これらのAHS研究では、農薬ばく露の主な効果は同じであったが、効果はほとんど無効であり、もしあるとすれば、カルバリル、クロルデン、メタクロルなどでは有意な逆効果が認められた。残りのAHS研究では、特定の農薬間

others. The remaining AHS studies, examined associations between specific pesticides, again showing no statistically significant associations between any of the examined pesticides and prostate cancer with the exception of a weak significant effect between butylate exposure and prostate cancer. The remaining evidence stems from, rather small and of modest quality, retrospective studies. Most studies (ID CAN_103, ID CAN_101, ID CAN_100, ID CAN_094, ID CAN_143, ID CAN_142) examined the effects of organochlorines with largely small and non-significant results. Two studies (IDs CAN_099, ID CAN_095) showed high significant increased risk associated with pesticide exposure and prostate cancer but both studies were of low quality, had very broad definitions of exposure and results need cautious interpretation and do not match with those reported from well conducted large prospective studies (e.g. AHS). Notably, one population-based case-control study (ID CAN_104) in a highly exposure area found strong association of ambient exposure to methyl bromide with prostate cancer risk, but the study did not observe evidence for exposure-response. In summary, most evidence for prostate cancer risk in relation to pesticide exposure concerns the effect of organoclorines with studies showing weak non-significant effects. A meta-analysis (Maele-Fabry 2003) on occupational exposure to pesticides and prostate cancer was also identified published. The pooled effect estimate, based on 22 epidemiological studies, was 1.13 (95% CI 1.04 to 1.22) with substantial heterogeneity across studies. In addition, the studies reviewed contained insufficient qualitative and quantitative information on exposure in order to distinguish the influence of pesticides from other occupational, environmental, and lifestyle factors (Maele-Fabry 2003). Overall, there is no evidence supporting an association between pesticide exposure and prostate cancer.

8.3. Lung cancer

Thirty studies contributing 45 analyses examined associations between pesticide exposure and lung cancer; previously published meta-analysis was not identified. Again, 23 out of 30 published studies and 30 of the 45 analyses were analyses of the AHS. Amongst the 50 different analyses of the AHS, only one statistically significant result was observed. Three studies examined broad pesticides definition as their exposure (ID CAN_080, ID CAN_082, ID CAN_083), one studied mosquito coil burns (ID CAN_081), while the remaining studies examined a range of different pesticides with an emphasis on organochlorine insecticides. The diversity of pesticide categories and the repeated use of the same cohort population (AHS) in more than half of the studies does not allow for quantitative synthesis. Notably, the association between mosquito coil burn and lung cancer was statistically significant with large effect size (3.78 (1.55, 6.90); yes vs. no use) but the study is relative small, retrospective with limited examination of confounders and of overall modest quality. Two case-control studies (ID CAN_082, ID CAN_082) reported over a two-fold increased risk of lung cancer for occupational exposure to pesticides but individual pesticides were not examined. Another case-control study (ID CAN_080) failed to replicate these observations between pesticide exposure and lung cancer mortality. Overall, the evidence on pesticide exposure and lung cancer is limited and inconclusive.

8.4. Childhood cancer

8.4.1. Childhood hematological neoplasms

Overall, 17 studies (and one abstract) which examined childhood hematological neoplasms in relation to pesticide exposure were identified. All 17 studies examined childhood leukemia and 4 of them also included other hematological neoplasms.

Previous meta-analysis on childhood leukemia concentrated on studies which assessed residential exposure to pesticides only. All studies that were included in the meta-analyses and were published after 2006 have been identified by our search which confirms that we identified all available evidence.

の関連を調査したが、いずれの農薬と前立腺がんとの間にも統計的に有意な関連は認められなかったが、ブチル酸塩へのばく露と前立腺がんとの間には弱い有意な影響が認められた。残りのエビデンスは、小規模で質の低い後ろ向き研究から得られたものである。ほとんどの研究(ID CAN_103、ID CAN_101、ID CAN_100、ID CAN_094、ID CAN_143、ID CAN_142）では、有機塩素の影響を調査したが、ほとんどが小規模で有意ではない結果であった。2件の研究（ID CAN_099、ID CAN_095）では、農薬ばく露と前立腺がんに関連した高く有意に増加したリスクが示されたが、いずれの研究も質が低く、ばく露の定義が非常に広く、結果は慎重な解釈が必要であり、適切に実施された大規模な前向き研究（AHSなど）で報告されたものとは一致しない。特筆すべきは、ばく露量の多い地域で行われた1件の集団ベースの症例対照研究（ID CAN_104）では、臭化メチルへのばく露と前立腺がんリスクとの間に強い関連が認められたが、この研究ではばく露反応関係を示すエビデンスは観察されなかった。まとめると、農薬ばく露に関連した前立腺がんリスクに関するほとんどのエビデンスは有機塩素の影響に関係しており、研究では有意ではない弱い影響が示されている。農薬への職業ばく露と前立腺がんに関するメタアナリシス（Maele-Fabry 2003）も発表されている。22の疫学研究に基づく統合効果推定値は1.13（95%CI 1.04～1.22）であり、研究間でかなりの不均一性があった。さらに、レビューされた研究には、農薬の影響を他の職業的、環境的、生活習慣的要因と区別するためのばく露に関する質的及び量的情報が不十分であった（Maele-Fabry 2003）。全体として、農薬ばく露と前立腺がんとの関連を支持するエビデンスはない。

8.3. 肺がん

30件の研究が45の分析を行っており、農薬ばく露と肺がんとの関連を調べているが、これまでに発表されたメタアナリシスは確認されなかった。ここでも、公表された30件の研究のうち23件、45件の分析のうち30件がAHSの分析であった。AHSの50種類の分析のうち、統計的に有意な結果が観察されたのは1件のみであった。3つの研究では、ばく露としての農薬の定義が広く（ID CAN_080、ID CAN_082、ID CAN_083）、1つの研究では蚊取り線香の火傷を調査し（ID CAN_081）、残りの研究では有機塩素系殺虫剤に重点を置いて様々な農薬を調査していた。殺虫剤のカテゴリーが多様であること、半数以上の研究で同じコホート集団（AHS）を繰り返し使用していることから、定量的な統合はできなかった。特筆すべきは、蚊取り線香の火傷と肺がんとの関連は、大きな効果量（3.78（1.55、6.90）；使用あり vs 使用なし）で統計的に有意であったが、この研究は相対的に小規模であり、交絡因子の調査が限られた後ろ向きであり、全体的に質は中等度であった。2件の症例対照研究（ID CAN_082、ID CAN_082）では、農薬への職業ばく露による肺がんリスクの2倍以上の増加が報告されているが、個々の農薬については調査されていない。別の症例対照研究（ID CAN_080）では、農薬ばく露と肺がん死亡率との間のこれらの観察を再現することはできなかった。全体として、農薬ばく露と肺がんに関するエビデンスは限られており、結論は出ていない。

8.4. 小児がん

8.4.1. 小児の造血器新生物

全体として、農薬ばく露に関連して小児の造血器新生物を調査した17件の研究（及び1件の要約）が同定された。17件の研究はすべて小児白血病を対象としており、そのうち4件には他の造血器新生物も含まれていた。

小児白血病に関するこれまでのメタアナリシスは、農薬への住居内ばく露のみを対象とした研究に集中していた。メタアナリシスに含まれ、2006年以降に発表されたすべての研究が我々の検索で同定され、利用可能なすべてのエビデンスが同定されたことを確認した。特定された研究は、国の登録ベースの症例対照研究ESCALE（Etude sur les cancers de l'enfant）（ID CAN_073）とNorthern Region Young Persons' Malignant Disease Registry（ID CAN_120）の2つの研究を除いて、一般的に小規模な

Identified studies were generally small with the exception of two studies on national registries, the Northern Region Young Persons' Malignant Disease Registry (ID CAN_120) and the national registry-based case–control study ESCALE (Etude sur les cancers de l'enfant) (ID CAN_073). Results from these studies should be cautiously interpreted, despite their large sample size, due to the large number of hypothesis examined (high false positive rate); each study reported 42 and 64 separate analysis respectively. All were case control studies and vast majority examined residential exposures with few studies on occupation exposure identified. Although most studies assessed use of, or exposure to, pesticides or pesticide subgroups (insecticides, herbicides, fungicides), some studies also attempted to collect information on specific pesticides (ID CAN_031, ID CAN_032) and one study (ID CAN_032) assessed biomarker levels. There were few data regarding frequency or duration of pesticide use, with most studies reporting only "ever/never" use of/exposure to the pesticide of interest. Although confounding is difficult to assess because there are few established risk factors for childhood hematological neoplasms, most studies examined or adjusted for at least a range of sociodemographic and maternal characteristics. Almost all studies assessed pesticide exposure separately for preconception, pregnancy, and childhood time windows. One study of very low quality and incomplete statistical analyses results examined all exposure time windows and other 2 (ID CAN_073, ID CAN_044) examined preconception and pregnancy jointly.

Three studies were excluded from further quantitative analyses: study ID CAN_040 was excluded due to lack of CIs; study ID CAN_030 due to duplicate data from Northern California Childhood Leukemia Study (duplicate with ID CAN_031), and study ID CAN_037 due to a unique study population (Down syndrome cases only). We divided the quantitative synthesis of results by the time period (window of exposure).

8.4.1.1. Exposure during pregnancy

Seven studies had information for pesticide exposures during pregnancy. Eleven out of 86 analyses were statistically significant corresponding to 5 studies which all examined acute leukaemia as outcome of interest. Largest effect estimates were reported from the national registry-based case–control study ESCALE (Etude sur les cancers de l'enfant). Insecticide use during pregnancy was significantly associated with childhood acute leukemia (OR = 2.1; 95% CI, 1.7–2.5) and paternal household use of pesticides was also related to acute leukemia (OR = 1.5; 95% CI, 1.2–1.8) in this study. We performed a series of quantitative synthesis of results. We first selected analyses with the largest sample size within each published report and synthesized results (Figure 10). This analysis was associated with large heterogeneity (I^2>80%) as each study had different exposure assessment (type of pesticide and parental route of exposure) and variability in outcome assessment. The remaining meta-analysis in Figure 10 show synthesis or results based on pesticide class examined in an effort to harmonize results with the previously published meta-analysis (Turner 2010) on 'Residential Pesticides and Childhood Leukemia'. We performed quantitative synthesis of all studies on insecticides and pesticides identified in this systematic review and subsequently we updated the previously published meta-analysis keeping only studies assessing residential exposure. Overall, the results show modest heterogeneity across studies, which can be attributed to variability in pesticide exposure definition, outcome definition, definition of exposure time windows etc. However, the meta-analysis show a consistent increased risk of childhood leukemia associated with exposure to unspecified pesticides and insecticide (Summary OR=1.69; 96% CI=1.35, 2.11). Our updated meta-analysis resulted in more conservative results compared to the meta-analysis published in 2010 but still supported an association between exposure to pesticides during pregnancy and childhood leukaemia. Still the evidence merits careful interpretation as there were concerns around publication bias in the original meta-analysis, the studies are typically small and the exposure is measured through non-validated self-reported questionnaires that are prone to misclassification. Funnel plot shows relative symmetry around studies of small size. Further evidence from large studies, using valid

ものであった。これらの研究の結果は、サンプルサイズが大きいにもかかわらず、調査された仮説の数が多い（偽陽性率が高い）ため、慎重に解釈されるべきである。各研究はそれぞれ42件、64件の個別の分析結果を報告している。すべての研究は症例対照研究であり、大多数は住居内ばく露を調査しており、職業ばく露に関する研究はほとんど見出されなかった。ほとんどの研究では、農薬または農薬のサブグループ（殺虫剤、除草剤、殺菌剤）の使用またはばく露を評価していたが、一部の研究では特定の農薬に関する情報の収集を試みており（ID CAN_031、ID CAN_032）、1つの研究（ID CAN_032）ではバイオマーカーレベルを評価していた。農薬の使用頻度や使用期間に関するデータはほとんどなく、ほとんどの研究では、対象となる農薬の「今までに使用したことがあるかないか」「使用したことがあるかないか」のみを報告している。小児の造血器新生物のリスク因子がほとんど確立されていないため、交絡因子の評価は困難であるが、ほとんどの研究では、少なくとも様々な社会人口統計学的及び母性の特性を調査または調整している。ほとんどすべての研究では、農薬ばく露を妊娠前、妊娠期、小児期に分けて評価している。非常に質が低く、統計分析の結果が不完全であった1件の研究では、すべてのばく露期間を調査し、他の2件（ID CAN_073, ID CAN_044）では、妊娠前と妊娠期を合わせて調査している。

研究ID CAN_040はCIが不足していたため除外され、研究ID CAN_030はNorthern California Childhood Leukemia Studyのデータが重複していたため（ID CAN_031と重複）、研究ID CAN_037は研究集団が特殊であったため（ダウン症患者のみ）、3つの研究が定量分析から除外された。結果の定量的統合を期間（ばく露の時間域）ごとに分けた。

8.4.1.1 妊娠期のばく露

7件の研究では妊娠期の農薬ばく露に関する情報が得られた。86件中11件の分析で統計的に有意な結果が得られたのは5件であり、すべての研究で急性白血病を対象とした結果であった。最大の効果推定値は、国の登録ベースの症例対照研究ESCALE（Etude sur les cancers de l'enfant）から報告されている。本研究では、妊娠期の殺虫剤使用は小児急性白血病と有意に関連し（OR = 2.1；95%CI, 1.7-2.5）、父方の住居での殺虫剤使用も急性白血病と関連し（OR = 1.5；95%CI, 1.2-1.8）、また、父方の住居での殺虫剤使用も急性白血病と関連した（OR = 1.5；95%CI, 1.2-1.8）。結果の一連の定量的統合を行った。まず、各発表報告書の中で最大のサンプルサイズを持つ分析を選択し、結果を統合した（図 10）。この分析は、各研究でばく露評価（農薬の種類と親のばく露経路）が異なり、影響評価にばらつきがあったため、大きな不均一性（I2>80%）と関連していた。図10の残りのメタアナリシスは、「住居用農薬と小児白血病」に関する以前に発表されたメタアナリシス（Turner 2010）と結果を調和させるために、調査した農薬のクラスに基づいた統合または結果を示している。我々は、この系統的レビューで確認された殺虫剤及び農薬に関するすべての研究を定量的に統合し、その後、住居ばく露を評価した研究のみを残して、以前に発表されたメタアナリシスを更新した。全体的に、結果は研究間で中等度の不均一性を示しており、これは農薬ばく露の定義、影響の定義、ばく露時間域の定義などにばらつきがあることに起因していると考えられる。しかし、メタアナリシスでは、特定されていない農薬及び殺虫剤へのばく露に関連した小児白血病のリスクの一貫した増加を示した（要約OR=1.69; 96% CI=1.35, 2.11）。我々の更新されたメタアナリシスでは、2010年に発表されたメタアナリシスと比較して、より保守的な結果となったが、妊娠期の農薬へのばく露と小児白血病との関連は依然として支持されている。しかし、元のメタアナリシスでは出版バイアスの懸念があったこと、研究の規模が一般的に小さいこと、ばく露は誤分類されやすい検証されていない自記式質問紙で測定されていることなどから、エビデンスは慎重に解釈する必要がある。ファンネルプロットは、小規模な研究を中心とした相対的な対称性を示している。住居用殺虫剤への出生前ばく露を減らすことに公衆衛生上のメリットがあるかどうかを確認するためには、過去のばく露の有効なバイオマーカーを用いた大規模研究からのさらなるエビデンスが必要である。

biomarkers of past exposure are needed to confirm whether there is public health merit in reducing prenatal exposure to residential pesticides.

8.4.1.2. Preconception

Four studies examined preconception as the time window of exposure (ID CAN_032, ID CAN_043, ID CAN_073, ID CAN_120) but none reported statistically significant results.

8.4.1.3. Childhood

Seven studies with information on exposure during childhood were identified (ID CAN_031, ID CAN_032, ID CAN_035, ID CAN_036, ID CAN_041, ID CAN_043, ID CAN_133). One study examined Endosulfan, which is no longer in use; the study was of very low quality and was not considered further. Meta-analysis of these studies is shown in Figure 14 below. Two analyses are presented A) one on identified studies from 2006 onwards based on the analysis of the largest sample size in each report (any pesticide) and B) an update on the 2010 meta-analysis on pesticide exposure during childhood and childhood leukemia. The meta-analysis on any pesticides had modest heterogeneity whereas the updated meta-analysis, which was restricted to residential exposure and insecticides/ unspecified pesticides only, displayed no heterogeneity in its results. The results of the updated meta-analysis are more conservative than the original meta-analysis but still very close to the pooled estimates reported in 2010 (Figure 14). Funnel plots indicated considerable symmetry around results. Overall, there is some evidence for association between childhood exposure to pesticide and childhood leukemia but this is weaker than exposure during pregnancy and requires more evidence from well-conducted large birth cohorts to draw firm conclusions.

8.4.2. Lymphomas

Evidence beyond leukaemia for childhood hematological neoplasms comes only from 3 studies, which reported many analyses (IDs CAN_073, ID CAN_120, ID CAN_133) among which analyses for Non-Hodgkin and Hodgkin lymphomas. All analyses were not statistically significant and had weak effect estimates.

8.4.3. Other childhood cancers

Seven studies on other childhood cancers were identified. Four studies examined brain cancer (ID CAN_006, ID CAN_011, ID CAN_089, ID CAN_133), one childhood germ cell tumor (ID CAN_114) and two examined a range of childhood cancers (ID CAN_120, ID CAN_133). Significant associations were only observed for brain cancers but again these pertain to only a small subset of many analyses and cannot be informative at this stage.

8.5. Colorectal cancer

Overall, 26 identified studies examined associations between pesticide exposure and colorectal cancer in 207 analyses. Separate analyses for colon cancer and rectum cancer were available in 24 and 11 studies respectively. A very large body of evidence comes from the AHS study, which examined all these 3 outcomes for associations with 194 out of the 207 identified analyses on colorectal cancer examining 50 different pesticides with no adjustments for multiple testing. Out of these 194 analyses, only 7 were statistically significantly positively associated with the outcome (Carbaryl, Aldicarb,

8.4.1.2. 妊娠前

4つの研究では、ばく露の時期として妊娠前を調査したが（ID CAN_032、ID CAN_043、ID CAN_073、ID CAN_120）、いずれも統計的に有意な結果の報告ではなかった。

8.4.1.3. 小児期

小児期のばく露に関する情報を有する7件の研究が確認された（ID CAN_031、ID CAN_032、ID CAN_035、ID CAN_036、ID CAN_041、ID CAN_043、ID CAN_133）。1件の研究では、現在使用されていないエンドスルファンを調査したが、その研究は非常に質が低く、これ以上の調査は行われなかった。これらの研究のメタアナリシスを以下の図14に示す。2つの分析が提示されており、A）各報告書の最大サンプルサイズの分析に基づいて2006年以降に同定された研究（任意の農薬）についての分析と、B）小児期及び小児白血病における農薬ばく露に関する2010年のメタアナリシスについての更新である。あらゆる農薬に関するメタアナリシスでは中等度の不均一性があったのに対し、更新されたメタアナリシスでは、住居ばく露と殺虫剤/特定されていない農薬のみに限定されており、結果に不均一性は見られなかった。更新されたメタアナリシスの結果は、元のメタアナリシスよりも保守的であるが、それでも2010年に報告された統合推定値に非常に近いものであった（図14）。ファンネルプロットでは、結果にかなりの対称性があることが示されている。全体的には、小児期の農薬ばく露と小児白血病との間には関連を示すいくつかのエビデンスがあるが、これは妊娠期のばく露よりも弱く、確固とした結論を出すためには、適切に実施された大規模な出生コホートからのより多くのエビデンスが必要である。

8.4.2. リンパ腫

白血病以外の小児の造血器新生物に関するエビデンスは3件の研究から得られているのみであり、その中には非ホジキンリンパ腫とホジキンリンパ腫に関する分析を含む多くの分析が報告されている（ID: CAN_073、ID: CAN_120、ID: CAN_133）。すべての分析は統計的に有意ではなく、効果推定値も弱いものであった。

8.4.3. その他の小児がん

その他の小児がんに関する研究が7件同定された。4件の研究では脳腫瘍（ID CAN_006、ID CAN_011、ID CAN_089、ID CAN_133）、1件の小児生殖細胞腫瘍（ID CAN_114）、2件の研究では様々な小児がん（ID CAN_120、ID CAN_133）が調査された。有意な関連が観察されたのは脳腫瘍のみであったが、これらは多くの分析のごく一部のサブセットに関連しており、現段階では情報を得ることはできない。

8.5. 大腸がん

全体では、26件の研究で農薬ばく露と大腸がんとの関連性が 207 件の分析で調査された。大腸がんと直腸がんについては、それぞれ24件と11件の研究で別々の分析が行われた。非常に多くのエビデンスがAHS研究から得られている。この研究では、50種類の農薬を用いた大腸がんに関する207の分析のうち194の分析で、これら 3 つの影響発現事象すべてとの関連性が調査されており、多重試験の調整は行われていない。これら194の分析のうち、影響発現事象と統計的に有意に関連したのは7つの分析のみであった（カルバリル、アルジカルブ、トキサフェン、ペンディメタリン、ジプロピルチオカルバミン酸 S-エチル（EPTC）、イマゼタピル、フォノフォス）が、偽陽性確率が高いため、解釈には注意が必要である。27の研究が発表されているにもかかわらず、全体的には7つの異なる集団からのエビデンスしか得られていない。この事実は、大腸がんに関連してこれらの研究のそれぞれで分析された異なる農薬の範囲とともに、結果の意味のある定量的な統合を可能にするものではない。表8は、複数の論文における1つのコホートからの重複データの公表の程度を示しており、結果の一貫性が良好である

Toxaphene, Pendimethalin, S-Ethyl dipropylthiocarbamate (EPTC), imazethapyr and Fonofos) but need to be interpreted with caution due to high false positive probability. Despite the fact that 27 published studies were identified, overall the evidence comes from only 7 different populations. This fact along with the range of different pesticides analysed by each of these studies in relation to colon cancer does not allow meaningful quantitative synthesis of the results. Table 8 shows the extent of publication of duplicate data from one cohort in multiple papers and shows good consistency of results. Previous meta-analyses on colorectal cancer and pesticide exposure have not been identified. Overall, the evidence for pesticides and colorectal cancer is very limited and current state of the literature does not support associations between pesticides and colorectal cancer.

8.6. Skin cancer

Seventeen studies examined associations between melanoma and pesticide exposure. The majority of studies assessed organochlorine pesticides. Again, 14 out of 17 studies on melanoma were results from the AHS examining in each paper different pesticides categories and different definitions of exposure with some supplication of results present. Of the 26 different analyses of the AHS, 8 were statistically significant and all stemming from the same publication (ID CAN_085) on dose response relationships for 50 agricultural pesticides with cutaneous melanoma. The study reported significant associations between cutaneous melanoma and maneb/mancozeb (≥ 63 exposure days: OR = 2.4; 95% CI, 1.2–4.9; trend p = 0.006), parathion (≥ 56 exposure days: OR = 2.4; 95% CI, 1.3–4.4; trend p = 0.003), and carbaryl (≥ 56 exposure days: OR = 1.7; 95% CI, 1.1–2.5; trend p = 0.013) (155). Other studies did not report results on these pesticides to allow examination of replication of results. One case-control study showed increased statistically significant risk between indoor pesticide exposure and melanoma whereas in the same study outdoors pesticide exposure was not associated with melanoma (106). The remaining studies on organochlorines showed heterogeneous results with few statistically significant results (Hexachlorobenzene (HCB), mirex), which do not provide evidence for an association between these pesticides and melanoma.

8.7. Breast cancer

Overall, 14 studies (and 3 abstracts) after 2006 examined the relationship between pesticide exposure and breast cancer. The vast majority of studies and analyses concentrate on organochlorine pesticide, which they are assessed through biomarker analyses. Two previous meta-analyses on breast cancer and DDT exposure have been published (Khanjani 2007, López-Cervantes 2004). Overall, previous meta-analyses did not show a significant association between any cyclodiene chemical and breast cancer except for heptachlor, but that was based on only two studies. Meta-analysis on identified studies in this systematic review on Dichlorodiphenyldichloroethylene (DDE) and breast cancer (5 studies) also shows no evidence for association. We have also performed a meta-analysis across all identified studies on breast cancer, selecting each time the analysis within each study with the largest sample size. Studies ID CAN_019 and ID CAN_023 were excluded from synthesis, as effect sizes and confidence interval to allow synthesis were not provided and study ID CAN_022 was excluded as it reported very tight confidence intervals which did not were assumed to be reported incorrectly. The synthesis here involves the pooled effect of many different pesticides definitions and biomarkers (DDE, lindane, and broad pesticide definition) and is difficult to be interpreted. The pooled effect shows a statistically significant increased risk of breast cancer (1.07 (0.87 to 1.31)) but this result need cautious interpretation. The meta-analysis combines very different categories of pesticides and is largely dominated by one study (ID CAN_022), which assessed pesticide exposure by self-reported residential pesticide use and is therefore of modest quality compared to the rest of the studies which assessed pesticides via biomarkers.

ことを示している。大腸がんと農薬ばく露に関するこれまでのメタアナリシスは確認されていない。全体的に、農薬と大腸がんに関するエビデンスは非常に限られており、現在の文献の状態では、農薬と大腸がんの関連性を支持するものではない。

8.6. 皮膚がん

17件の研究では、メラノーマと農薬ばく露との関連が調査された。大半の研究は有機塩素系農薬を対象としたものであった。ここでも、メラノーマに関する17件の研究のうち14件がAHSの結果であり、各論文では異なる農薬のカテゴリーやばく露の定義が異なっており、いくつかの結果が提示されていた。AHSの26の異なる分析のうち、8つは統計的に有意であり、すべて同じ出版物（ID CAN_085）に由来するもので、50種類の農薬と皮膚メラノーマとの量反応関係が報告されている。この研究では、皮膚メラノーマとmaneb/mancozeb（63日以上のばく露日数：OR = 2.4；95%CI、1.2-4.9；トレンドp = 0.006）、parathion（56日以上のばく露日数：OR = 2.4；95%CI、1.3-4.4；トレンドp = 0.003）及びcarbaryl（56日以上のばく露日数：OR = 1.7；95%CI、1.1-2.5；トレンドp = 0.013）との間の有意な関連が報告されている（155）。他の研究では、これらの農薬に関して再現性を調査できるような結果を報告していない。1件の症例対照研究では、屋内での農薬ばく露とメラノーマとの間に統計的に有意なリスクの増加が示されたが、同じ研究では屋外での農薬ばく露はメラノーマとは関連していなかった(106)。有機塩素系農薬に関する残りの研究では、統計的に有意な結果がほとんど得られない不均質な結果が得られており（ヘキサクロロベンゼン（HCB）、マイレックス）、これらの農薬とメラノーマとの関連を示すエビデンスは得られてない。

8.7. 乳がん

全体では、2006年以降の14件の研究（うち3件は要約）が農薬ばく露と乳がんとの関係を調査した。大半の研究と分析は有機塩素系農薬に焦点を当てており、バイオマーカー分析によって評価されている。乳がんとDDTばく露に関する2つの過去のメタアナリシスが発表されている(Khanjani 2007, López-Cervantes 2004）。全体的に、以前のメタアナリシスでは、ヘプタクロルを除き、シクロジエン系化学物質と乳がんとの間に有意な関連は示されなかったが、それはわずか2件の研究に基づくものであった。ジクロロジフェニルジクロロエチレン（DDE）と乳がんに関するシステマティックレビューで同定された研究（5研究）のメタアナリシスでも、関連を示すエビデンスは示されなかった。我々はまた、乳がんに関する同定されたすべての研究でメタアナリシスを実施し、サンプルサイズが最も大きい各研究内の分析を毎回選択した。研究ID CAN_019とID CAN_023は、統合を可能にする効果量と信頼区間が提供されていなかったため、統合から除外された。また、研究ID CAN_022は、誤って報告されたとは想定されていない非常に狭い信頼区間を報告していたため除外された。ここでの統合には、多くの異なる農薬の定義とバイオマーカー（DDE、リンデン、広義の農薬定義）の統合効果が含まれており、解釈が難しい。統合効果は統計的に有意な乳がんリスクの増加（1.07（0.87～1.31））を示したが、この結果は慎重な解釈が必要である。メタアナリシスでは、非常に異なるカテゴリーの農薬を組み合わせており、主に1つの研究（ID CAN_022）が占めているが、これは住居用農薬の自己申告による農薬ばく露を評価したもので、バイオマーカーを介して農薬を評価した他の研究に比べて質が低いものである。

8.8. Bladder cancer

Sixteen studies examining bladder cancer in relation to pesticide exposure were identified; however, 13 were studies from the same population the AHS as previously observed for other cancer outcomes. Among the 25 different analyses presented, only one provided statistically significant results for occupational exposure to imazethapyr in the AHS. However, due to multiple testing the results need cautious interpretation and based on the evidence reviewed in this report there is no suggestion for an association between pesticide exposure and bladder cancer.

8.9. Kidney cancer

Ten studies examined kidney cancer in relation to pesticide exposure; however, data from two populations only, the AHS and the BC (British Columbia) sawmill workers cohort study. Results form the BC sawmill workers cohort study (ID CAN_129 and ID CAN_125) were both on occupational exposure to pentachlorophenol and tetrachlorophenol but examining different approaches to statistical analyses. Results from the AHS were on different pesticide classes. Overall, no statistically significant results were observed and the limited number of contributing populations (n=2) does not allow further quantitative synthesis.

8.10. Pancreatic cancer

Seven studies examined pancreatic cancer in relation to pesticide exposure; 4 were reports from the AHS. The overwhelming majority of analyses considered organochlorine pesticides. In a small case-control study of modest quality significantly increased concentrations of hexachlorobenzene (HCB), sum of chlordanes and polybrominated diphenylethers (PBDEs) were found in the pancreatic cancer cases compared to healthy controls (ID CAN_090). In the AHS, among 46 different analyses, significant associations were reported for Pendimethalin and S-Ethyl dipropylthiocarbamate (EPTC). Applicators in the top half of lifetime pendimethalin use had a 3.0-fold (95% CI 1.3–7.2, p-trend 5 0.01) risk compared with never users, and those in the top half of lifetime EPTC use had a 2.56-fold (95% CI 5 1.1–5.4, p-trend=0.01) risk compared with never users. Organochlorines were not associated with an excess risk of pancreatic cancer in the AHS. These findings suggest that herbicides may be associated with pancreatic cancer but require replication by future studies as they all come from a single population without adjustments for multiple testing.

8.11. Testicular cancer

Overall, 8 studies examined testicular cancer. Two studies also reported outcomes for seminoma cancer. All but one study assessed biomarker levels and concentrated on organochlorine pesticides with a range of different biomarkers assessed and studies showing a weak effect for an association with testicular cancer. However, information on more than 4 studies was available for p-p'DDE only and quantitative synthesis showed a non-significant effect and modest heterogeneity (Figure 20). Quantitative synthesis across any pesticide was not performed due to heterogeneity of biomarkers assessed in each study. Overall, there is no evidence to support an association between pesticide exposure and testicular cancer based on evidence reviewed herein.

8.12. Stomach cancer

Six studies examined association between pesticide exposure and stomach cancer. All studies examined occupational exposure to pesticides, a range of pesticide classes was studies; 2 studies had a prospective design but all had modest to small sample sizes. In agreement with previous meta-analysis

8.8. 膀胱がん

農薬ばく露に関連して膀胱がんを調査した16件の研究が同定されたが、13件は他の発がん影響について以前に観察されたのと同様にAHSの同じ集団からの研究であった。25の異なる分析結果のうち、AHSにおけるイマゼタピルへの職業ばく露について統計的に有意な結果を示したのは1件のみであった。しかし、複数の試験を行っているため、結果は慎重に解釈する必要があり、報告書で調査されたエビデンスに基づいても、農薬ばく露と膀胱がんとの関連は示唆されていない。

8.9. 腎臓がん

10件の研究が農薬ばく露に関連して腎臓がんを調査したが、データはAHSとBC（ブリティッシュコロンビア州）製材所労働者コホート研究の2つの集団からのみであった。BC州製材所労働者コホート研究（ID CAN_129及びID CAN_125）の結果は、いずれもペンタクロロフェノール及びテトラクロロフェノールへの職業ばく露に関するものであったが、統計分析のアプローチが異なっていた。AHSの結果は、異なる農薬クラスに関するものであった。全体的に、統計的に有意な結果は観察されず、寄与した集団の数が限られているため（n=2）、これ以上の定量的な統合はできなかった。

8.10. 膵臓がん

農薬ばく露に関連して膵臓がんを調査した研究は7件、AHSからの報告は4件であった。分析の圧倒的多数は有機塩素系農薬を対象としたものであった。質の低い小規模な症例対照研究では、ヘキサクロロベンゼン（HCB）、クロルデンの和及びポリ臭化ジフェニルエーテル（PBDE）の濃度が健常対照者と比較して膵臓がん症例で有意に上昇していた（ID CAN_090）。AHSでは、46種類の分析のうち、PendimethalinとS-Ethyl dipropylthiocarbamate（EPTC）について有意な関連が報告されている。ペンディメタリンの生涯使用量の上位半分の散布者は、非使用者と比較して3.0倍（95%CI 1.3-7.2、pトレンド5 0.01）のリスクを有し、EPTCの生涯使用量の上位半分の散布者は、非使用者と比較して2.56倍（95%CI 5 1.1-5.4、pトレンド=0.01）のリスクを有していた。有機塩素系薬剤は、AHSにおける膵臓がんの過剰リスクとは関連していなかった。これらの知見は、除草剤が膵臓がんと関連している可能性を示唆しているが、これらはすべて単一の集団から得られたものであり、多重検定調整を行っていないため、今後の研究で反復する必要がある。

8.11. 精巣がん

全体では8件の研究で精巣がんが調査された。2件の研究では精上皮腫への影響も報告された。1件を除くすべての研究がバイオマーカーレベルを評価し、有機塩素系殺虫剤に集中しており、さまざまなバイオマーカーが評価され、精巣がんとの関連には弱い影響を示した研究もあった。しかし、p-p'DDEのみについては4件以上の研究の情報が得られ、定量的統合では有意ではない効果と適度な不均一性が示された（図20）。各研究で評価されたバイオマーカーの不均一性のため、どの農薬についても定量的統合は行われなかった。全体的に、ここで調査されたエビデンスに基づいて、農薬ばく露と精巣がんとの関連を支持するエビデンスはない。

8.12. 胃がん

6件の研究で、農薬ばく露と胃がんとの関連が調査された。すべての研究は農薬への職業ばく露を調査したもので、農薬のクラスは多岐にわたっていた；2件の研究は前向きデザインであったが、すべての研究でサンプルサイズは中等度から低度であった。農家に関する以前のメタアナリシス（Saphir 1998）と一致するように、研究は不十分で、主に有意でない結果を報告していた。United Farm Workers of America（UFW）コホートにおける胃がんのコホート内症例対照研究（ID CAN_028）では、有意な関連が報告された。フェノキシ酢酸除草剤2,4-ジクロロフェノキシ酢酸（2,4-D）の使用量が多い地域で

on farmers (Saphir 1998), studies reported weak and mainly non-significant results. A nested case-control study (ID CAN_028) of gastric cancer embedded in the United Farm Workers of America (UFW) cohort reported significant associations: working in areas with high use of the phenoxyacetic acid herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) was associated with gastric cancer (OR 1.85; 95% CI 1.05–3.25); use of the organochlorine insecticide chlordane was also associated with the disease (OR 2.96; 95% CI 1.48–5.94). Gastric cancer was associated with use of the acaricide propargite (OR 2.86; 95% CI 1.56–5.23). Nonetheless, the study is limited by a relatively small number of cases and controls, multiple testing and exposure misclassification, as assessment was ecological in nature. In the AHS, based on 15 exposed cases, stomach cancer risk increased monotonically with increasing methyl bromide use (RR = 3.13; 95 % CI, 1.25–7.80 for high use compared with no use; p for trend = 0.02). However, again the associations suffer from multiple testing as all other cancer subtypes have been associated with methyl bromide use in this study (ID CAN_147). Meta-analysis selecting the analysis with largest sample size is shown in Figure 21 but results require careful consideration. Despite a statistical significant pooled large effect size, this is dominated by two studies (ID CAN_125, ID CAN_147), which examine pentachlorophenol and methyl bromide; two compounds that are not approved in the European Union.

8.13. Liver cancer

Five studies (including 11 separate analyses) and one conference abstract examined associations between pesticide exposure and liver cancer. The majority of analyses examined exposure to organochlorine pesticides and all studies examined occupational exposure to pesticides. Both studies on DDT (IDs CAN_076 and ID CAN_079) reported statistically significant associations with liver cancer; the remaining analyses were non-statistically significant. These two studies largely dominate the meta-analysis on liver cancer, which shows a statistically significant pooled result largely driven by the DDT studies.

8.14. Cancer subgroups with few studies

As illustrated in Table 6, for a large number of individual cancers only very few studies are available to allow synthesis of evidence for each cancer subgroup. Our systematic review did not identify any previously published meta-analyses on these cancer subtypes to allow for comparisons with previously published evidence (prior to 2006). Generally the results on these cancer subtypes were of small effect and not statistically significant with few exceptions concerning occupational exposure only. Given the large number of analyses within each study, these results need cautious interpretation and, based on these data, there is no evidence to suggest association between pesticide exposure and these cancer subtypes.

There were also a large number of studies examining all cancers (composite cancer outcome) in relation to pesticide. Cancers represent a very heterogeneous group of disorders and simultaneous examination of all cancer subtypes may introduce bias in the associations. Overall, 30 analyses examining “all cancers” were identified and 28 of them were analyses of the same cohort, the AHS, not allowing further synthesis of the results. Only 4 results out of 31 were statistically significant were associated with poor quality of studies and therefore do not merit interpretation at this stage.

働くことは、胃がんと関連していた（OR 1.85；95%CI 1.05-3.25）。有機塩素系殺虫剤クロルデンの使用もこの疾患と関連していた（OR 2.96；95%CI 1.48-5.94）。胃がんは、殺ダニ剤プロパルギトの使用と関連していた（OR 2.86；95%CI 1.56-5.23）。にもかかわらず、評価が生態学的なものであったため、この研究は症例数と対照数が比較的少ないこと、多重検定及びばく露の誤分類によって制限されている。AHSでは、15例のばく露例に基づいて、胃がんリスクは臭化メチルの使用量の増加とともに単調に増加した（RR = 3.13；95%CI、非使用と比較して高頻度使用では1.25-7.80；トレンドのp = 0.02）。しかし、この研究では他のすべてのがんのサブタイプが臭化メチル使用と関連していたため、やはり多重検定の問題がある（ID CAN_147）。最大のサンプルサイズで分析を選択したメタアナリシスは図21に示されているが、結果は慎重に調査する必要がある。統計的に有意な統合された大きな効果量にもかかわらず、この結果は、欧州連合で承認されていない2つの化合物であるペンタクロロフェノールと臭化メチルを調査している2つの研究（ID CAN_125, ID CAN_147）の影響が大きい。

8.13. 肝臓がん

5件の研究（11件の個別の分析を含む）と1件の学会発表の要約で、農薬ばく露と肝臓がんとの関連が調査された。分析の大部分は有機塩素系農薬へのばく露を対象としており、すべての研究は農薬への職業ばく露を対象としていた。DDTに関する両研究（ID：CAN_076及びID：CAN_079）では、肝がんとの統計的に有意な関連が報告されたが、残りの分析では統計的に有意ではなかった。これら2つの研究が肝臓がんに関するメタアナリシスの大部分を占めており、統合された結果は統計学的に有意であり、主にDDT研究に牽引されている。

8.14. 研究数が少ないがんサブグループ

表6に示されているように、多数のがんについては、各がんサブグループのエビデンスを総合的に判断できる研究は非常に限られている。我々のシステマティックレビューでは、過去に発表されたエビデンス（2006年以前）との比較を可能にするために、これらのがんサブタイプに関する過去に発表されたメタアナリシスを確認しなかった。一般的に、これらのがんサブタイプに関する結果では影響は小さく、職業ばく露のみに関する少数の例外を除いて統計的に有意ではなかった。各研究内の分析数が多いことを考えると、これらの結果は慎重に解釈する必要があり、これらのデータに基づいて、農薬ばく露とこれらのがんサブタイプとの間の関連を示唆するエビデンスはない。

また、農薬に関連してすべてのがん（複合発がん影響）を調査した研究も多数あった。がんは非常に異質な疾患群であり、すべてのがんサブタイプを同時に調査すると、関連にバイアスがかかる可能性がある。全体では、「すべてのがん」を対象とした30の分析が同定されたが、そのうち28の分析は同じコホート（AHS）を対象としたものであり、結果をさらに統合することはできなかった。31件のうち統計的に有意な結果が得られたのは4件のみで、質の低い研究と関連していたため、現段階では解釈に値しない。

Table 6: Summary of eligible studies identified per cancer subgroup

Cancers	N studies	Meta-analysis recommended	Previous meta-analysis identified
Haematological neoplasms	88	Yes	Yes
Prostate cancer	39	No	Yes
Lung cancer	30	Yes	No
All cancers	30	No	No
Childhood cancer	45	Yes	Yes
Colorectal cancer	26	No	No
Skin cancer	17	Yes	No
Bladder cancer	16	Yes	No
Breast cancer	14	Yes	Yes
Kidney cancer	10	No	No
Pancreatic cancer	7	No	No
Testicular cancer	8	No	No
Lip, oral cavity and pharynx cancer	5	No	No
Stomach cancer	6	No	No
Liver cancer	5	No	No
Brain cancer	6	No	No
Bone cancer	5	No	No
Oesophageal cancer	5	No	No
Larynx cancer	3	No	No
Biliary tract cancer	2	No	No
Soft-tissue	2	No	No
Female reproductive system cancer	2	No	No
Other	9	No	No

表 6：がんサブグループごとに同定された調査対象研究の要約

がん	研究数	メタアナリシス推奨	以前のメタアナリシス
造血器新生物	88	Yes	Yes
前立腺がん	39	No	Yes
肺がん	30	Yes	No
すべてのがん	30	No	No
小児がん	45	Yes	Yes
大腸がん	26	No	No
皮膚がん	17	Yes	No
膀胱がん	16	Yes	No
乳がん	14	Yes	Yes
腎臓がん	10	No	No
膵臓がん	7	No	No
精巣がん	8	No	No
口唇・口腔・咽頭のがん	5	No	No
胃がん	6	No	No
肝臓がん	5	No	No
脳腫瘍	6	No	No
骨がん	5	No	No
食道がん	5	No	No
喉頭がん	3	No	No
胆道がん	2	No	No
軟組織	2	No	No
女性生殖器系がん	2	No	No
その他	9	No	No

Table 7: Summary results across eligible studies that reported information on the same pesticide class and risk of leukaemia (DDE: Dichlorodiphenyldichloroethylene)

Study ID	Publication Date	Pesticide Class	Pesticide Type	Outcome	N	OR	95% LCI	95% UCI	Level of Adjustment
DDE									
CAN_064	2010	p,p'-DDE	Biomarker	Chronic Lymphocytic Leukemia	210	0.78	0.28	2.21	+++
CAN_063	2010	p,p'-DDE	Questionnaire	Chronic Lymphocytic Leukemia	148	0.62	0.29	1.3	++
CAN_056	2008	p,p'-DDE	Biomarker	Chronic Lymphocytic Leukemia	71	1	0.4	2.5	+
Insecticides									
CAN_072	2006	Insecticides	Questionnaire	All leukemias	1304	1	0.7	1.4	+
CAN_049	2009	Insecticides	Questionnaire	Chronic Lymphocytic Leukemia	37	0.8	0.3	2.1	+
CAN_024	2010	Insecticides	Questionnaire	Acute Myeloid Leukemia	158	1.52	0.16	2.04	+++
Herbicides									
CAN_072	2006	Herbicides	Questionnaire	All leukemias	1260	1.4	0.8	2.3	++
CAN_049	2009	Herbicides	Questionnaire	Chronic Lymphocytic Leukemia	39	0.5	0.2	1.3	+
CAN_024	2010	Herbicides	Questionnaire	Acute Myeloid Leukemia	45	1.83	0.99	3.38	+++
CAN_058	2008	Herbicides	Questionnaire	Chronic Lymphocytic Leukemia	523	1.15	0.76	1.74	++

Table 8: Examples of identified studies from the Agricultural Health Study (AHS) that evaluated the same biomarkers of pesticide exposure in relation to colorectal cancer (DDVP: 2,2-dichlorovinyl dimethyl phosphate)

Study ID	Pesticide	Outcome	Comparison	Sample size	Effect Estimate (OR)	Lower 95% CI	Upper 95% CI	Adjustments
CAN_122	Dichlorvos/DDVP	Colon cancer	Highest tertile of exposure vs no	202	1.48	0.78	2.8	+
CAN_024	Dichlorvos/DDVP	Colon cancer	Ever vs. never	56813	1.5	0.9	2.4	++
CAN_024	Fonofos	Colon cancer	Ever vs. never	56813	1.5	1	2.2	++
CAN_119	Fonofos	Colon cancer	Highest tertile of exposure vs no	126	1.66	0.92	3.03	++
CAN_024	Malathion	Colorectal cancer	Ever vs. never	56813	0.8	0.6	1.1	++
CAN_121	Malathion	Colorectal cancer	Highest tertile of exposure vs no	58	0.84	0.48	1.48	++
CAN_118	Toxaphene	Rectum cancer	Yes vs. no	75	2	1.1	3.5	+++
CAN_024	Toxaphene	Rectum cancer	Ever vs. never	56813	2.1	1.2	3.6	++

表 7：同一農薬クラスと白血病リスク（DDE：ジクロロジフェニルジクロロエチレン）についての情報を報告した調査対象試験全体の要約結果

Study ID	掲載日	殺虫剤クラス	殺虫剤の種類	影響	N	OR	95% LCI	95% UCI	Level of Adjustment
DDE									
CAN_064	2010	p,p'-DDE	バイオマーカー	慢性リンパ性白血病	210	0.78	0.28	2.21	+++
CAN_063	2010	p,p'-DDE	質問紙	慢性リンパ性白血病	148	0.62	0.29	1.3	++
CAN_056	2008	p,p'-DDE	バイオマーカー	慢性リンパ性白血病	71	1	0.4	2.5	+
Insecticides									
CAN_072	2006	Insecticides	質問紙	すべての白血病	1304	1	0.7	1.4	+
CAN_049	2009	Insecticides	質問紙	慢性リンパ性白血病	37	0.8	0.3	2.1	+
CAN_024	2010	Insecticides	質問紙	急性骨髄性白血病	158	1.52	0.16	2.04	+++
Herbicides									
CAN_072	2006	Herbicides	質問紙	すべての白血病	1260	1.4	0.8	2.3	++
CAN_049	2009	Herbicides	質問紙	慢性リンパ性白血病	39	0.5	0.2	1.3	+
CAN_024	2010	Herbicides	質問紙	急性骨髄性白血病	45	1.83	0.99	3.38	+++
CAN_058	2008	Herbicides	質問紙	慢性リンパ性白血病	523	1.15	0.76	1.74	++

表 8：大腸がん（DDVP：2,2-ジクロロビニルジメチルリン酸塩）に関連して農薬ばく露の同じバイオマーカーを評価した農業健康調査（Agricultural Health Study：AHS）から同定された研究の例

Study ID	殺虫剤	影響	比較	サンプルサイズ	効果推定値(OR)	下位 95% CI	上位 95% CI	調整
CAN_122	ジクロロボス/DDVP	大腸がん	Highest tertile of exposure vs no	202	1.48	0.78	2.8	+
CAN_024	ジクロロボス/DDVP	大腸がん	Ever vs. never	56813	1.5	0.9	2.4	++
CAN_024	フォノフォス	大腸がん	Ever vs. never	56813	1.5	1	2.2	++
CAN_119	フォノフォス	大腸がん	Highest tertile of exposure vs no	126	1.66	0.92	3.03	++
CAN_024	マラチオン	直腸がん	Ever vs. never	56813	0.8	0.6	1.1	++
CAN_121	マラチオン	直腸がん	Highest tertile of exposure vs no	58	0.84	0.48	1.48	++
CAN_118	トキサフェン	直腸がん	Yes vs. no	75	2	1.1	3.5	+++
CAN_024	トキサフェン	直腸がん	Ever vs. never	56813	2.1	1.2	3.6	++

Table 9: Studies on biomarkers of pesticide exposure and testicular cancer with more than >2 studies per biomarker (DDE: Dichlorodiphenyldichloroethylene; HCB: Hexachlorobenzene)

Study ID	Pesticide	Effect estimate type	Comparison level	Total N	Effect estimate	95% LCI	95% UCI	Adjustments
CAN_111	Dieldrin	OR	high tertile vs low	418	0.79	0.44	1.41	++
CAN_115	Dieldrin	OR	high tertile vs low	60	2.1	0.5	9.5	+
CAN_113	HCB	OR	yes/no	57	4.4	1.7	12	+
CAN_115	HCB	OR	high tertile vs low	70	2.9	0.5	15.2	+
CAN_111	Heptachlor epoxide	OR	high tertile vs low	407	0.67	0.35	1.29	++
CAN_115	Heptachlor epoxide	OR	high tertile vs low	68	2.4	0.6	9.1	+
CAN_111	Mirex	OR	high tertile vs low	557	0.87	0.5	1.53	++
CAN_112	Mirex	RR	high tertile vs low	1333	0.24	0.9	1.74	+++
CAN_115	Mirex	OR	high tertile vs low	66	1.2	0.4	3	+
CAN_111	o,p-DDT	OR	high tertile vs low	514	1.3	0.67	2.53	++
CAN_115	o,p'-DDT	OR	high tertile vs low	71	1.4	0.4	4.5	+
CAN_116	o,p'-DDT	Mean difference	unit increase	60	0.46	n/a	n/a	n/a
CAN_111	p,p'-DDT	OR	high tertile vs low	533	1.17	0.68	2	++
CAN_112	p,p'-DDT	RR	high tertile vs low	1493	1.13	0.71	1.82	+++
CAN_115	p,p'-DDT	OR	high tertile vs low	63	2.1	0.6	7.2	+
CAN_116	p,p'-DDT	Mean difference	unit increase	60	-1.2	n/a	n/a	n/a
CAN_111	p,p'-DDE	OR	high tertile vs low	554	0.61	0.32	1.14	++
CAN_112	p,p'-DDE	RR	high tertile vs low	884	1.71	1.23	2.38	+++
CAN_113	p,p'-DDE	OR	yes/no	44	1.3	0.5	3	+
CAN_115	p,p'-DDE	OR	high tertile vs low	65	2.2	0.7	6.5	+
CAN_116	p,p'-DDE	Mean difference	unit increase	60	-15.29	n/a	n/a	n/a
CAN_117	p,p'-DDE	OR	high tertile vs low	98	3.21	0.77	13.3	+
CAN_111	Oxychlordane	OR	high tertile vs low	538	0.93	0.5	1.73	++
CAN_112	Oxychlordane	RR	high tertile vs low	841	1.27	0.92	1.76	+++
CAN_115	Oxychlordane	OR	high tertile vs low	68	3.2	0.6	16.8	+
CAN_111	Total chlordanes	OR	high tertile vs low	562	0.93	0.51	1.68	++
CAN_112	Total chlordanes	RR	high tertile vs low	842	1.51	1.09	2.1	+++
CAN_113	Sum of chlordanes	OR	yes/no	49	1.9	0.7	5	+
CAN_115	Total chlordanes	OR	high tertile vs low	70	2.3	0.6	7.2	+
CAN_111	Trans -nonachlor	OR	high tertile vs low	564	0.89	0.49	1.61	++
CAN_112	Trans -nonachlor	RR	high tertile vs low	875	1.46	1.07	2	+++
CAN_115	Trans -nonachlor	OR	high tertile vs low	62	2.6	0.7	8.9	+

表 9：農薬ばく露のバイオマーカーと精巣がんについて、1 つのバイオマーカーにつき 2 件以上の研究を行った研究（DDE：ジクロロジフェニルジクロロエチレン、HCB：ヘキサクロロベンゼン）

Study ID	殺虫剤	効果推定型	比較レベル	合計数	効果の推定	95% LCI	95% UCI	調整
CAN_111	ディルドリン	OR	high tertile vs low	418	0.79	0.44	1.41	++
CAN_115	ディルドリン	OR	high tertile vs low	60	2.1	0.5	9.5	+
CAN_113	HCB	OR	yes/no	57	4.4	1.7	12	+
CAN_115	HCB	OR	high tertile vs low	70	2.9	0.5	15.2	+
CAN_111	ヘプタクロルエポキシド	OR	high tertile vs low	407	0.67	0.35	1.29	++
CAN_115	ヘプタクロルエポキシド	OR	high tertile vs low	68	2.4	0.6	9.1	+
CAN_111	ミレックス	OR	high tertile vs low	557	0.87	0.5	1.53	++
CAN_112	ミレックス	RR	high tertile vs low	1333	0.24	0.9	1.74	+++
CAN_115	ミレックス	OR	high tertile vs low	66	1.2	0.4	3	+
CAN_111	o,p-DDT	OR	high tertile vs low	514	1.3	0.67	2.53	++
CAN_115	o,p'-DDT	OR	high tertile vs low	71	1.4	0.4	4.5	+
CAN_116	o,p'-DDT	Mean difference	unit increase	60	0.46	n/a	n/a	n/a
CAN_111	p,p'-DDT	OR	high tertile vs low	533	1.17	0.68	2	++
CAN_112	p,p'-DDT	RR	high tertile vs low	1493	1.13	0.71	1.82	+++
CAN_115	p,p'-DDT	OR	high tertile vs low	63	2.1	0.6	7.2	+
CAN_116	p,p'-DDT	Mean difference	unit increase	60	-1.2	n/a	n/a	n/a
CAN_111	p,p'-DDE	OR	high tertile vs low	554	0.61	0.32	1.14	++
CAN_112	p,p'-DDE	RR	high tertile vs low	884	1.71	1.23	2.38	+++
CAN_113	p,p'-DDE	OR	yes/no	44	1.3	0.5	3	+
CAN_115	p,p'-DDE	OR	high tertile vs low	65	2.2	0.7	6.5	+
CAN_116	p,p'-DDE	Mean difference	unit increase	60	-15.29	n/a	n/a	n/a
CAN_117	p,p'-DDE	OR	high tertile vs low	98	3.21	0.77	13.3	+
CAN_111	オキシクロルデン	OR	high tertile vs low	538	0.93	0.5	1.73	++
CAN_112	オキシクロルデン	RR	high tertile vs low	841	1.27	0.92	1.76	+++
CAN_115	オキシクロルデン	OR	high tertile vs low	68	3.2	0.6	16.8	+
CAN_111	全クロルデン	OR	high tertile vs low	562	0.93	0.51	1.68	++
CAN_112	全クロルデン	RR	high tertile vs low	842	1.51	1.09	2.1	+++
CAN_113	クロルデンの和	OR	yes/no	49	1.9	0.7	5	+
CAN_115	全クロルデン	OR	high tertile vs low	70	2.3	0.6	7.2	+
CAN_111	トランス-ノナクロル	OR	high tertile vs low	564	0.89	0.49	1.61	++
CAN_112	トランス-ノナクロル	RR	high tertile vs low	875	1.46	1.07	2	+++
CAN_115	トランス-ノナクロル	OR	high tertile vs low	62	2.6	0.7	8.9	+

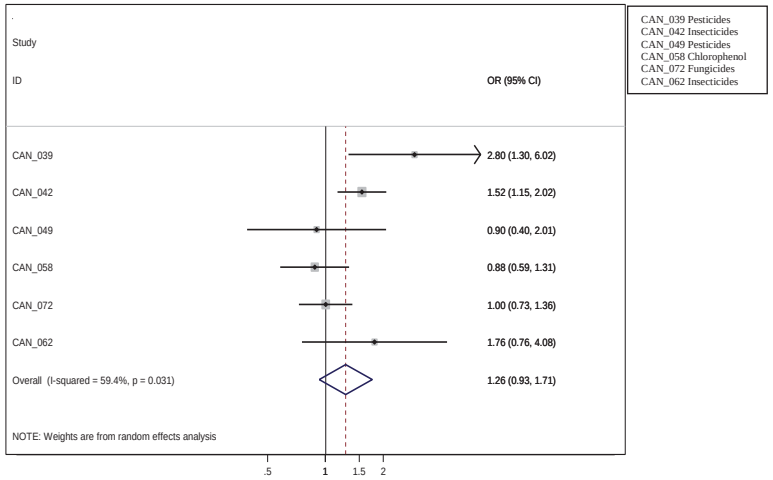


Figure 8: Random effects meta-analysis of the association between exposure to pesticides and Leukemia

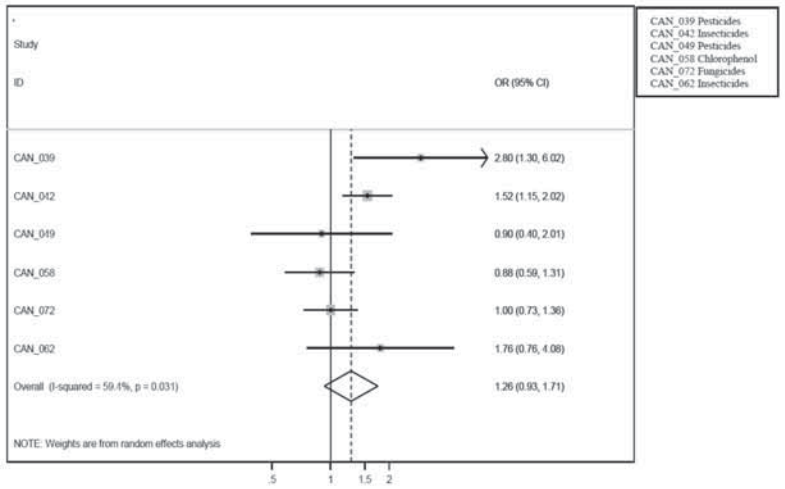


図8：農薬ばく露と白血病との関連のランダム効果メタアナリシス

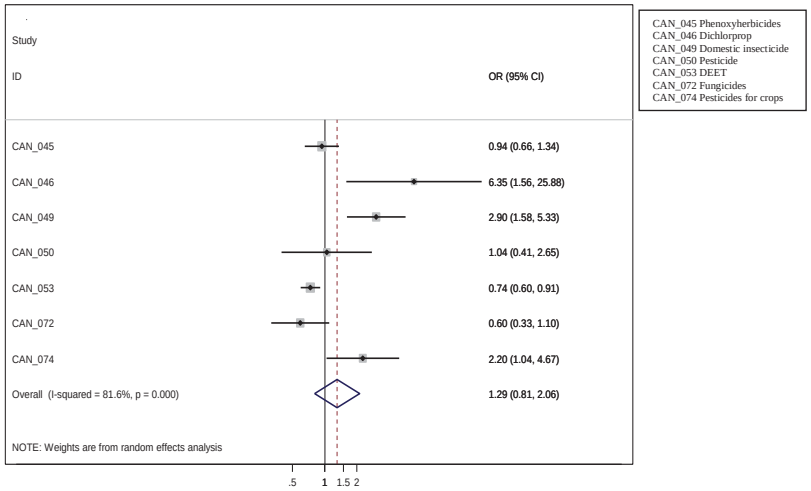


Figure 9: Random effects meta-analysis of the association between exposure to pesticides and Hodgkin Lymphoma

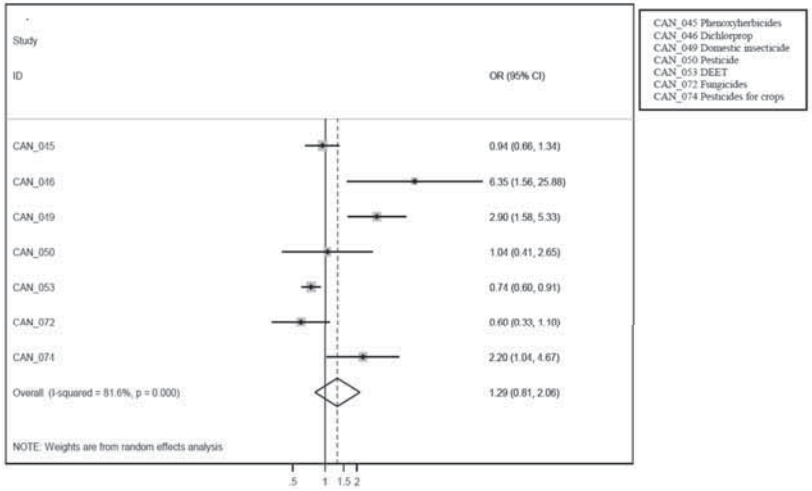


図9：農薬ばく露とホジキンリンパ腫との関連のランダム効果メタアナリシス

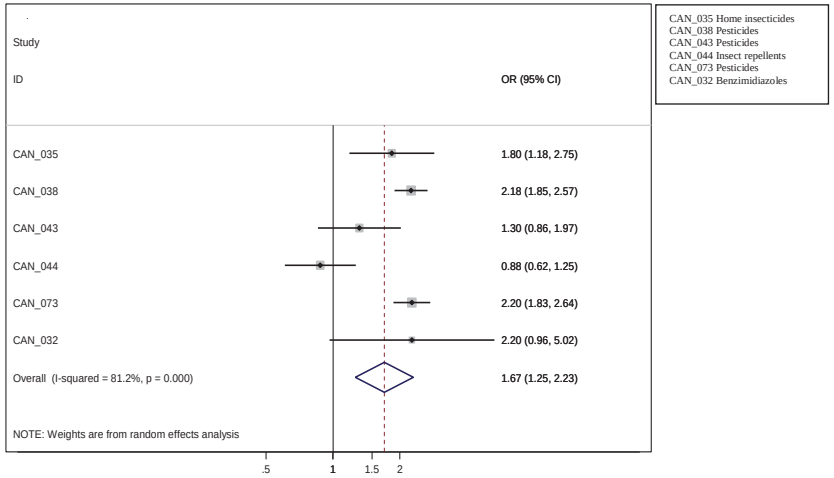


Figure 10: Random effects meta-analysis of the association between childhood leukemia and exposure to pesticides during pregnancy (Any exposure to pesticide during pregnancy and childhood leukemia)

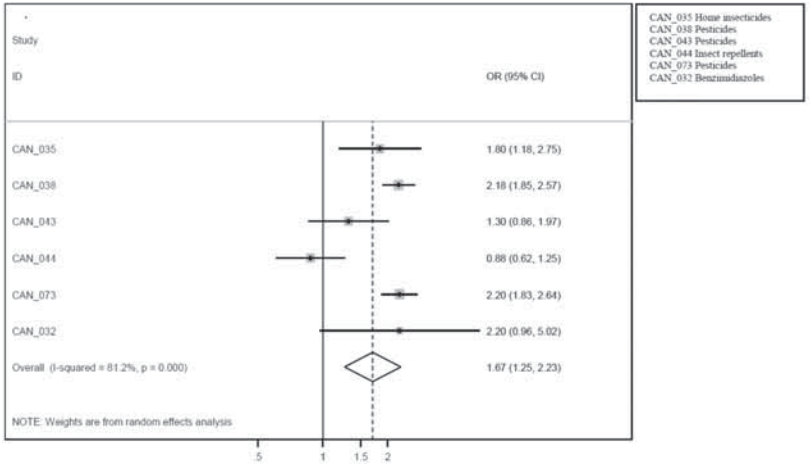


図10：小児白血病と妊娠期の農薬ばく露との関連のランダム効果メタアナリシス（妊娠期のあらゆる農薬ばく露と小児白血病）

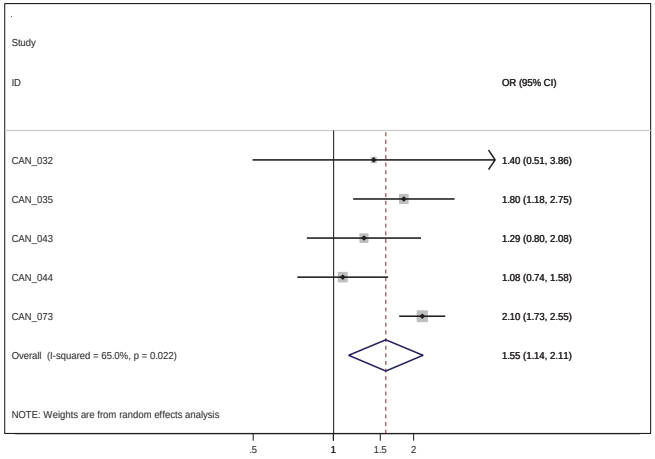


Figure 11: Random effects meta-analysis of the association between childhood leukemia and exposure to pesticides during pregnancy (Exposure to insecticides during pregnancy and childhood leukemia)

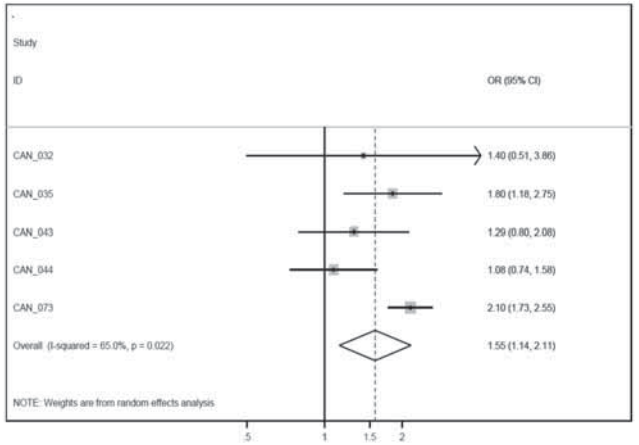
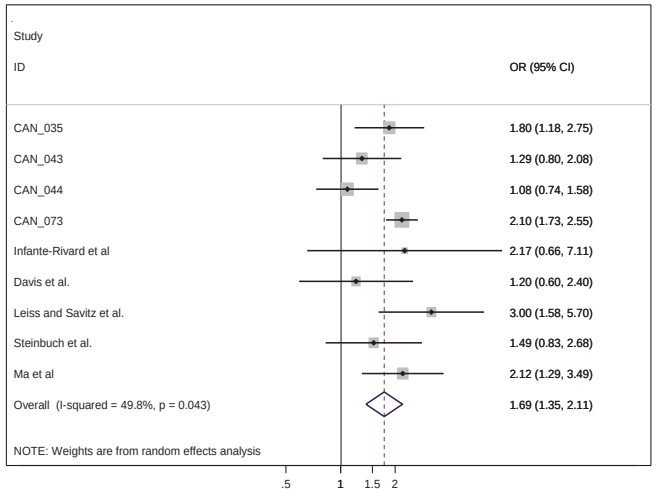


図11：小児白血病と妊娠期の農薬ばく露との関連のランダム効果メタアナリシス（妊娠期の殺虫剤ばく露と小児白血病）



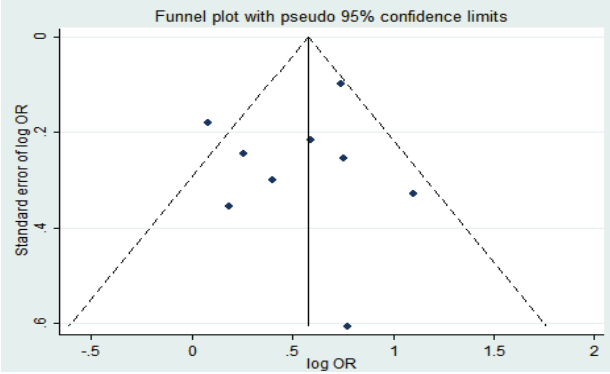
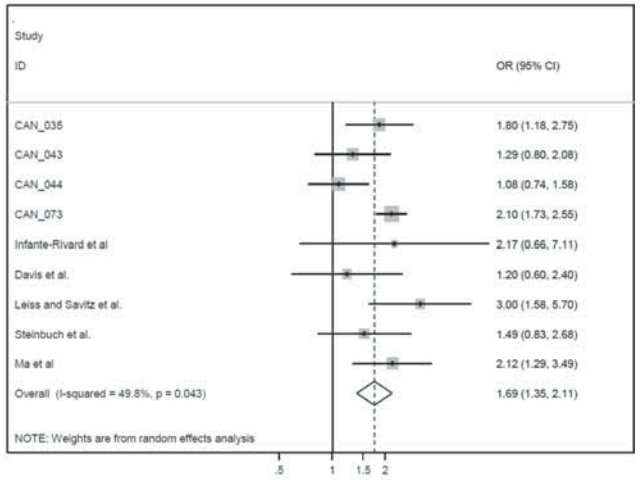


Figure 12: Random effects meta-analysis of the association between childhood leukemia and exposure to pesticides during pregnancy (Residential exposure to insecticide during pregnancy and childhood leukemia) (update to meta-analysis 2010 using published effect sizes; Turner 2010) and associated funnel plot



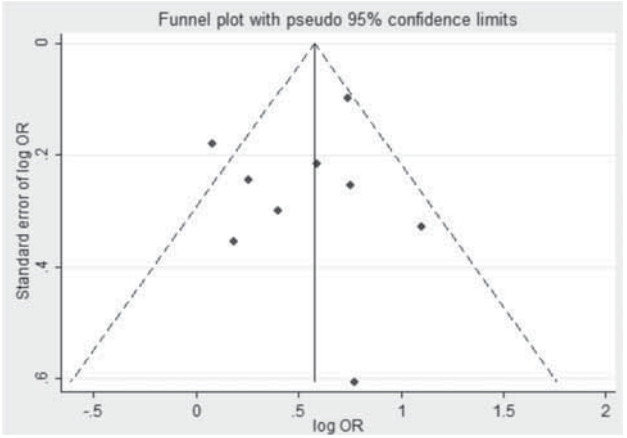


図12：妊娠期の農薬ばく露と小児白血病との関連のランダム効果メタアナリシス（妊娠期の殺虫剤への住居内ばく露と小児白血病（公表されている効果量を用いたメタアナリシス2010の更新；Turner 2010）、ならびに関連するファンネルプロット）

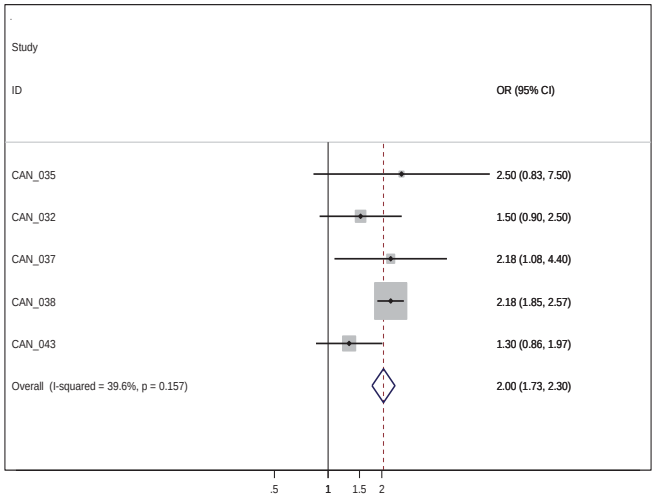


Figure 13: Random effects meta-analysis of the association between childhood leukemia and exposure to pesticides during pregnancy (Exposure to unspecified pesticides during pregnancy and childhood leukemia)

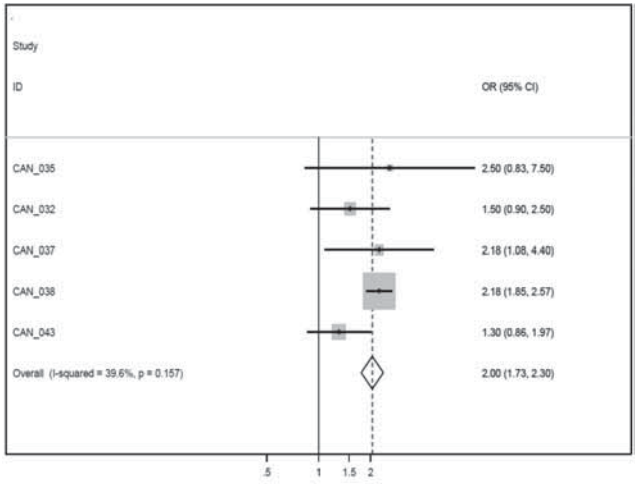
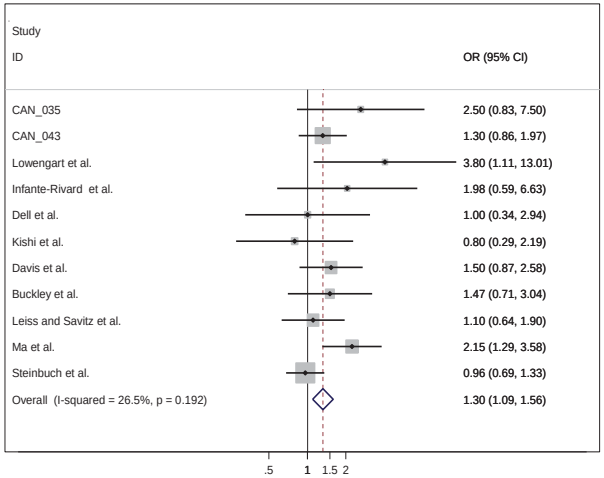


図13：小児白血病と妊娠期の農薬ばく露との関連のランダム効果メタアナリシス（妊娠期の不特定の農薬ばく露と小児白血病）



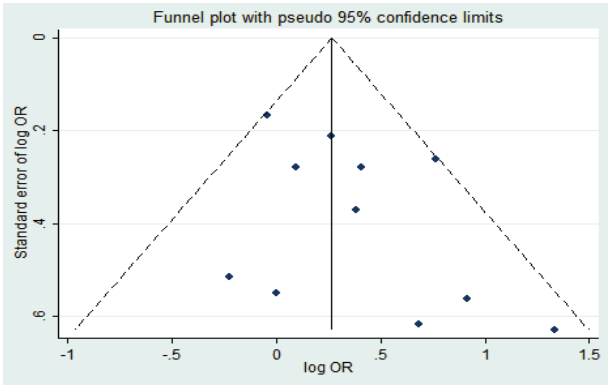
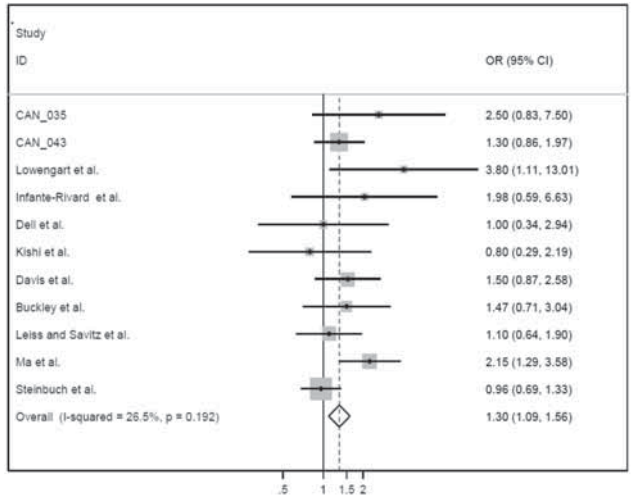


Figure 14: Random effects meta-analysis of the association between childhood leukemia and exposure to pesticides during pregnancy (Residential exposure to unspecified pesticides during pregnancy and childhood leukemia (update to meta-analysis 2010, Turner 2010) and associated funnel plot)



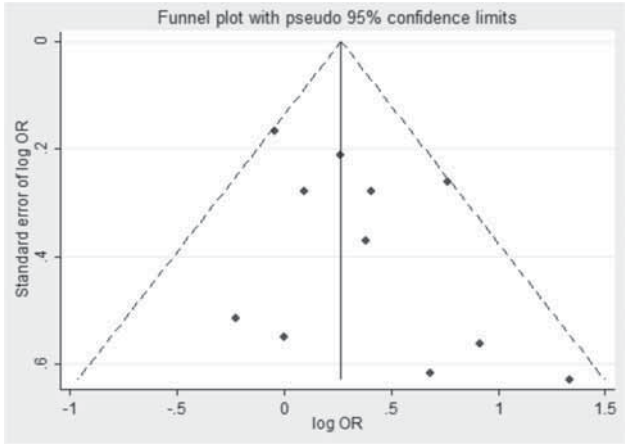


図14：妊娠期の農薬ばく露と小児白血病との関連のランダム効果メタアナリシス（妊娠期の不特定の農薬への住居内ばく露と小児白血病（メタアナリシス2010、Turner 2010への更新）、ならびに関連するファンネルプロット）

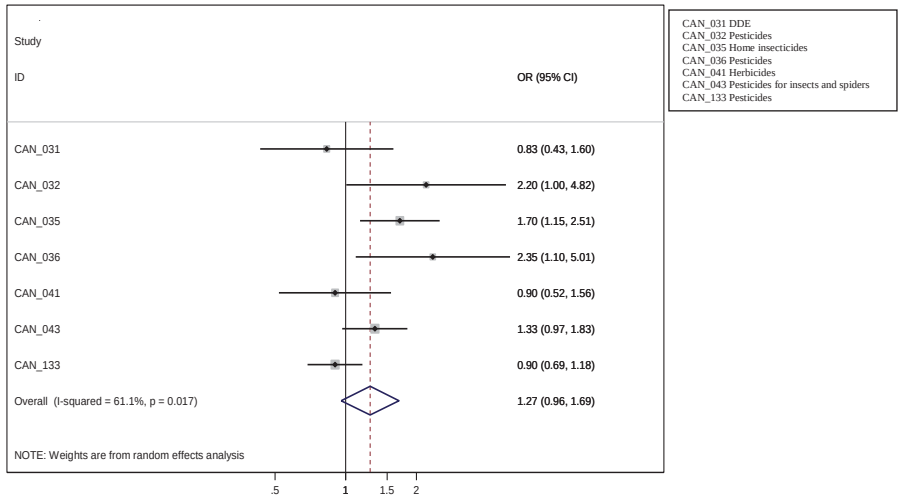


Figure 15: Random effects meta-analysis of the association between childhood leukemia and exposure to pesticides during childhood (Any exposure to pesticide during childhood and childhood leukemia)

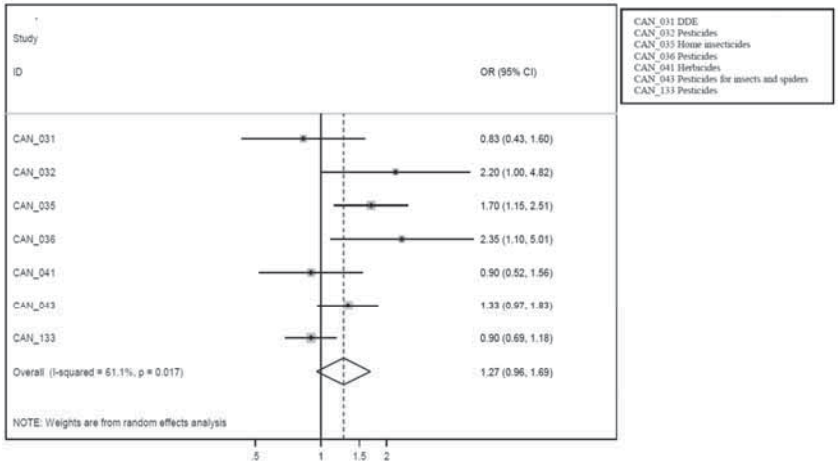


図15：小児白血病と小児期の農薬ばく露との関連のランダム効果メタアナリシス（小児期のあらゆる農薬ばく露と小児白血病）

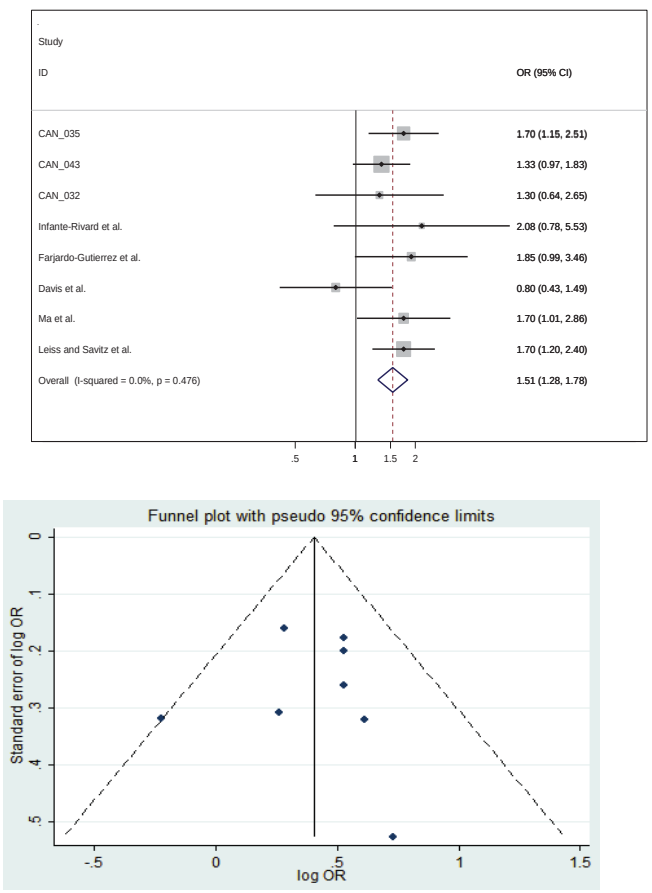
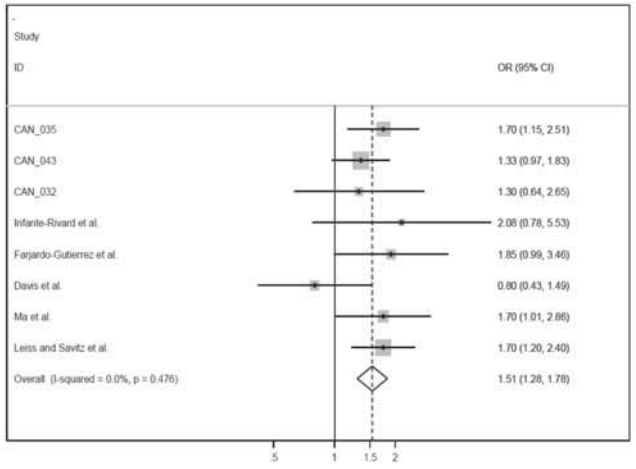


Figure 16: Random effects meta-analysis of the association between childhood leukemia and exposure to pesticides during childhood (Residential exposure to insecticide during childhood and childhood leukemia (update to meta-analysis 2010 using published effect sizes, Turner 2010) and associated funnel plot)



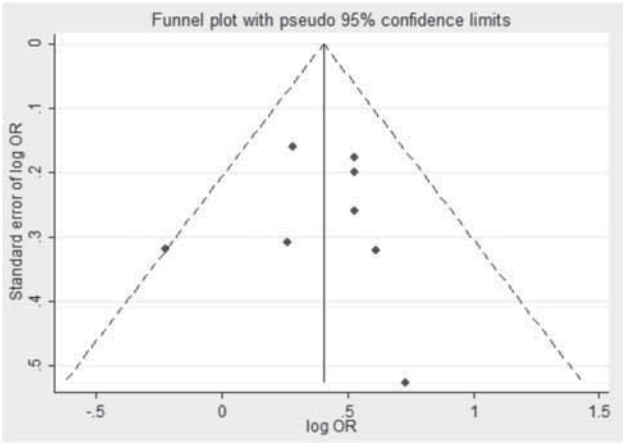
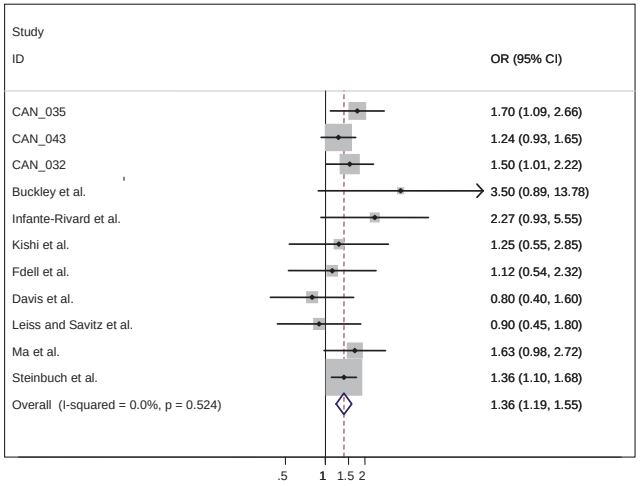


図16：小児白血病と小児期の農薬ばく露との関連のランダム効果メタアナリシス（小児期の殺虫剤への住居内ばく露と小児白血病（公表されている効果量を用いたメタアナリシス2010の更新、Turner 2010）、ならびに関連するファンネルプロット）



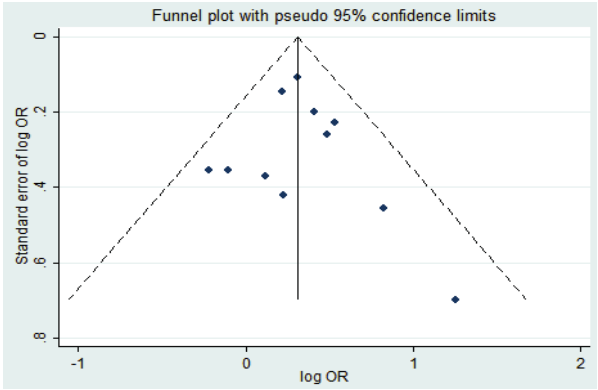
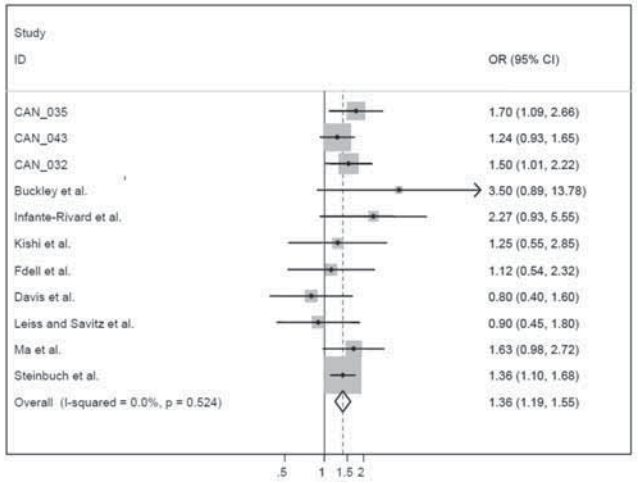


Figure 17: Random effects meta-analysis of the association between childhood leukemia and exposure to pesticides during childhood (Residential exposure to unspecified pesticides during childhood and childhood leukemia (update to meta-analysis 2010 using published effect sizes, Turner 2010) and associated funnel plot)



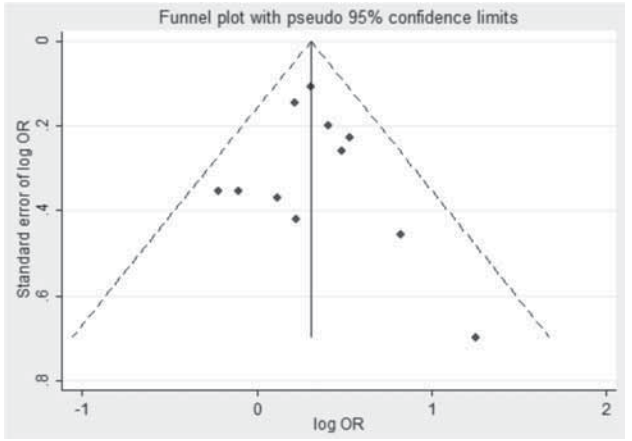


図17：小児白血病と小児期の農薬ばく露との関連のランダム効果メタアナリシス（小児期の不特定の農薬への住居内ばく露と小児白血病（公表されている効果量を用いたメタアナリシス2010の更新、Turner 2010）、ならびに関連するファンネルプロット）

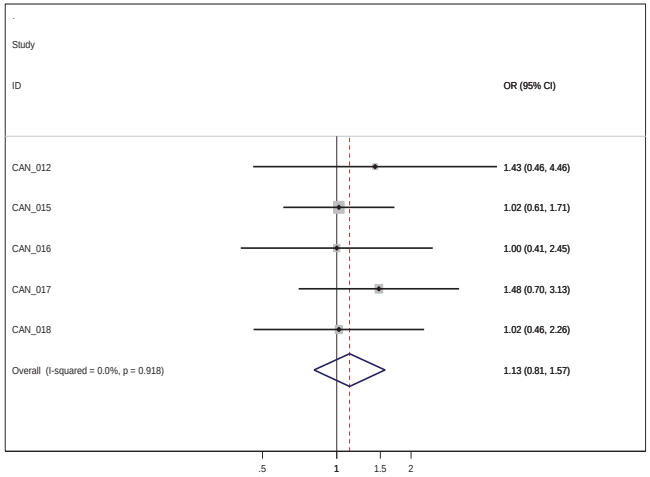


Figure 18: Random effects meta-analysis for studies with information on Dichlorodiphenyldichloroethylene (DDE) and breast cancer on studies that examined DDE exposure to pesticide with breast cancer

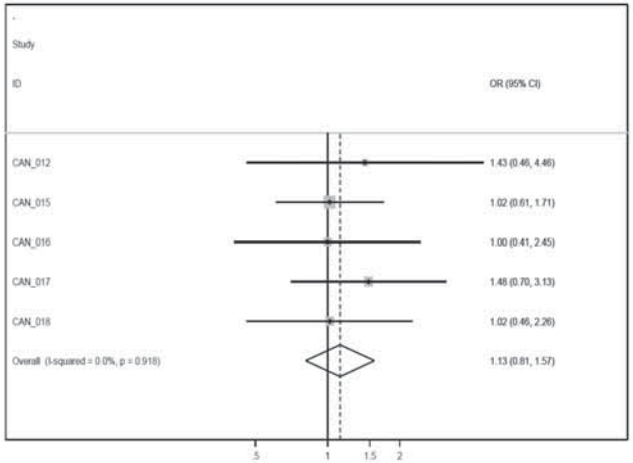


図18：農薬のジクロロジフェニルジクロロエチレン（DDE）ばく露と乳がんを調査した研究でのDDEの情報と乳がんのランダム効果メタアナリシス

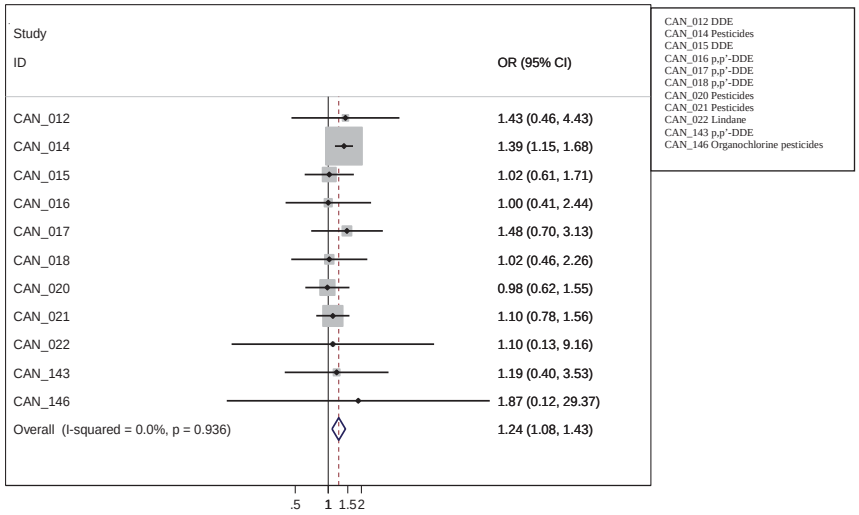


Figure 19: Random effects meta-analysis for studies with information on Dichlorodiphenyldichloroethylene (DDE) and breast cancer selecting analyses with the largest sample size within each study (pesticides assessed in each study are shown in on the right key).

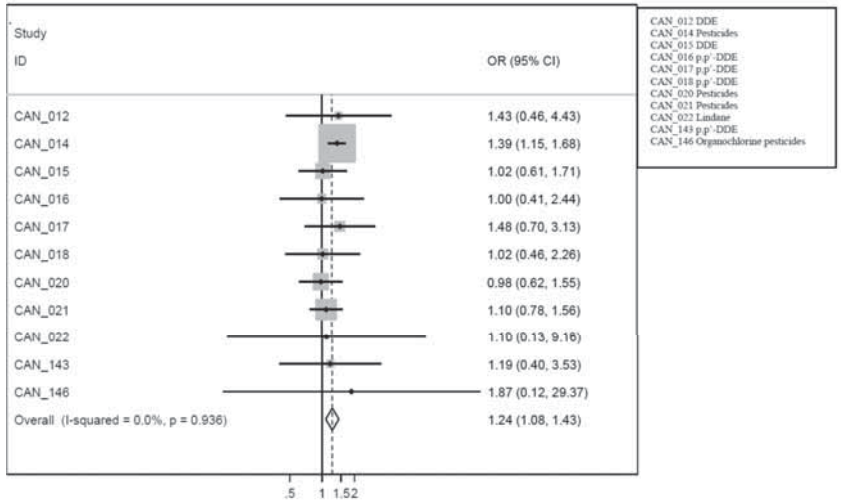


図19：各研究内で最大のサンプルサイズでの分析を選択したジクロロジフェニルジクロロエチレン(DDE)の情報と乳がんのランダム効果メタアナリシス（各研究で評価された農薬は右に示されている）

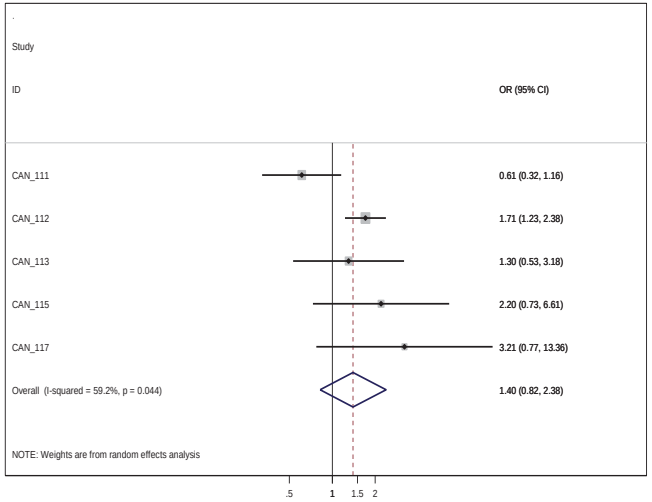


Figure 20: Random effects meta-analysis for studies with information on Dichlorodiphenyldichloroethylene (DDE) and testicular cancer

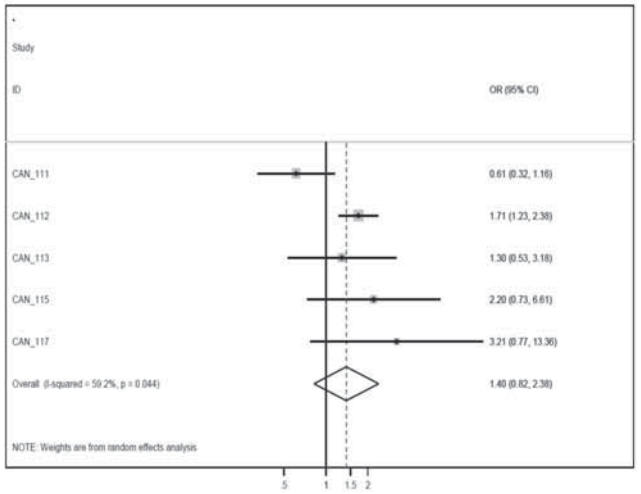


図20：ジクロロジフェニルジクロロエチレン（DDE）に関する情報と精巣がんのランダム効果メタアナリシス

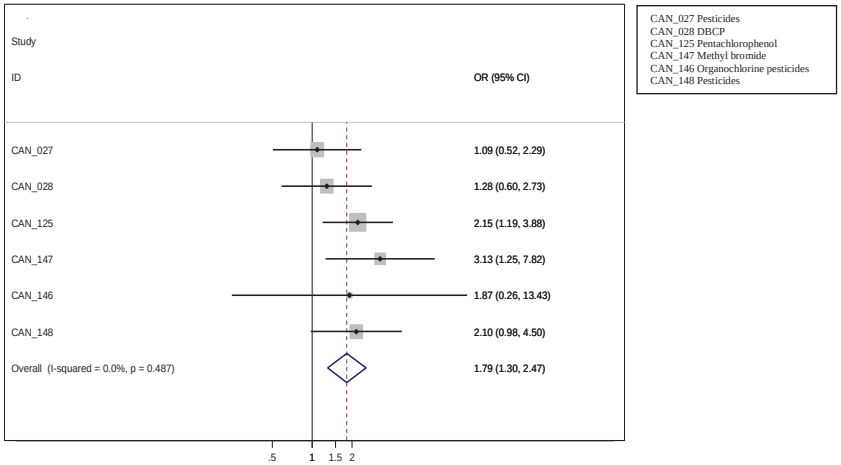


Figure 21: Random effects meta-analysis for studies that examined any exposure to pesticide with stomach cancer selecting analyses with the largest sample size within each study

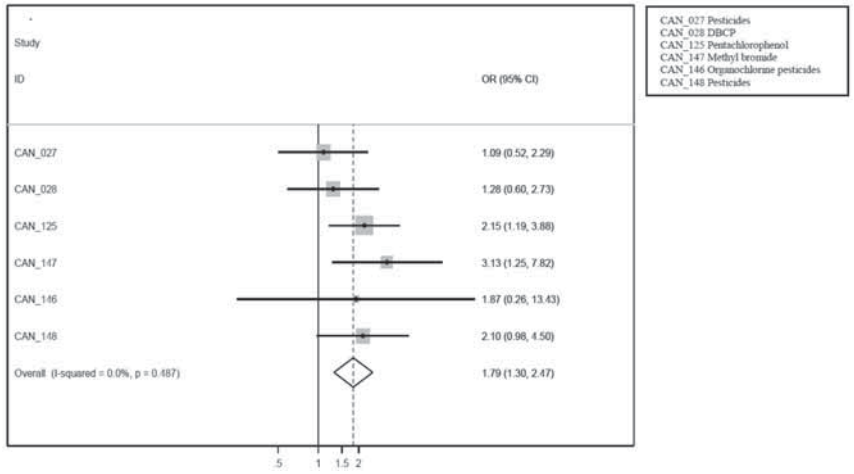


図21:あらゆる農薬ばく露と胃がんを調査した研究のうち、各研究内で最大のサンプルサイズでの分析を用いた研究のランダム効果メタアナリシス

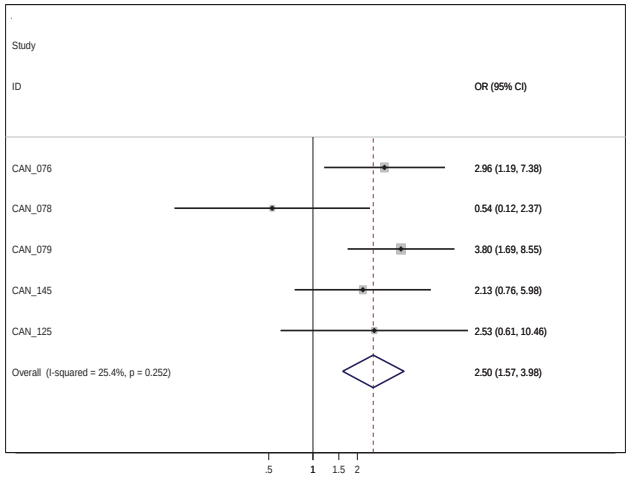


Figure 22: Random effects meta-analysis for studies that examined any exposure to pesticide with liver cancer selecting analyses with the largest sample size within each study (pesticides assessed in each study are shown on the right key)

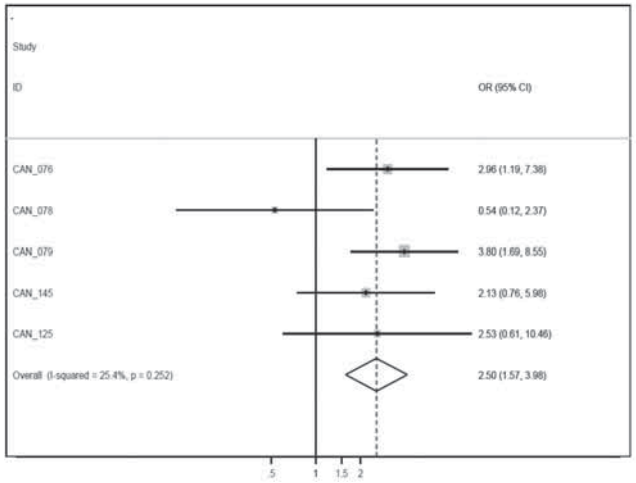


図22：あらゆる農薬ばく露と肝臓がんを調査した研究のうち、各研究内で最大のサンプルサイズの分析を用いた研究のランダム効果メタアナリシス（各研究で評価された農薬は右に示されている）

9. Child health

Overall, 84 individual studies examined the effect of pesticide exposure on child health outcomes (median sample size: 267; IQR 119-811), contributing 821 separate analyses in the *data extraction database*. More than 120 health-related outcomes were assessed with a large proportion focusing on congenital malformations and developmental parameters including but not restricting to somatometrics (Table 10). As seen with other outcomes, the diversity of the exposure definition is remarkable and poses special challenges to data synthesis. Only 38 out of the 84 were prospective cohort studies and other 5 were nested case-controls; the majority of evidence comes from retrospective case-control analyses, which are prone to recall bias in exposure measurement. The sample size in the reported analyses was often small; it ranged between 23 and 183,313 participants (median 267) and the largest studies in the domain are smaller than the largest studies assessed in the cancer field. Here, we observed no large clusters of publications coming from large, well-known studies in the field, such as the Agricultural Health Study (AHS), while 26 studies assessed occupational exposures. In addition, the presence of studies with information on biomarkers of exposure was more prominent here (n=49, 58%) while 3 studies assessed occupational exposure through JEM. The different outcome categories examined are presented in Table 10 along with the number of studies contributing to each outcome category and a decision on quantitative synthesis (Table 11). Due to heterogeneity of data and small number of studies identified, statistical synthesis of the data (meta-analysis) was only performed for urological malformations only.

9.1. Prematurity

Fifteen studies assessed the association between pesticide exposure during pregnancy and prematurity with a median sample size of 193 (IQR 87-469), contributing 54 separate extracted comparisons in the database. More than half of the studies were retrospective and in more than three-fourths of the studies, the exposure was assessed through a biomarker. A large variety of individual pesticides were assessed with DDT metabolites being assessed more frequently (8 studies). Nevertheless no single pesticide and related biomarker was assessed in more than 4 studies using the same comparison unit, thus a quantitative synthesis was not performed. The largest prospective study (ID CH 091) assessed a Dutch population of greenhouse workers and reported a decreased risk of preterm birth among male greenhouse workers (OR= 0.47; 95%CI= 0.35–0.65) while the observed increased risk in women was not statistically significant (OR= 1.14, 95%CI= 0.57–2.31) .The remaining studies reported statistically non-significant results with effect estimates pointing towards a positive association. Moreover, no meta-analysis of published studies was identified. Based on these data, there is no recent evidence to suggest a robust, clinically significant association between pesticide exposure and prematurity in general.

9.2. Restricted fetal growth

Twelve studies assessed the association between pesticide exposure during pregnancy and restricted fetal growth and/or small for gestational age neonates with a median sample size of 422 (IQR 178-1,630), contributing 44 separate extracted comparisons in the database. Sixty percent of the studies were prospective, three assessed occupational exposure and in more than two-thirds of the studies, the exposure was assessed through a biomarker. A large variety of individual pesticides were assessed with DDT metabolites being assessed more frequently (4 studies). Nevertheless no single pesticide and related biomarker was assessed in more than 4 studies using the same comparison unit, thus a

9. 小児の健康

全体では 84 件の個別研究が農薬ばく露の小児への健康影響を調査し（サンプルサイズ中央値：267、IQR 119-811）、データ抽出データベースでは 821 件の分析が行われた。120 以上の健康関連影響が評価されており、その大部分は先天性奇形と身体測定を含むがそれに限定されない発生パラメータに焦点を当てている（表 10）。他の影響に見られるように、ばく露の定義の多様性には目を見張るものがあり、データ統合に特別な問題を与えている。84 件のうち 38 件のみが前向きコホート研究であり、他の 5 件はコホート内症例対照研究であった。エビデンスの大部分は後ろ向き症例対照分析に由来しており、これはばく露量測定においてリコールバイアスがかかりやすい。報告された分析におけるサンプルサイズはしばしば小さく、23～183,313人（中央値267人）であり、この領域の最大の研究は、がん分野で評価された最大の研究よりも小さい。ここでは、農業健康調査（Agricultural Health Study：AHS）のような、この分野の大規模でよく知られた研究に由来する多数の出版物まとまっては観察されなかったが、26件の研究が職業ばく露を評価していた。さらに、ばく露のバイオマーカーに関する情報を有する研究の存在は、ここではより多かった（n=49、58%）が、3つの研究はJEMによる職業ばく露を評価した。調査した異なるカテゴリーに属する影響を、各カテゴリーに寄与した研究数と定量的統合の決定とともに表 10 に示す（表 11）。データの不均一性と同定された研究数が少なかったため、データの統計的統合（メタアナリシス）は泌尿器の奇形のみを対象に実施した。

9.1. 未熟児

妊娠期の農薬ばく露と未熟児との関連を評価した研究は 15 件あり、サンプルサイズの中央値は 193 件（IQR 87-469）で、データベースには 54 件の比較が抽出されている。半数以上の研究が後ろ向きで、4分の3以上の研究ではバイオマーカーを用いてばく露が評価されていた。個々の農薬の評価は多種多様で、DDT代謝物の評価がより頻繁に行われていた（8件の研究）。それにもかかわらず、同じ比較単位を使用した 4 件以上の研究では、単一の農薬と関連するバイオマーカーの評価は行われず、定量的な統合は行われなかった。最大の前向き研究（ID CH 091）では、オランダの温室労働者を対象とし、温室労働者の男性における早産リスクの減少（OR= 0.47; 95%CI= 0.35-0.65）が報告されたが、女性におけるリスクの増加は統計的に有意ではなかった（OR= 1.14, 95%CI= 0.57-2.31）。残りの研究では、正の関連を示す推定効果が得られたが、統計的に有意な結果はなかった。さらに、発表された研究のメタアナリシスは確認されなかった。これらのデータに基づいて、農薬ばく露と未熟児との間に臨床的に有意な関連を示唆する最近のエビデンスはない。

9.2. 胎児の発育制限

12の研究では、妊娠期の農薬ばく露と胎児の発育制限及び/または在胎不当過小児との関連を評価しており、サンプルサイズの中央値は422（IQR 178-1,630）で、データベースには44件の個別の比較が抽出されていた。研究の60%は前向きで、3つの研究では職業ばく露を評価し、3分の2以上の研究ではバイオマーカーを用いてばく露を評価している。個々の農薬の評価は多種多様で、DDT代謝物の評価がより頻繁に行われていた（4件の研究）。それにもかかわらず、同じ比較単位を使用した 4 件以上の研究では、単一の農薬と関連するバイオマーカーの評価は行われず、定量的な統合は行われなかった。最大の研究（ID RPD 26）では、後ろ向きコホートを対象に、飲料水中のアトラジンが在胎不当過小（SGA）及び早産の罹患率の増加と関連しているかどうかを評価した。著者らの報告によると、妊娠第 3 期及び全妊娠期間の飲料水中のアトラジンは、SGA（Small for Gestational Age）の罹患率の有意な増加

quantitative synthesis was not performed. The largest study (ID RPD 26) assessed in a retrospective cohort whether atrazine in drinking water is associated with increased prevalence of small-for-gestational age and preterm birth. The authors reported that atrazine in drinking water during the third trimester and the entire pregnancy was associated with a significant increase in the prevalence of SGA (Small for Gestational Age); atrazine in drinking water > 0.1 µg/L during the third trimester resulted in a 17–19% increase in the prevalence of SGA compared with the control group (< 0.1 µg/L). All the remaining studies reported statistically non-significant results without a consistent pattern regarding the effect direction of the effect magnitude. Moreover, no meta-analysis of published studies was identified. Based on these data, there is no recent evidence to suggest a robust, clinically significant association between pesticide exposure and prematurity in general.

9.3. Somatometrics (Body size metrics)

Numerous studies examined the association between pesticide exposure and growth.

9.3.1. Birth length / Height

Length at birth and height was assessed in 13 and 8 studies, respectively, contributing 78 separate comparisons in the database. In the vast majority of the studies, the exposure was assessed through a biomarker. A large variety of individual pesticides were assessed with DDT metabolites being assessed more frequently; nevertheless no single pesticide and related biomarker was assessed in more than 4 studies, thus a quantitative synthesis was not performed.

The largest prospective study (ID CH 073) assessing a North American population born before 1980, reported that only the highest prenatal concentrations of p,p'-DDE (>60 mg/l), as compared with the lowest (<15 mg/l), were statistically significantly associated with decreased height at age 7 years [adjusted coefficient (SE) -2.21 cm (0.67)]. The remaining studies reported conflicting results without a consistent pattern either towards the effect direction or the effect magnitude. Moreover, no meta-analysis was identified. Given the large number of analyses these results need cautious interpretation and, based on these data, there is no recent evidence to suggest a robust, clinically significant association between pesticide exposure and birth length or height in general.

9.3.2. Body weight

Twenty-six studies assessed the association between pesticide exposure during pregnancy and birth weight, contributing 134 separate extracted comparisons in the database. Another 5 studies assessed the association between pesticide and ponderal index. In a large number of comparisons, the exposure was assessed through a biomarker. A large variety of individual pesticides were assessed with DDT metabolites being assessed more frequently (11 studies). Nevertheless no single pesticide and related biomarker was assessed in more than 4 studies using the same comparison unit, thus a quantitative synthesis was not performed. The largest prospective study (ID CH 014) was a Agricultural Health Study (AHS) publication and reported that first-trimester pesticide-related tasks were not associated with birth weight and that, after multiple analyses, ever use of the pesticide carbaryl was associated with decreased birth weight (−82 g, 95% CI = −132, −31). The remaining studies reported conflicting results without a consistent pattern either towards the effect direction or the effect magnitude. Moreover, no meta-analysis of published studies was identified. We identified though a meta-analysis of individual participants data from European cohorts which reported that a 1-µg/L increase in p,p´-

と関連しており、妊娠第 3 期に飲料水中のアトラジンが 0.1 µg/L を超えると、対照群（0.1 µg/L 未満）と比較して SGA の罹患率が 17～19%増加した。残りのすべての研究では、効果量の方向性に関する一貫したパターンがなく、統計的に有意ではない結果が報告された。さらに、発表された研究のメタアナリシスは確認されなかった。これらのデータに基づいて、農薬ばく露と未熟児との間に臨床的に有意な関連を示唆する最近のエビデンスはない。

9.3. 身体測定（体格計測）

農薬ばく露と発育の関連を調査した研究は数多くある。

9.3.1. 出生時の体長/身長

出生時の体長と身長はそれぞれ13件と8件の研究で評価され、データベースでは78件の比較が行われた。大半の研究では、バイオマーカーを用いてばく露が評価されている。個々の農薬の評価は多種多様で、DDT代謝物の評価がより頻繁に行われていたが、4件以上の研究では単一の農薬と関連するバイオマーカーの評価は行われておらず、定量的な統合は行われていない。

1980 年以前に生まれた北米の集団を対象とした最大の前向き研究（ID CH 073）では、出生前の p,p'-DDE の最高濃度（>60 mg/l）のみが、最低濃度（<15 mg/l）と比較して、7 歳時の身長低下と統計的に有意に関連していることが報告された［調整係数（SE） -2.21 cm（0.67）］。残りの研究では、効果の方向性または効果量に一貫したパターンがなく、相反する結果が報告された。さらに、メタアナリシスは確認されなかった。多数の分析を考慮すると、これらの結果は慎重に解釈する必要があり、これらのデータに基づいて、農薬ばく露と出生時の体長または身長の間に、妥当で臨床的に有意な関連を示唆する最近のエビデンスはない。

9.3.2. 体重

妊娠期の農薬ばく露と出生時体重との関連を評価した研究は 26 件あり、データベースには 134 件の個別抽出比較が掲載されている。他の 5 件の研究では、農薬とポンデラル指数との関連を評価した。多くの比較では、バイオマーカーを用いてばく露が評価された。個々の農薬の評価は多種多様で、DDT の代謝物の評価がより頻繁に行われた（11 研究）。しかし、同じ比較単位を使用した 4 件以上の研究では、単一の農薬と関連するバイオマーカーの評価は行われず、定量的な統合は行われなかった。最大の前向き研究（ID CH 014）は農業健康研究（Agricultural Health Study: AHS）の論文で、妊娠3ヶ月までの農薬関連作業は出生時体重とは関連しておらず、複数回の分析の結果、カルバリル農薬の使用があった場合は出生時体重の減少と関連していた（-82 g、95% CI = -132, -31）と報告された。残りの研究では、効果の方向性や効果量に一貫したパターンがなく、相反する結果が報告された。さらに、発表された研究のメタアナリシスは確認されなかった。しかし、我々はp,p´-DDEの1µg/Lの増加は出生時体重の7gの減少（95% CI= -18, 4g）と関連していた（Govarts E 2012）ことを報告したヨーロッパのコホートの個々の参加者のデータのメタアナリシスを同定した。分析の数が多いことを考えると、これらの結果は慎重な解釈が必要であり、これらのデータに基づくと、農薬ばく露と出生体重との間の妥当で臨床的に有意な関連を示唆する最近のエビデンスはない。

DDE was associated with a 7-g decrease in birth weight (95% CI= -18, 4 g) (Govarts E 2012). Given the large number of analyses these results need cautious interpretation and, based on these data, there is no recent evidence to suggest a robust, clinically significant association between pesticide exposure and birth weight in general.

Twenty-six studies assessed the association between pesticide exposure and body weight at various time-points after birth, contributing 68 separate extracted comparisons in the database. In almost 85% of the assessed comparisons, the exposure was assessed through a biomarker. A large variety of individual pesticides were assessed with DDT metabolites being assessed more frequently (10 studies). Nevertheless no single pesticide and related biomarker was assessed in more than 4 studies using the same outcome definition, the same time-point for the outcome assessment, the same pesticide, and the same comparison unit, thus a quantitative synthesis was not performed. The largest study (ID CH 074) assessing DDT exposure in a Mexican population of boys born in 2002 and 2003, reported that, overall, associations between prenatal DDE level and Body Mass Index (BMI) at any given age were not observed and that the predicted values showed that children with the highest exposure (DDE: 49.00 mg/g) compared to those least exposed (DDE: <3.01 mg/g) grew similarly and they had a BMI similar to the referent group. The remaining studies reported conflicting results without a consistent pattern either towards the effect direction or the effect magnitude. Moreover, no meta-analysis was identified. Given the large number of analyses these results need cautious interpretation and, based on these data, there is no recent evidence to suggest a robust, clinically significant association between pesticide exposure and body weight in general.

9.3.3. Head circumference

Fourteen and three studies assessed the association between pesticide exposure during pregnancy and head circumference at birth and after birth, respectively, contributing 85 separate extracted comparisons in the database. In more than two-thirds of the comparisons, the exposure was assessed through a biomarker. A large variety of individual pesticides were assessed for birth head circumference, with DDT metabolites being assessed more frequently (7 studies). Nevertheless no single pesticide and related biomarker was assessed in more than 4 studies using the same comparison unit, thus a quantitative synthesis was not performed. The largest prospective study (ID CH 026) was a Generation R study publication which explored associations between maternal occupational exposure to various chemicals and fetal growth in 4,680 pregnant women participating in this population-based prospective cohort study in the Netherlands (2002–2006). For fetal head circumference, only maternal occupational exposure to alkylphenolic compounds showed a statistically significant lower growth rate (-0.01752 SD per gestational week) compared with non-exposed mothers, adjusted for potential confounders. The remaining studies reported conflicting results without a consistent pattern either towards the effect direction or the effect magnitude. Moreover, no meta-analysis of published studies was identified. Given the large number of analyses the reported study results need cautious interpretation and, based on these data, there is no recent evidence to suggest a robust, clinically significant association between pesticide exposure and head circumference in general.

9.3.4. Congenital malformations

Five studies examined the association between pesticide exposure and congenital malformations in general. The largest study (ID CH 002) assessed a Canadian farm population, reported 146 potential associations, did not yield statistically significant results in the primary analysis and proposed that pre-

26件の研究が、出生後の様々な時点での農薬ばく露と体重との関連を評価しており、データベースには68件の個別の比較が抽出された。評価された比較のほぼ85%では、バイオマーカーを介してばく露が評価された。個々の農薬の評価は多岐にわたり、DDT代謝物の評価がより頻繁に行われた(10研究)。しかし、同じ定義の影響、同じタイムポイントでの影響評価、同じ農薬、同じ比較単位を使用した 4件以上の研究において評価された単一の農薬とそれに関連するバイオマーカーはなく、定量的な統合は行われなかった。2002 年と 2003 年に生まれたメキシコの男子集団における DDT ばく露を評価した最大の研究（ID CH 074）では、全体的に、出生前の DDE レベルと任意の年齢における BMI（Body Mass Index）との間の関連は観察されず、予測値は、最も高いばく露量（DDE: 49.00 mg/g）の小児と最も低いばく露量（DDE: <3.01 mg/g）の小児とでは発育が似通っており、BMI は参照グループと同程度であったことを示した。残りの研究では、効果の方向性や効果量に一貫したパターンがなく、相反する結果が報告された。さらに、メタアナリシスは確認されなかった。分析数が多いことから、これらの結果は慎重な解釈が必要であり、これらのデータに基づいて、農薬ばく露と体重との間に臨床的に有意な関連を示唆する最近のエビデンスはない。

9.3.3. 頭囲

妊娠期の農薬ばく露と出生時及び出生後の頭囲との関連を評価した研究はそれぞれ 14 件と 3 件あり、データベースには 85 件の個別比較が抽出されている。3 分の 2 以上の比較では、バイオマーカーを用いてばく露が評価されていた。出生時の頭囲については、多種多様な農薬が評価されており、中でも DDT 代謝物がより頻繁に評価されていた（7 研究）。それにもかかわらず、同じ比較単位を用いた 4 件以上の研究では、単一の農薬と関連するバイオマーカーの評価は行われず、定量的な統合は行われていない。最大の前向き研究（ID CH 026）は、オランダの集団ベースの前向きコホート研究（2002-2006）に参加した 4,680 人の妊婦を対象に、様々な化学物質への母親の職業ばく露と胎児の発育との関連を調査したジェネレーション R 研究の出版物である。胎児頭囲については、アルキルフェノール化合物への母親の職業ばく露のみが、潜在的な交絡因子を調整した上でばく露していない母親と比較して統計的に有意に低い成長率（妊娠週あたり-0.01752 SD）を示した。残りの研究では、効果の方向性や効果量に一貫したパターンがなく、相反する結果が報告されている。さらに、発表された研究のメタアナリシスは確認されなかった。分析数が多いことを考えると、報告された研究結果は慎重に解釈する必要があり、これらのデータに基づいて、農薬ばく露と頭囲との間に臨床的に有意な関連を示唆する最近のエビデンスはない。

9.3.4. 先天性奇形

5件の研究では、農薬ばく露と先天性奇形全般との関連が調査された。最大の研究（ID CH 002）はカナダの農場の集団を評価し、146の潜在的な関連を報告したが、主要分析では統計的に有意な結果は得られず、シアナジン（OR = 4.99、95%CI：1.63-15.27）及びジカンバ（OR = 2.42、95%CI：1.06-5.53）への妊娠前のばく露が、男児の先天性奇形のリスクの増加と関連していることが提案された。それにもかかわらず、利用可能な比較研究の数及び本研究におけるばく露と影響が自己報告であることを考慮すると、今回の知見は慎重に調査されるべきである。残りの4件の後ろ向き研究では、相反する結果が報告された（ID CH 043、職業ばく露（父親）、OR: 3.42、95% CI: 1.97-5.92; ID CH 035、少なくとも片方の親の職業ばく露、OR = 1.3、95%CI = 0.4-3.9；ID CH 008、母体の尿中メトラクロルの HR、95% 0.4-1.4）。）多数の分析を考慮すると、これらの結果は慎重な解釈が必要であり、これらの

conception exposure to cyanazine (OR = 4.99, 95% CI: 1.63–15.27) and dicamba (OR = 2.42, 95% CI: 1.06–5.53) were associated with increased risk of birth defects in male offspring. Nevertheless, given the number of the available comparisons and the self-reported nature of the exposure and outcomes in this study, the present findings should be considered with caution. The remaining four retrospective studies reported conflicting results (ID CH 043, occupational exposure (father), OR: 3.42, 95% CI: 1.97–5.92; ID CH 035, at least one parent exposed, OR = 1.3, 95%CI = 0.4 - 3.9; ID CH 008, HR for maternal urine metolachor, 95% 0.4-1.4). Given the large number of analyses these results need cautious interpretation and, based on these data, there is no recent evidence to suggest association between pesticide exposure and congenital malformations in general.

9.3.5. Neural tube defects

Identified studies examined associations between pesticide exposure and neural tube defects (N=4 studies), including anencephaly and spina bifida and providing a very large number of reported analyses between different pesticides and neural tube defects, anencephaly and spina bifida with no adjustments for multiple testing (average 27 analyses per paper). Out of the 134 extracted analyses, 43 were statistically significantly positively associated with the outcome (of which 14 borderline significant) but need to be interpreted with caution due to high false positive probability. The range of different pesticides analysed by each of the 5 studies as well as the varying definitions of pesticide exposure do not allow for a meaningful quantitative synthesis of the results even using the “any pesticide” exposure definition since there is also considerable heterogeneity between studies regarding the exposure period as well as the parent analysed; three studies assessed maternal exposure, one study assessed paternal exposure and one study both. Previous meta-analyses on neural tube defects and pesticide exposure have not been identified. Overall, the evidence for pesticides and neural tube defects is limited and the current state of the most recent literature does not support a robust association. Of note, the largest study in the field (ID CH 044) investigated whether maternal residential proximity to applications of specific pesticides or physicochemical groups of pesticides during early gestation increases the risk of these malformations, included 731 cases and 940 controls and after reporting 107 different analyses for individual pesticides, pesticide physicochemical categories and any exposure, no exposure and multiple exposure definitions yielded 15 statistically significant results without correction for multiple testing and without a particular pattern with regards to a pesticide category or an additive effect.

9.3.6. Urogenital malformations

Overall, 19 studies examined urogenital malformations, namely cryptorchidism (n=9) and hypospadias (n=9).

Cryptorchidism was assessed in nine mostly retrospective studies, of a median sample size of 199 (IQR 136-710). Four studies assessed DDT levels; hexachorobenzene (HCB) and chrordane were assessed in one study each, while general pesticide exposure was assessed in 2 studies. When we attempted to investigate the association between exposure to any pesticide and cryptorchidism across all assessed studies, the observed effect was not statistically significant (OR 1.19, 95% CI 0.96 – 1.49, I^2 24%) (Figure 23). Moreover, when we assessed the potential association between DDT exposure and cryptorchism, we again observed a statistically non-significant association (OR 1.47, 95% CI 0.98- 2.2, I^2 51%) (Figure 24). Given the large number of analyses, these results need cautious interpretation and, based on these data, there is no recent evidence to suggest a robust, clinically significant association between any pesticide exposure and cryptorchidism.

データに基づいて、農薬ばく露と先天性奇形との関連を示唆する最近のエビデンスはない。

9.3.5. 神経管閉鎖障害

同定された研究では、農薬ばく露と無脳症や二分脊椎を含む神経管閉鎖障害との関連を調査しており（N=4研究）、種々の農薬と神経管閉鎖障害、無脳症、二分脊椎との間の分析が非常に多く報告されており、多重検定の調整は行われていない（1論文あたり平均27分析）。抽出された134の分析のうち、43の分析は結果と統計的に有意に関連していたが（うち14の分析は境界線上で有意であった）、偽陽性の確率が高いので注意して解釈する必要がある。5つの研究のそれぞれで分析された農薬の種類の多さと、農薬ばく露の定義の違いにより、ばく露期間や対象とした親に関しても研究間でかなりの不均一性があるため、「何らかの農薬」ばく露の定義を用いても、結果の意味のある定量的な統合を行うことはできない。神経管閉鎖障害と農薬ばく露に関するこれまでのメタアナリシスは確認されていない。全体的に、農薬と神経管閉鎖障害に関するエビデンスは限られており、最新の文献の現状では、妥当な関連を支持するものではない。注目すべきは、この分野で最大の研究（ID CH 044）では、妊娠初期に特定の農薬または農薬の物理化学的グループの使用に母親が居住している場所に近いことが、これらの奇形のリスクを増加させるかどうかが調査され、731例と940例の対照が含まれ、個々の農薬、農薬の物理化学的カテゴリー、任意のばく露、ばく露なし、多重ばく露の定義について107の異なる分析を報告した後、多重試験の補正なしで、農薬のカテゴリーまたは相加効果に関して特定のパターンを持たない15の統計的に有意な結果が得られたことである。

9.3.6. 泌尿生殖器の奇形

全体では、19件の研究で泌尿生殖器の奇形、すなわち停留精巣（n=9）と尿道下裂（n=9）が調査された。

停留精巣は9件の研究で評価されたが、そのうちの9件はほとんどが後ろ向き研究であり、サンプルサイズの中央値は199件（IQR 136-710）であった。4件の研究ではDDTレベルが評価され、ヘキサクロロベンゼン（HCB）とクロルデンはそれぞれ1件ずつ評価され、一般的な農薬ばく露は2件の研究で評価された。評価したすべての研究で、いずれかの農薬へのばく露と停留精巣との関連を調査しようとしたところ、観察された影響は統計的に有意ではなかった（OR 1.19、95%CI 0.96～1.49、I2 24%）（図 23）。さらに、DDTばく露と停留精巣との間の潜在的な関連を評価したところ、再び統計的に有意ではない関連が観察された（OR 1.47、95% CI 0.98-2.2、I2 51%）（図 24）。多数の分析を考慮すると、これらの結果は慎重に解釈する必要があり、これらのデータに基づいて、あらゆる農薬ばく露と停留精巣との間に、臨床的に有意な関連を示唆する最近のエビデンスはない。

尿道下裂は主に9件の後ろ向き研究で評価され、サンプルサイズの中央値は784人（IQR 200 - 861）であった。2件の研究ではDDTレベルが評価され、6件の研究では農薬ばく露一般が評価された。評価されたすべての研究において、何らかの農薬への母親のばく露（妊娠前及び妊娠期）と尿道下裂との関連を調査しようとしたところ、観察された影響は統計的に有意ではなかった（OR 1.02、95%CI 0.74-1.39、I2 72%）（図25）。特定の農薬を評価した 3 つの研究（DDT、n=2；クロルデン、n=1）を分析に含めると、再び統計的に有意でない関連が観察された（OR 1.00、95% CI 0.84-1.16、I2 66%）（図26）。我々のシステマティックレビューでは、1966年1月から2008年3月までに英語で出版され、PubMedに索引付けされたオリジナルの研究を含む1つのメタアナリシスを検索した（Rocheleau CM, 2009）。2007年以前に発表された9件の研究がすべての研究の包含基準を満たしており、著者らは、尿道下裂の

Hypospadias was assessed in 9 mostly retrospective studies, of a median sample size of 784 (IQR 200 - 861). Two studies assessed DDT levels, while general pesticide exposure was assessed in 6 studies. When we attempted to investigate the association between maternal exposure to any pesticide (during preconception and pregnancy) and hypospadias across all assessed studies, the observed effect was not statistically significant (OR 1.02, 95% CI 0.74 – 1.39, I^2 72%) (Figure 25). When we included in the analysis the three studies that assessed a specific pesticide (DDT, n=2; chrordane, n=1), we again observed a statistically non-significant association (OR 1.00, 95% CI 0.84- 1.16, I^2 66%) (Figure 26). Our systematic review retrieved one meta-analysis including original research published in English and indexed in PubMed from January 1966 through March 2008 (Rocheleau CM, 2009). Nine studies published before 2007 met all study inclusion criteria and the authors reported that elevated but marginally significant risks of hypospadias were associated with maternal occupational exposure (PRR of 1.36, CI=1.04-1.77), and paternal occupational exposure (PRR of 1.19, CI=1.00-1.41). Due to the different time-periods for the literature assessment and the resulting minimal overlap between our review and the published meta-analysis, we were able to synthesize the two efforts and again we retrieved a statistically non-significant result (OR 1.14, 95% CI 0.84 – 1.55, I^2 73%). Thus, there is no recent evidence to suggest a robust, clinically significant association between any pesticide exposure and cryptorchidism.

9.4. Child health outcomes with few studies

For all the assessed outcomes not included in Table 10, too few studies are available to allow synthesis of evidence for each outcome alone; these outcomes comprise a vast variety of captured information ranging from well-defined clinical entities yet with too few studies, such as gastroschisis, cardiac birth defects, diaphragmatic hernia, and esophageal atresia, as well as a large numbers of metrics pertaining to broad clinical entities but with a prominent lack of harmonization and standardization in the outcome definition. For example, outcomes related to neurodevelopment were assessed extensively; nevertheless the metrics used, ranging from IQ measurement to perceptual reasoning, deemed any further attempt towards a quantitative synthesis impossible. Our systematic review did not identify any previously published meta-analyses on these outcomes to allow for comparisons with previously published evidence (prior to 2006). Generally the results on these outcomes were of small effect and not statistically significant with few exceptions. Given the large number of analyses these results need cautious interpretation and, based on these data, there is no evidence to suggest association between pesticide exposure and these outcomes.

リスクの上昇は、母親の職業ばく露（PRR1.36、CI=1.04-1.77）及び父親の職業ばく露（PRR1.19、CI=1.00-1.41）と関連していたが、わずかに有意であったと報告している。異なる期間に文献評価した結果として、我々のレビューと発表されたメタアナリシスとの重複が最小限であったために、我々は2つの成果を統合することができ、再び我々は統計的に有意ではない結果を取得した（OR 1.14、95%CI 0.84 - 1.55、I2 73%）。このように、いかなる農薬ばく露と停留精巣との間に、妥当で臨床的に有意な関連を示唆する最近のエビデンスはない。

9.4. 研究が少ない小児健康影響

Table 10にはない健康影響には、個々の健康影響のエビデンスの統合には研究数が少なすぎるものがある。すなわち、これらの健康影響には、腹壁裂、心臓先天異常、横隔膜ヘルニア、食道閉鎖症などのような明確に定義されてはいるが研究数が少ない臨床所見から、広範な臨床所見に関連する多数の指標からなるが健康影響の定義の一致と標準化が著しく欠如しているものまで、多種多様な情報が収集されている。例えば、神経発達に関連した健康影響は広範囲に評価されているが、IQ測定から知覚推論に至るまで使用されている指標は、定量的な統合を目指したさらなる試みは不可能であると考えられた。我々のシステマティックレビューでは、以前に発表されたエビデンス（2006年以前）との比較を可能にするために、これらの健康影響に関する以前に発表されたメタアナリシスは確認されなかった。一般的に、これらの健康影響に関する結果は効果量が小さく、統計的に有意ではなかった（少数の例外を除く）。分析数が多いことを考えると、これらの結果は慎重に解釈する必要があり、これらのデータに基づいて、農薬ばく露とこれらの影響との関連を示唆するエビデンスはない。

Table 10: Assessed outcomes in the field of child health as defined by eligible studies

Health outcome		
Abnormal urogenital distance	Body mass index (BMI) Z-score	Increased serum prolactin levels
Abnormal body mass index (BMI)	Body fat percentages (log transformed)	Increased serum total testosterone level
Abnormal bone age	Chordee	IQ
Abnormal breast size	Coarctation of the aorta	LH dysregulation
Abnormal change of body mass index	Congenital diaphragmatic hernia (CDH)	Low annual height velocity
Abnormal change of height	Congenital heart defects	Major congenital anomalies
Abnormal chest circumference	Congenital malformations	Male genital malformations
Abnormal gestational age	Cretinism	Maternal age
Abnormal head circumference-for-age	Crown-Heel Length	Maternal weight gain
Abnormal height	Cryptorchidism	Miscarriage or stillbirth
Abnormal hip circumference	Decreased inhibin B levels	Musculoskeletal defects
Abnormal length	Decreased serum FSH levels	Neural tube defects
Abnormal ovarian measurements	Decreased serum inhibin B levels	Obesity
Abnormal penis length (stretched)	Decreased serum SHBG levels	Oestradiol dysregulation
Abnormal penis width	Decreased testicular volume	Perceptual Reasoning
Abnormal serum DHT levels	Decreased testosterone levels	Performance IQ
Abnormal sitting height	Decresed serum LH levels	Ventricular septal defect
Abnormal standing height	Duration of lactation	Placental weight
Abnormal Tanner stage	Esophageal atresia	Placental weight
Abnormal upper arm circumference	Fetal death	Ponderal Index
Abnormal upper arm fold circumference	Fetal head circumference	Ponderal index
Abnormal uterine measurements	Fetal length	Precocious puberty
Abnormal waist circumference	Fetal weight	Preeclampsia
Abnormal weight	FGR	Premature breast development
Abnormal weight-for-length	Freedom from distractability	Premature oestradiol secretion
Affected breast development	FSH dysregulation	Premature puberty onset (pubic hair)
Anal position index	Gastroschisis	Prematurity
Androstendione dysregulation	Gestational age	Processing speed
Anencephaly	Gynecomastia	Rapid infant weight gain
Anti-mullerian hormone dysregulation	Head Circumference	SGA
APGAR 1-minute score	Hypospadias	SHC
APGAR 5-minute score	Idiopathic precocious puberty	Spina bifida
Atrioventricular septal defect	Increased FSH levels	Sum of four skin folds
Birth head circumference	Increased levels of SHBG	Testosterone dysregulation

表 10：対象となる研究で定義された小児健康分野で評価された影響

健康影響		
尿路性器距離の異常	体格指数（BMI）Z スコア	血清プロラクチン値の上昇
異常なボディマス指数（BMI）	体脂肪率（対数変換）	血清トータルテストステロン値の上昇
骨年齢の異常	尿道索	IQ
胸の大きさの異常	大動脈の動脈硬化	LH 調節障害
肥満度指数の異常変化	先天性横隔膜ヘルニア（CDH）	年間の高さ速度が低い
身長の異常な変化	先天性心疾患	重篤な先天性異常
胸囲の異常	先天性奇形	男性性器奇形
在胎月齢の異常	クレチン症	母体年齢
年齢に応じた頭囲の異常	頭踵長	母体の体重増加
異常な高さ	停留精巣	流産・死産
股関節周囲の異常	インヒビン B 値の低下	筋骨格系の欠陥
身長の異常	血清 FSH 値の低下	神経管障害
卵巣の異常測定	血清インヒビン B 値の低下	肥満
ペニスの長さの異常（伸びる）	血清 SHBG 値の低下	エストラジオールの調節障害
ペニスの幅の異常	精巣容積の減少	知覚推論
血清 DHT 値の異常	テストステロン値の低下	パフォーマンス IQ
異常な座高	血清 LH 値の低下	心室中隔欠損
異常な立位の高さ	授乳期間	胎盤重量
異常なタナー段階	食道閉鎖症	胎盤重量
上腕囲の異常	胎児の死亡	ポンデラルインデックス
屈曲上腕囲の異常	胎児頭囲	ポンデラルインデックス
子宮の測定値の異常	胎児の長さ	思春期早発
ウエスト周りの異常	胎児の体重	子癇前症
異常な体重	FGR	早熟な乳房の発達
長さに対する重量の異常	注意散漫でない	早期エストラジオール分泌
乳房の発達への影響	FSH の調節障害	思春期早発症（陰毛）
Anal position index	腹壁裂	未熟児
アンドロステンジオンの調節障害	在胎月齢	処理速度
無脳症	女性化乳房	乳幼児の急激な体重増加
抗ミュラーホルモンの調節障害	頭囲	SGA
APGAR 1 分間のスコア	尿道下裂	ＳＨＣ
APGAR 5 分間のスコア	特発性早熟性思春期	二分脊椎
房室中隔欠損症	FSH 値の上昇	皮下脂肪計測
出生時の頭囲	SHBG の増加	テストステロンの調節障害
出生時の体長	LH/テストステロン比率の増加	ファロー四徴症

Birth height	Increased ratio LH/testosterone	Tetralogy of Fallot
Birth Weight	Increased serum AMH levels	Transposition of the great arteries
Birth weight, adjusted for gestational age	Increased serum androstenedione levels	Verbal comprehension
BMI	Increased serum DHEAS levels	Verbal IQ
BMI at delivery	Increased serum free testosterone level	Working memory
BMI before pregnancy		

出生時体重	血清 AMH 値の上昇	大動脈の転換
出生時体重、在胎月齢で調整	血清アンドロステンジオン値の上昇	言語理解
BMI	血清 DHEAS 値の上昇	言語性 IQ
出産時の BMI	血清遊離テストステロン値の上昇	ワーキングメモリ
妊娠前の BMI		

Table 11: Summary of studies identified per outcome subgroup with more than 4 studies (NA: not available)

Outcome	N studies	Meta-analysis done	Previous meta-analysis result
Congenital malformations			
General	5	No	NA
Neural tube defects	4	No	NA
Urogenital malformations	19	Yes	Hypospadias: maternal occupational exposure (RR 1.36; 95% CI 1.04–1.77), and paternal occupational exposure (RR 1.19; 95% CI 1.00–1.41)
Development	40	No	NA
Growth			
Height/Birth length	21	No	NA
Weight	26	No	Birth weight (individual participants' data meta-analysis of 12 European cohorts): A 1-µg/L increase in p,p´-DDE was associated with a 7-g decrease in birth weight (95% CI: -18, 4 g).
Head circumference	17	No	NA
Sexual maturation	9	No	NA

表 11：4 件以上の研究がある影響のサブグループごとに同定された研究の要約（NA：利用できない）

影響	研究数	メタアナリシス実施	前回のメタアナリシス結果
先天性奇形			
全身	5	No	NA
神経管閉鎖障害	4	No	NA
泌尿生殖器の奇形	19	Yes	尿道下裂：母方の職業ばく露（RR 1.36；95%CI 1.04-1.77）及び父方の職業ばく露（RR 1.19；95%CI 1.00-1.41）
発生	40	No	NA
発育			
身長/出産時長	21	No	NA
体重	26	No	出生時体重（ヨーロッパの 12 のコホートを対象とした個々の参加者のデータメタアナリシス）：p,p´-DDE の 1µg/L 増加は、出生時体重の 7g 減少と関連していた（95%CI：-18.4g）
頭囲	17	No	NA
性的成熟	9	No	NA

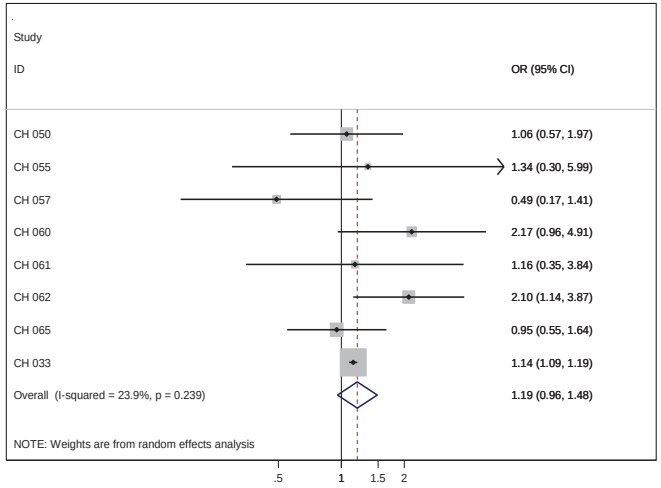


Figure 23: Random effects meta-analysis for studies with information on pesticide exposure and risk of cryptorchidism

Ntzani EE, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I Pesticide epidemiology

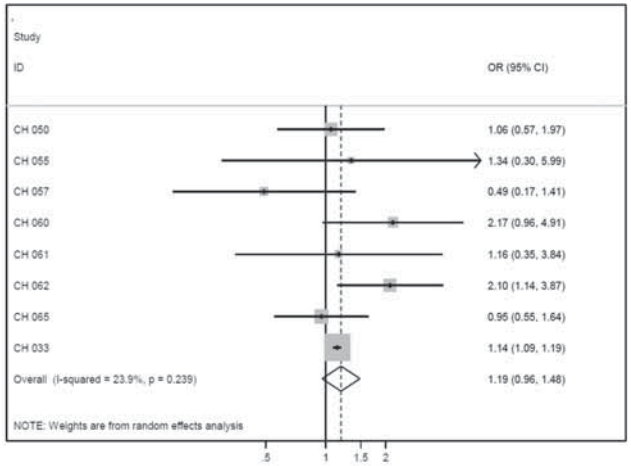


図23：農薬ばく露に関する情報と停留精巣のリスクのランダム効果メタアナリシス

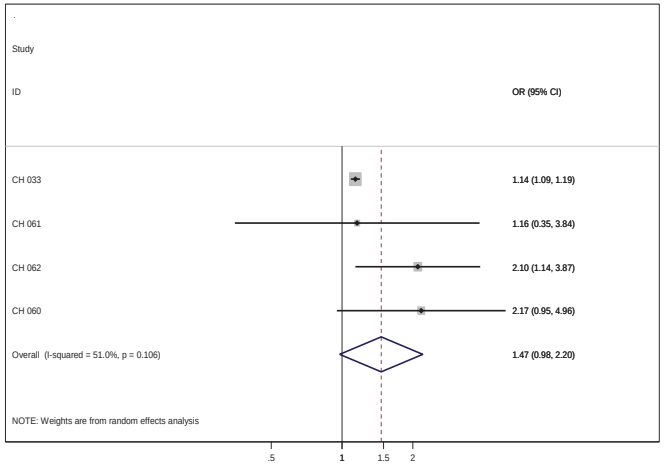


Figure 24: Random effects meta-analysis for studies with information on DDT exposure and risk of cryptorchidism

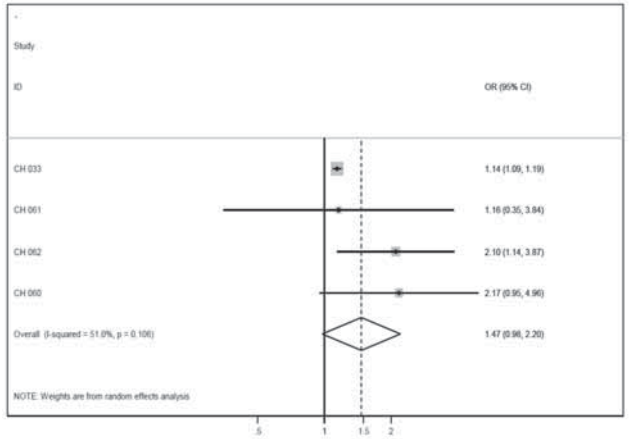


図24：DDTばく露に関する情報と停留精巣のリスクのランダム効果メタアナリシス

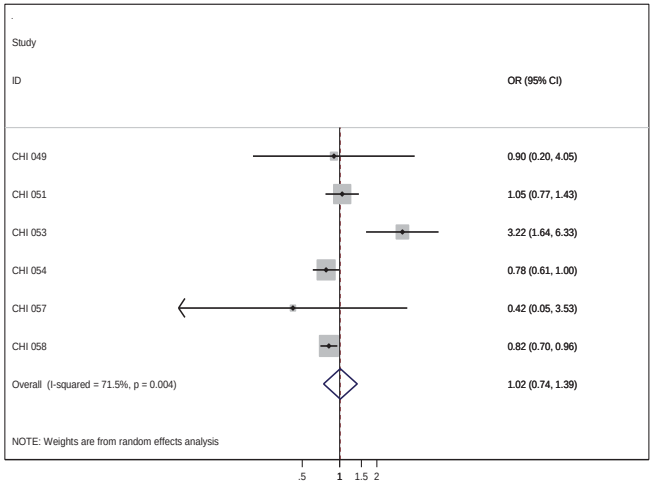


Figure 25: Random effects meta-analysis for studies with information on general pesticide exposure and risk of hypospadias

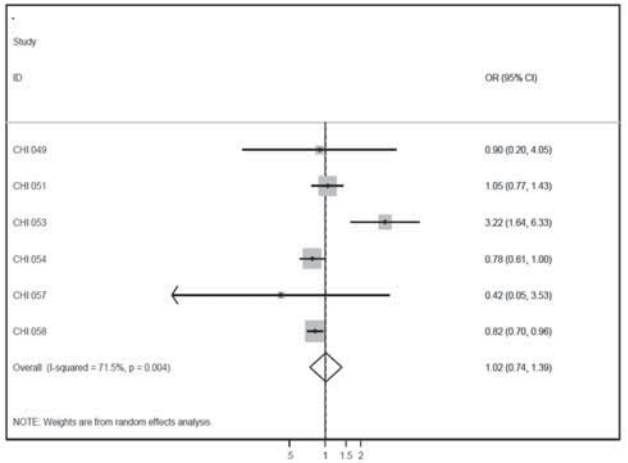


図25：農薬ばく露一般に関する情報と尿道下裂のリスクのランダム効果メタアナリシス

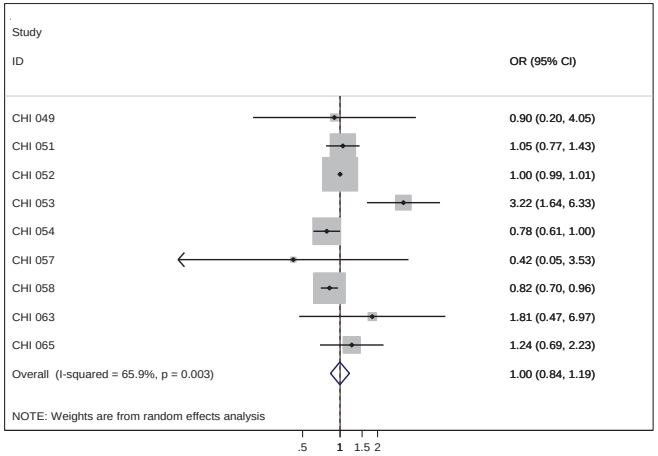


Figure 26: Random effects meta-analysis for studies with information on general pesticide exposure and risk of hypospadias, including studies on specific pesticides

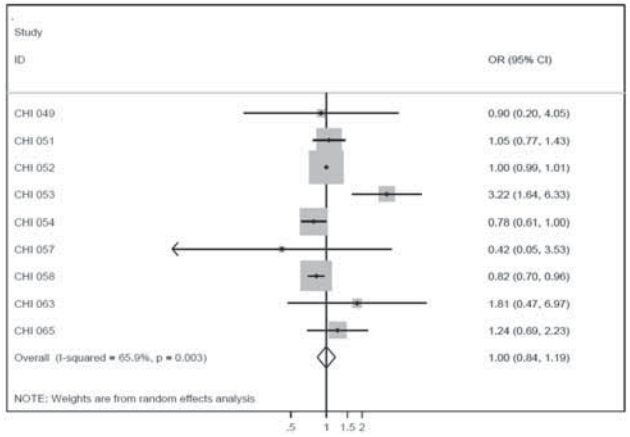


図26：特定の農薬に関する研究を含む農薬ばく露一般に関する情報と尿道下裂のリスクのランダム効果メタアナリシス

10. Reproductive diseases

Overall, 63 publications examined the effect of pesticide exposure on child health outcomes (median sample size: 299; IQR 111-544), contributing 578 separate analyses in the *data extraction database*. More than one third of the analyses (n=217, 38%) assess the sperm/semen quality, whereas other cluster of studies/analyses examine among others reproductive related hormones, infertily and spontaneous abortion As seen with other outcomes, the diversity of the exposure definition is remarkable and poses special challenges to data synthesis. Only 4 out of the 64 were prospective cohort studies whereas the vast majority of the studies were cross sectional (n=45, 70%). The sample size in the reported analyses was rather small; it ranged between 41 and 29,649 participants (median 161) and the largest studies in the domain are smaller than the largest studies assessed in the cancer field. Here, we observed a cluster of publications coming from INUENDO (INUit-ENDOcrine) research group (n=8), a project that has been established in three European countries together with a population of Inuits from Greenland and aims to enlighten the impact of Persistent Organic Pollutants (POPs) on human reproductive function. Almost 2/3 of the studies were conducted in Europe and America (n=22 and 20 respectively). Twenty-two studies assessed occupational exposures and, in addition, more than half of the studies had information on biomarkers of exposure (n=38, 59%), 3 studies assessed occupational exposure through Job Exposure Matrix (JEM), whereas 2 studies used both questionnaires and biomarkers. The different outcome categories examined are presented in Table 12 along with the number of studies contributing to each outcome category and a decision on quantitative synthesis. Due to heterogeneity of data, statistical synthesis of the data (meta-analysis) was only performed for abortion.

10.1. Impaired sperm parameters

Twenty-five studies (median 189: IQR 87-336) assessed the association of pesticides on sperm/semen quality using a variety of outcomes. The total analyses conducted for these outcomes are 217 and the sample size of the conducted analyses is small ranging from 41 to 763. The largest study is a European cross-sectional study from INDUENDO research group (ID RPD 009) and assess the impact of p,p'-DDE to sperm concentration, sperm motility and sperm morphology and showed that the sperm motility was negatively associated with p,p'-DDE across the four populations under study. Another large study from the same group (ID RPD 012) did not provide evidence that Persistent Organic Pollutants (POPs) may interfere with male reproductive function. Even though a large number analyses have been conducted no single pesticide and related biomarker was assessed in more than 4 studies using the same comparison unit and analysis, thus a quantitative synthesis was not performed.

10.2. Fecundability disorders

Eight studies including 30 different analyses assess the effect of pesticides on low fecundability. The sample sizes are rather small ranging from 41 to 2,365 participants. Different effect sizes and analyses are used for the assessment of potential associations therefore the synthesis of the results through meta-analysis is not feasible. The largest study (ID RPD 038) that examined pesticide exposure of female greenhouse farm workers reported a reduced fecundability (OR=0.68, 95% CI=0.49-0.94). However the second largest study in the field (ID RPD 034) on female greenhouse farm workers did not shown a significant association (OR=1.11, 95%CI=0.96-1.29). Fourteen additional analyses did not report significant findings; therefore the evidence is contradictory in the field.

10. 生殖疾患

全体では、63の論文が農薬ばく露の小児健康影響を調査しており（サンプルサイズ中央値：299、IQR 111-544）、データ抽出データベースには578の個別の分析が含まれていた。分析の3分の1以上（n=217、38%）が精子/精液の質を評価しているのに対し、他の研究/分析では生殖関連ホルモン、不妊、自然流産などを評価している。他の影響に見られるように、ばく露の定義の多様性は顕著であり、データ統合に特別な問題を与えている。64件のうち4件のみが前向きコホート研究であり、大多数の研究は横断研究であった（n=45、70%）。報告されている分析のサンプルサイズはかなり小さく、41人から29,649人の範囲であった（中央値161）。この領域での最大の研究は、がん分野で評価された最大の研究よりも小規模である。ここでは、グリーンランドのイヌイットの集団とともにヨーロッパ3カ国で設立されたプロジェクトであるINUENDO（INUit-ENDOcrine）研究グループ（n=8）からの出版物を調査した。研究のほぼ3分の2がヨーロッパとアメリカで実施された（それぞれn=22と20）。22件の研究が職業ばく露を評価し、さらに半数以上の研究がばく露のバイオマーカーに関する情報を有し(n=38, 59%)、3件の研究が職業ばく露を職業ばく露マトリックス(JEM)で評価し、2件の研究が質問紙とバイオマーカーの両方を使用した。調査した異なる影響カテゴリーを、各カテゴリーに寄与した研究の数と定量的統合の決定とともに表12に示した。データの不均一性のため、データの統計的統合（メタアナリシス）は流産についてのみ実施された。

10.1 障害のある精子パラメータ

25件の研究（中央値 189件：IQR 87-336）が、様々な影響を用いて農薬と精子/精液の質との関連を評価した。これらの結果について実施された分析の総数は217件で、実施された分析のサンプルサイズは41～763件と小規模である。最大の研究はINDUENDO研究グループによるヨーロッパの横断研究（ID RPD 009）で、p,p'-DDEの精子濃度、精子運動性、精子形態への影響を評価し、精子運動性は研究対象の4つの集団においてp,p'-DDEと負の関係があることが示された。同じグループによる別の大規模研究（ID RPD 012）では、残留性有機汚染物質（POPs）が男性の生殖機能を阻害する可能性のエビデンスは示されていない。多数の分析が行われたにもかかわらず、同じ比較単位と分析を用いた 4 件以上の研究では、単一の農薬と関連するバイオマーカーは評価されていないため、定量的な統合は行われなかった。

10.2 生殖能障害

30種類の分析を含む 8件の研究が、低生殖能に対する農薬の影響を評価している。サンプルサイズは 41 から2,365 人とかなり小さい。潜在的な関連の評価には異なる効果量と分析が使用されているため、メタアナリシスによる結果の統合は不可能である。温室栽培農場の女性労働者の農薬ばく露を調査した最大規模の研究（ID: RPD 038）では、生殖能の低下が報告された（OR=0.68、95% CI=0.49-0.94）。しかし、温室栽培農場の女性労働者を対象とした2番目に大きなフィールド研究（ID RPD 034）では、有意な関連は示されなかった（OR=1.11、95%CI=0.96-1.29）。14の追加分析では有意な結果は報告されなかったため、フィールド調査ではエビデンスが矛盾している。

10.3. Spontaneous abortion

Ten studies of spontaneous abortion focused on occupational exposure. We were able to synthesize data from six studies that provided an effect estimate and a metric of its variation. The summary OR was 1.52 (95%: 1.09-2.13) using random effects models and large heterogeneity was observed (I^2=63%) (Figure 27). However, the largest cross-sectional study on this outcome conducted by the INUENDO research group (ID RPD 003) did not shown any statistical effect (OR=1) between p,p'-DDE and abortion. One more study compared full-time vs. part time farming and did not report a significant association (p-value=0.99). Three other studies did not provide adequate information for their inclusion in the meta-analysis.

10.4. Reproductive hormones

Nineteen studies (median sample size 257: IQR 97-322) contributing with 250 analyses for various reproductive hormones were identified in this systematic review. The studies were comparable to the other large group of impaired sperm parameters sample size-wise; their range was from 62 to 887. The largest study is a European cross-sectional study that assess the effect of hexachlorobenzene on the levels of testosterone and estradiol. Hormonal status of 14- to 15- year-old male adolescents was studies in relation to internal exposure to pollutants. The study shows that the exposure is associated with substantial differences in hormone concentrations. Different patterns were observed in study conducted by the INUENDO research group where the overall analysis between DDE and reproductive related hormones did not reveal any significant results. However in center-specific analysis, gonadotropin levels and sex-hormone-binding globulin seem to be affected by exposure on p,p'-DDE supporting substantial variations between different populations. The large variety of outcomes and pesticides assessed did not allow for any quantitative synthesis of the data.

10.5. Reproductive outcomes with few studies

For all the assessed outcomes not included in Table 12, assessment of menstrual cycles cannot allow synthesis of the available evidence. Our systematic review did not identify any previously published meta-analyses on these outcomes to allow for comparisons with previously published evidence (prior to 2006). Results on different menstrual outcomes showed that it is unlikely that exposure to DDE is a main cause of menstrual disturbances.

10.3. 自然流産

自然流産に関する10件の研究では、職業ばく露に焦点が当てられていた。効果推定値とその変動の指標を提供した6件の研究からデータを統合することができた。ランダム効果モデルを用いた要約ORは1.52（95%：1.09-2.13）であり、大きな不均一性が観察された（I2=63%）（図27）。しかし、INUENDO研究グループが実施したこの影響に関する最大の横断研究（ID RPD 003）では、p,p'-DDEの農業労働と流産との間に統計的効果（OR=1）は示されなかった。さらに 1 つの研究では、フルタイムとパートタイムを比較したが、有意な関連は報告されていない（p 値=0.99）。他の 3 つの研究では、メタアナリシスに含めるのに十分な情報が得られなかった。

10.4 生殖ホルモン

このシステマティックレビューでは、様々な生殖ホルモンについて250の分析を行った19の研究（サンプルサイズ中央値257：IQR 97-322）が同定された。これらの研究は、精子障害パラメータに関する他の大規模なグループのサンプルサイズに匹敵するものであり、その範囲は62から887までであった。最大の研究は、テストステロンとエストラジオールのレベルに対するヘキサクロロベンゼンの影響を評価したヨーロッパの横断研究である。14〜15歳の男性青年のホルモン状態は、汚染物質への内部ばく露に関連して研究された。この研究では、ばく露はホルモン濃度の大きな差異と関連していることが示された。INUENDO研究グループが行った研究では、DDEと生殖関連ホルモンの全体的な分析では有意な結果は得られなかったが、異なるパターンが観察された。しかし、センターごとの分析では、ゴナドトロピン濃度と性ホルモン結合グロブリンはp,p'-DDEばく露の影響を受けているようであり、母集団間に大きなばらつきがあることが示唆された。評価された結果と農薬の種類が多いため、データの定量的な統合はできなかった。

10.5. 研究数が少ない生殖影響

表12に含まれていないすべての影響については、月経周期の評価では利用可能なエビデンスを統合することができない。我々のシステマティックレビューでは、過去に発表されたエビデンス（2006年以前）との比較を可能にするために、これらの影響に関する過去に発表されたメタアナリシスは確認しなかった。異なる月経影響に関する結果から、DDEへのばく露が月経障害の主な原因であるとは考えにくいことが示された。

Table 12: Summary of studies identified per outcome subgroup with more than 4 studies (NA: not available)

Outcome	N studies	Meta-analysis done	Previous meta-analysis result
Impaired sperm parameters	25	No	NA
Fecundability disorders	8	No	NA
Abortion	10	Yes	NA
Reproductive hormones	19	No	NA

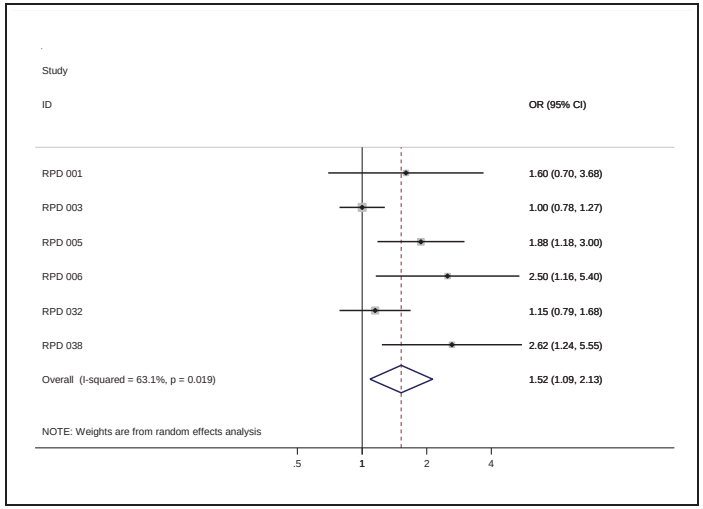


Figure 27: Random effects meta-analysis for studies with information on pesticide exposure and risk of abortion

表 12：4 件以上の研究がある影響サブグループごとに同定された研究の要約（NA：利用不可）

影響	研究数	メタアナリシス実施	前回のメタアナリシス結果
精子障害パラメータ	25	No	NA
生殖能障害	8	No	NA
流産	10	Yes	NA
生殖ホルモン	19	No	NA

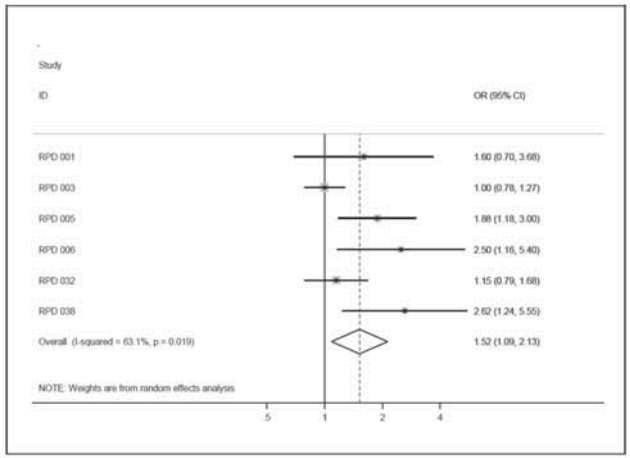


図27：農薬ばく露に関する情報と流産リスクのランダム効果メタアナリシス

11. Neurological diseases

Overall, 60 publications examined the effect of pesticide exposure on neurological outcomes (median sample size: 390; IQR 246-781), contributing 573 separate analyses in the *data extraction database*. More than thirty health-related outcomes were assessed with the largest proportion focusing on Parkinson's disease with 32 studies (Table 13). As seen with other outcomes, the diversity of the exposure definition is remarkable and poses special challenges to data synthesis. Only 8 out of the 60 were prospective cohort studies and other 2 were nested case-controls; the majority of evidence comes from retrospective case-control analyses, which are prone to recall bias in exposure measurement. The sample size in the reported analyses was often small; it ranged between 46 and 143,325 participants (median 390) and the largest studies in the domain are smaller than the largest studies assessed in the cancer field. Here, we also observed large clusters of publications coming from large, well-known studies in the field, such as the Agricultural Health Study (AHS), while 43 studies assessed occupational exposures. In addition, the presence of studies with information on biomarkers of exposure was far less prominent here (n=7, 12%). The different outcome categories examined are presented in Table 13; due to the small number of studies identified per assessed outcome, statistical synthesis of the data (meta-analysis) was only performed for Parkinson's disease and amyotrophic lateral sclerosis.

11.1. Parkinson's disease

Thirty-two studies assessed the association between pesticide exposure and Parkinson's disease with a median sample size of 399 (IQR 286-711), contributing 266 separate extracted comparisons in the database. Eighty percent of the retrieved studies assessed occupational exposures, only 10% were prospective and the exposure was assessed through a biomarker in a small number of studies (10%). A large variety of individual pesticides were assessed with the following pesticides being assessed more frequently: general pesticide (28 studies), as well as DDT (5 studies), paraquat (9 studies).

We initially assessed the association between general pesticide use and Parkinson's disease. The observed effect indicated a statistically significant association with the presence of considerable heterogeneity (random-effects OR 1.58, 95% CI 1.35 – 2.85, I^2 61%) (Figure 28). With the exception of four studies where specific pesticides were assessed (e.g. paraquat), all the other studies assessed mainly occupational general pesticide use in mainly a retrospective fashion via a questionnaire. The results of the meta-analysis are in accordance with the largest studies on that research question.

We then proceeded to assess the association between DDT exposure and Parkinson's disease. The observed effect indicated a non-statistically significant association without the presence of heterogeneity (random-effects OR=1.01, 95% CI=0.78–1.30, I^2=0%) (Figure 29). Finally, we assessed the association between paraquat exposure and Parkinson's disease. The observed effect indicated a statistically significant association with the presence of moderate heterogeneity (random-effects OR=1.32, 95% CI=1.10–1.60, I^2=34%) (Figure 30). The results of the meta-analysis are in accordance with the largest studies on these research questions.

Our literature search yielded 7 systematic reviews and/or meta-analyses on the association between pesticide exposure and Parkinson's disease published from 2000 to 2013 (Pezzoli 2013, Van-Maele Fabry 2012, van der Mark 2012, Dick 2006, Priyadarshi 2001, Priyadarshi 2000, Allen 2013). Despite the considerable time interval between the oldest and most recent research synthesis effort and the different methodologies endorsed (prospective studies only assessed, methodological assessment of

11. 神経疾患

全体では 60 の論文が農薬ばく露の神経学的影響に及ぼす効果を調査しており（サンプルサイズ中央値：390、IQR 246-781）、データ抽出データベースでは 573 件の個別分析が行われた。30 以上の健康関連影響が評価されており、パーキンソン病に焦点を当てた研究が最も多く 32 件あった（表 13）。他の影響に見られるように、ばく露の定義の多様性には目を見張るものがあり、データ統合に特別な問題を与えている。60 件のうち 8 件のみが前向きコホート研究で、残りの 2 件はコホート内症例対照研究であった。報告された分析におけるサンプルサイズはしばしば小さく、参加者数は 46～143,325 人（中央値 390 人）であり、この領域における最大の研究は、がん分野で評価された最大の研究よりも小規模であった。ここでは、農業健康調査（Agricultural Health Study：AHS）のようなこの分野の大規模でよく知られた研究からの多くの出版物のまとまりも観察されたが、一方で 43 件の研究が職業ばく露を評価していた。さらに、ばく露のバイオマーカーに関する情報を持つ研究の存在は、ここではあまり目立たなかった（n=7、12%）。評価された影響カテゴリーを表 13 に示す。評価された影響ごとに同定された研究の数が少ないため、データの統計的統合（メタアナリシス）はパーキンソン病と筋萎縮性側索硬化症についてのみ実施された。

11.1 パーキンソン病

農薬ばく露とパーキンソン病との関連を調査した研究は32件あり、サンプルサイズの中央値は399件（IQR 286-711）で、データベースには266件の比較が抽出されている。検索された研究の80%は職業ばく露を評価していたが、前向き研究はわずか10%で、ばく露をバイオマーカーを介して評価した研究は少数であった（10%）。個々の農薬の評価は多岐にわたったが、一般的な農薬（28件）、DDT（5件）、パラコート（9件）などの農薬がより頻繁に評価されていた。

まず、一般的な農薬の使用とパーキンソン病との関連を評価した。観察された効果は、かなりの不均一性が存在し、統計的に有意な関連を示した（ランダム効果OR 1.58、95%CI 1.35～2.85、I2 61%）（図 28）。特定の農薬を評価した 4 つの研究（例：パラコート）を除いて、他のすべての研究では、主に質問紙による後ろ向きな方法で、主に職業上の一般的な農薬使用を評価している。メタアナリシスの結果は、この研究の課題に関する最大の研究と一致している。

次に、DDTばく露とパーキンソン病との関連を評価した。観察された効果は、不均一性の存在なしに統計学的に有意ではないことが示された（ランダム効果OR=1.01、95%CI=0.78-1.30、I2=0%）（図29）。最後に、パラコートばく露とパーキンソン病との関連を評価した。観察された効果は、中等度の不均一性の存在下で統計的に有意な関連を示した（ランダム効果OR=1.32、95%CI=1.10-1.60、I2=34%）（図30）。メタアナリシスの結果は、これらの研究課題に関する最大規模の研究と一致している。

我々の文献検索では、2000年から2013年までに発表された農薬ばく露とパーキンソン病との関連に関する7つのシステマティックレビュー及び/またはメタアナリシスが得られた（Pezzoli 2013, Van-Maele Fabry 2012, van der Mark 2012, Dick 2006, Priyadarshi 2001, Priyadarshi 2000, Allen 2013）。研究統合の最も古い取り組みと最新の取り組みとのかなりの時間的間隔、また、方法論（前向き研究のみの評価、対象研究の方法論的評価など）の違いにもかかわらず、結果はメタアナリシス全体で一貫しており、2006年からの現在の取り組みとも一致している（表14）。

the included studies, etc.), the results are consistent across the meta-analyses and are also consistent with the present effort spanning from 2006 (Table 14).

11.2. Amyotrophic lateral sclerosis (ALS)

Seven studies assessed the association between pesticide exposure and amyotrophic lateral sclerosis with a median sample size of 356 (IQR 201-1156), contributing 11 separate extracted comparisons in the database. All the retrieved studies assessed occupational exposures, while 4 also assessed residential exposure. Only one study was prospective and the exposure was assessed through a questionnaire in most of the studies (n=6).

We assessed the association between general pesticide use and ALS. The observed effect indicated a statistically significant association with the presence of small heterogeneity (fixed-effects OR=1.58, 95% CI=1.31 – 1.90, I^2 10%) (Figure 31) and the results of the meta-analysis are in accordance with the largest studies on that research question.

Our literature search yielded 2 systematic reviews and/or meta-analyses on the association between pesticide exposure and ALS published in 2012 (Kamel 2012, Malek 2012). Regarding these efforts, the results are consistent with our findings and the authors' report of evidence on an association of exposure to pesticides and risk of ALS in male cases compared to controls (OR=1.88, 95% CI: 1.36-2.61), although the chemical or class of pesticide was not specified by the majority of studies.

11.3. Neurological outcomes with few studies

With the exception of Parkinson's disease and amyotrophic lateral sclerosis, for all the remaining neurological outcomes, too few studies are available after 2006 to allow synthesis of evidence for each outcome alone; these outcomes comprise a vast variety of captured information ranging from well-defined clinical entities yet with too few studies, such as hearing loss or diabetic neuropathy, as well as a large number of metrics pertaining to neurological endophenotypes but with a prominent lack of harmonization and standardization in the outcome definition. Our systematic review did not identify any previously published meta-analyses on these outcomes to allow for comparisons with previously published evidence (prior to 2006). Generally the results on these outcomes were of small effect and not statistically significant with few exceptions. Given the large number of analyses these results need cautious interpretation and, based on these data, there is no evidence to suggest association between pesticide exposure and these outcomes.

11.2. 筋萎縮性側索硬化症（ALS）

7件の研究が農薬ばく露と筋萎縮性側索硬化症との関連を評価しており、サンプルサイズの中央値は356（IQR 201-1156）で、データベースには11件の個別の比較が抽出されている。検索されたすべての研究は職業ばく露を評価しており、4つの研究は住居ばく露も評価していた。前向き研究は1件のみで、ほとんどの研究では質問紙を用いてばく露を評価していた（n=6）。

我々は一般的な農薬使用とALSとの関連を評価した。観察された効果は、小さな不均一性（固定効果OR=1.58、95%CI=1.31～1.90、I2 10%）の存在とともに統計的に有意な関連を示し（図31）、メタアナリシスの結果は、その研究課題に関する最大の研究に沿ったものであった。

文献検索を行った結果、2012 年に発表された農薬ばく露と ALS の関連に関する 2 つのシステマティックレビュー及び／またはメタアナリシスが得られた（Kamel 2012, Malek 2012）。これらの結果によれば、大多数の研究では農薬の化学物質やクラスが特定されていなかったが、我々の知見や男性で対照と比較して農薬へのばく露とALSの関連を示すエビデンス（OR=1.88、95% CI: 1.36-2.61）についての著者らの報告と一致していた。

11.3. 研究数の少ない神経学的影響

パーキンソン病と筋萎縮性側索硬化症を除いて、残りのすべての神経学的影響については、2006年以降の研究が少なすぎて、それぞれの影響だけでエビデンスを統合することができない。我々のシステマティックレビューでは、2006年以前に発表されたエビデンスとの比較を可能にするために、これらの影響に関する以前に発表されたメタアナリシスは確認されなかった。一般的に、これらの影響に関する結果は効果が小さく、統計的に有意ではなかったが、少数の例外を除いては有意であった。分析数が多いことを考えると、これらの結果は慎重に解釈する必要があり、これらのデータに基づいて、農薬ばく露とこれらの影響との関連を示唆するエビデンスはない。

Table 13: Assessed outcomes in the field of neurology

Health outcome		
Abnormal alternating hand movements	Alzheimer's disease	Narcolepsy with cataplexy
Abnormal ankle reflex	Amyotrophic lateral sclerosis	Neurological symptoms
Abnormal distal motor amplitude	Cryptogenic polyneuropathy	Parkinson's disease
Abnormal distal motor latency	Decline in hand-grip strength	Parkinsonism
abnormal facial expression	Delayed memory impairment	Peripheral neuropathy
abnormal nerve conduction velocity	Dementia	Progressive supranuclear palsy
Abnormal postural tremor	Essential tremor	Restless legs syndrome
Abnormal posture	Gait disorder	Romberg sign
Abnormal short F-wave latency	Hearing loss	Sporadic Motor Neuron Disease
Abnormal toe proprioception	Multiple System Atrophy	Subclinical neuropathy
Abnormal toe vibration perception	Narcolepsy (with and without cataplexy)	Tandem gait abnormality

表 13：神経学分野で評価された影響

健康影響	
手の交代運動の異常	アルツハイマー病
足首反射の異常	筋萎縮性側索硬化症
遠位運動振幅の異常	原因不明の多発神経障害
遠位運動潜時の異常	握力の低下
表情の異常	遅延記憶障害
神経伝導速度異常	認知症
異常な姿勢振戦	本態性振戦
異常な姿勢	歩行障害
短 F 波潜時の異常	難聴
足尖の固有知覚の異常	多系統萎縮症
足尖の振動知覚の異常	ナルコレプシー（カタプレキシーの有無にかかわらず）
カタプレキシーを伴うナルコレプシー	
神経症状	
パーキンソン病	
パーキンソン症候群	
未梢神経障害	
進行性核上性麻痺	
レストレスレッグス症候群	
ロンベルグ徴候	
散発性運動ニューロン病	
潜在的神経障害	
つま足歩行異常	

Table 14: Characteristics of the studies assessing pesticide exposure and Parkinson's disease risk (n/a: not available)

ID	Year	Location	Study design	Exposure type	Exposure assessment	Comparison unit	Adjustment	Sample size
DDT								
NRD 027	2007	America	Cohort	Occupational	Direct exposure questionnaire	ever/never	yes	8899
NRD 025	2011	America	Case-control	Occupational	Direct exposure questionnaire	ever/never	yes	808
NRD 032	2010	America	Case-control	Occupational	Direct exposure questionnaire	ever vs. never	yes	578
NRD 33	2010	Europe	Nested case-control	Environmental	Biomarker	per IQR increase	yes	292
NRD 019	2008	America	Case-control	Mixed	Direct exposure questionnaire	ever/never	no	184
Paraquat								
NRD 019	2008	America	Case-control	Mixed	Direct exposure questionnaire	ever/never	no	184
NRD 027	2007	America	Cohort	Occupational	Direct exposure questionnaire	ever/never	yes	7393
NRD 023	2009	America	Case-control	Environmental	Residential history	yes/no	yes	709
NRD 030	2009	America	Case-control	Occupational	Direct exposure questionnaire	ever/never	yes	1030
NRD 037	2011	America	Nested case-control	Occupational	Direct exposure questionnaire	ever/never	yes	468
NRD 020	2009	America	Case-control	Environmental	Residential history	yes/no	yes	709
NRD 022	2010	America	Case-control	Occupational	Direct exposure questionnaire	ever vs. never	yes	578
NRD 038	2010	America	Case-control	Occupational	Occupation	yes/no	yes	58
NRD 020	2009	America	Case-control	Environmental	Residential history	yes/no	yes	709
農薬								
NRD 033	2010	ヨーロッパ	Nested case-control.	環境	バイオマーカー (HCB)	per IQR increase	yes	292
NRD 058	2010	ヨーロッパ	Case-control	混合	直接ばく露について	yes/no	no	330

表 14：農薬ばく露とパーキンソン病リスクを評価した研究の特徴（n/a：なし）

ID	年	場所	研究デザイン	ばく露ばく露評価タイプ	比較単位	調整	サンプルサイズ
DDT							
NRD 027	2007	アメリカ	Cohort	職業 直接ばく露についての質問紙	ever/never	yes	8899
NRD 025	2011	アメリカ	Case-control	職業 直接ばく露についての質問紙	ever/never	yes	808
NRD 032	2010	アメリカ	Case-control	職業 直接ばく露についての質問紙	ever vs. never	yes	578
NRD 033	2010	ヨーロッパ	Nested case-control	環境 バイオマーカー	per IQR increase	yes	292
NRD 019	2008	アメリカ	Case-control	混合 直接ばく露についての質問紙	ever/never	no	184
パラコート							
NRD 019	2008	アメリカ	Case-control	混合 直接ばく露についての質問紙	ever/never	no	184
NRD 027	2007	アメリカ	Cohort	職業 直接ばく露についての質問紙	ever/never	yes	7393
NRD 023	2009	アメリカ	Case-control	環境 居住履歴	yes/no	yes	709
NRD 030	2009	アメリカ	Case-control	職業 直接ばく露についての質問紙	ever/never	yes	1030
NRD 037	2011	アメリカ	Nested case-control	職業 直接ばく露についての質問紙	ever/never	yes	468
NRD 020	2009	アメリカ	Case-control	環境 居住履歴	yes/no	yes	709
NRD 022	2010	アメリカ	Case-control	職業 直接ばく露についての質問紙	ever vs. never	yes	578
NRD 038	2010	アメリカ	Case-control	職業 職歴	yes/no	yes	58
NRD 020	2009	アメリカ	Case-control	環境 居住履歴	yes/no	yes	709
農薬							
NRD 033	2010	ヨーロッパ	Nested case-control.	環境 バイオマーカー (HCB)	per IQR increase	yes	292
NRD 058	2010	ヨーロッパ	Case-control	混合 直接ばく露について	yes/no	no	330

ID	Year	Location	Study design	Exposure type	Exposure assessment	Comparison unit	Adjustment	Sample size
NRD 038	2010	America	Case-control	Occupational	Occupational history	yes/no	yes	58
NRD 020	2009	America	Case-control	Environmental	Residential history	yes/no	yes	709
Pesticides								
NRD 033	2010	Europe	Nested case-control	Environmental	Biomarker (HCB)	per IQR increase	yes	292
NRD 058	2010	Europe	Case-control	Mixed	Direct exposure questionnaire (insecticides)	yes/no	no	330
NRD 034	2010	Asia	Case-control	Occupational	Direct exposure questionnaire	ever/never	n/a	608
NRD 018	2008	Europe	Case-control	Occupational	Direct exposure questionnaire	ever/never	yes	233
NRD 017	2008	America	Case-control	Mixed	Direct exposure questionnaire	ever/never	yes	1666
NRD 014	2006	America	Cohort	Occupational	Direct exposure questionnaire	ever/never	yes	143325
NRD 029	2009	Europe	Case-control	Mixed	Direct exposure questionnaire and JEM	ever/never	no	388
NRD 036	2011	Europe	Cohort	Occupational	JEM	JEM class		
NRD 015	2007	Asia	Case-control	Occupational	Direct exposure questionnaire	yes/no	yes	308
NRD 020	2009	America	Case-control	Occupational	Occupational history	yes/no	yes	709
NRD 028	2008	America	Case-control	Mixed	Direct exposure questionnaire	ever/never	yes	615
NRD 023	2009	America	Case-control	Environmental	Residential history	yes/no	yes	709

ID	年	場所	研究デザイン	ばく露タイプ	ばく露評価	比較単位	調整	サンプルサイズ
					の質問紙（殺虫剤）			
NRD 034	2010	アジア	Case-control	職業	直接ばく露についての質問紙	ever/never	n/a	608
NRD 018	2008	ヨーロッパ	Case-control	職業	直接ばく露についての質問紙	ever/never	yes	233
NRD 017	2008	アメリカ	Case-control	混合	直接ばく露についての質問紙	ever/never	yes	1666
NRD 014	2006	アメリカ	Cohort	職業	直接ばく露についての質問紙	ever/never	yes	143325
NRD 029	2009	ヨーロッパ	Case-control	混合	直接ばく露についての質問紙と JEM	ever/never	no	388
NRD 036	2011	ヨーロッパ	Cohort	職業	JEM	JEM class		
NRD 015	2007	アジア	Case-control	職業	直接ばく露についての質問紙	yes/no	yes	308
NRD 020	2009	アメリカ	Case-control	職業	職歴	yes/no	yes	709
NRD 028	2008	アメリカ	Case-control	混合	直接ばく露についての質問紙	ever/never	yes	615
NRD 023	2009	アメリカ	Case-control	環境	居住履歴	yes/no	yes	709
NRD 016	2007	ヨーロッパ	Case-control	混合	職歴・直接ばく露についての質問紙	high vs. no exposure	yes	2756
NRD 024	2010	ヨーロッパ	Case-control	職業	職歴	yes/no	no	387
NRD 025	2011	アメリカ	Case-control	職業	直接ばく露についての質問紙	ever/never	yes	808
NRD 058	2006	アメリカ	Case-control	混合	直接ばく露についての質問紙	ever/never	no	278
NRD 027	2007	アメリカ	Cohort	職業	直接ばく露についての質問紙	ever/never	yes	65183
NRD 035	2010	アジア	Case-control	職業	職歴	yes/no	no	525
NRD 030	2006	アメリカ	Case-control	職業	直接ばく露についての質問紙	yes/no	yes	430
NRD 030	2009	アメリカ	Case-control	職業	直接ばく露について	ever/never	yes	1030

ID	Year	Location	Study design	Exposure type	Exposure assessment	Comparison unit	Adjustment	Sample size
NRD 016	2007	Europe	Case-control	Mixed	Occupational history and direct exposure questionnaire	high vs. no exposure	yes	2756
NRD 024	2010	Europe	Case-control	Occupational	Occupational history	yes/no	no	387
NRD 025	2011	America	Case-control	Occupational	Direct exposure questionnaire	ever/never	yes	808
NRD 058	2006	America	Case-control	Mixed	Direct exposure questionnaire	ever/never	no	278
NRD 027	2007	America	Cohort	Occupational	Direct exposure questionnaire	ever/never	yes	65183
NRD 035	2010	Asia	Case-control	Occupational	Occupational history	yes/no	no	525
NRD 026	2006	America	Case-control	Occupational	Direct exposure questionnaire	yes/no	yes	430
NRD 030	2009	America	Case-control	Occupational	Direct exposure questionnaire	ever/never	yes	1030
NRD 022	2009	Europe	Case-control	Occupational	Direct exposure questionnaire	ever/never	yes	781
NRD 019	2008	America	Case-control	Occupational	Direct exposure questionnaire	yes/no	no	184
NRD 032	2010	America	Case-control	Occupational	Direct exposure questionnaire	ever vs. never	yes	352
NRD 032	2010	America	Case-control	Occupational	Direct exposure questionnaire	ever vs. never	yes	578
NRD 003	2010	Europe	Case-control	n/a	n/a	yes/no	yes	264

ID	年	場所	研究デザイン	ばく露ばく露評価タイプ	比較単位	調整	サンプルサイズ
NRD 016	2007	ヨーロッパ	Case-control	n/a	n/a	yes/no	yes	2756
NRD 024	2010	ヨーロッパ	Case-control	職業	直接ばく露についての質問紙	yes/no	no	387
NRD 025	2011	アメリカ	Case-control	職業	直接ばく露についての質問紙	ever/never	yes	808
NRD 058	2006	アメリカ	Case-control	職業	直接ばく露についての質問紙	ever/never	no	278
NRD 027	2007	アメリカ	Cohort	職業	直接ばく露についての質問紙	ever/never	yes	65183
NRD 035	2010	アジア	Case-control	職業	直接ばく露についての質問紙	yes/no	no	525
NRD 026	2006	アメリカ	Case-control	職業	直接ばく露についての質問紙	yes/no	yes	430
NRD 030	2009	アメリカ	Case-control	職業	直接ばく露についての質問紙	ever/never	yes	1030
NRD 022	2009	ヨーロッパ	Case-control	職業	直接ばく露についての質問紙	ever/never	yes	781
NRD 019	2008	アメリカ	Case-control	職業	直接ばく露についての質問紙	yes/no	no	184
NRD 032	2010	アメリカ	Case-control	職業	直接ばく露についての質問紙	ever vs. never	yes	352
NRD 032	2010	アメリカ	Case-control	職業	直接ばく露についての質問紙	ever vs. never	yes	578
NRD 003	2010	ヨーロッパ	Case-control	n/a	n/a	yes/no	yes	264

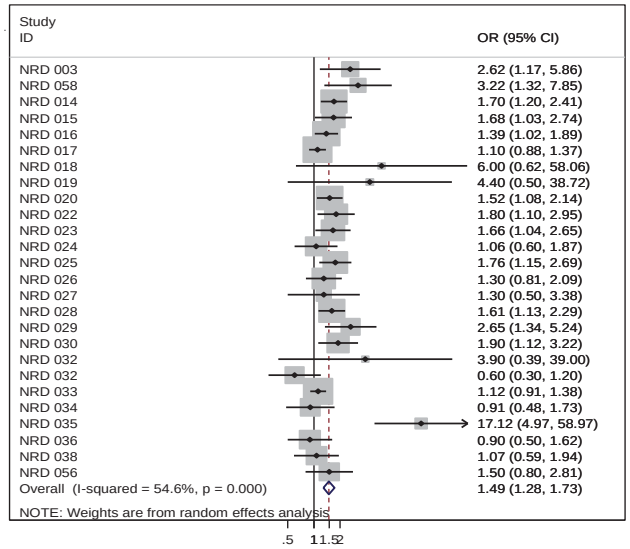


Figure 28: Random effects meta-analysis for studies with information on any pesticide exposure and risk of Parkinson's disease (study with ID NRD 033, specifically assessed hexachlorobenzene)

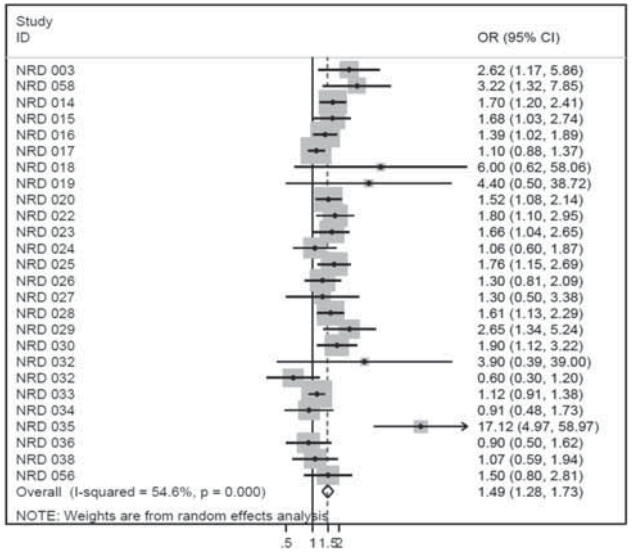


図28：農薬ばく露に関する情報とパーキンソン病のリスクのランダム効果メタアナリシス（ID NRD 033の研究、特にヘキサクロロベンゼンを評価）

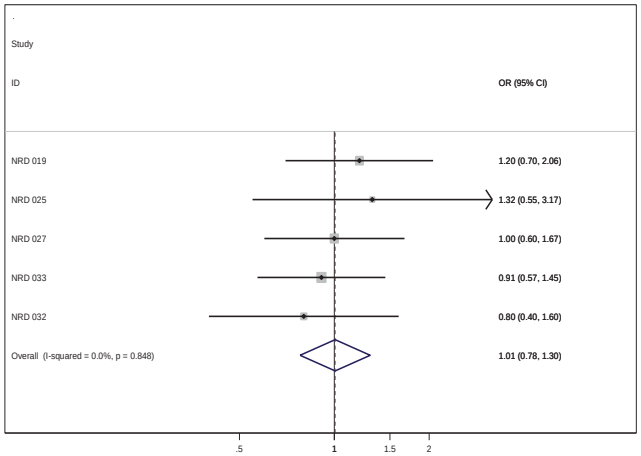


Figure 29: Fixed-effects meta-analysis for studies with information on exposure and risk of Parkinson's disease

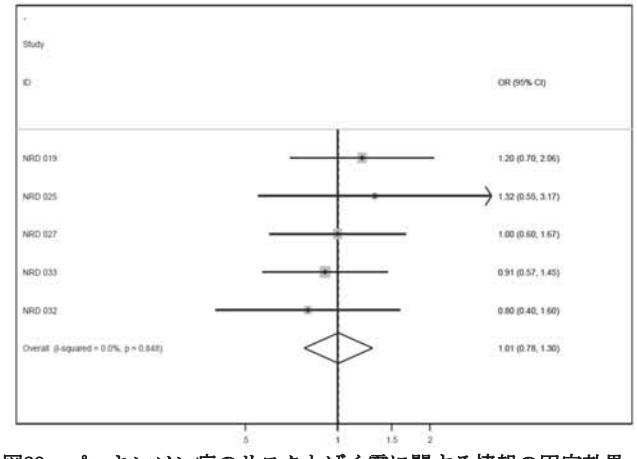


図29：パーキンソン病のリスクとばく露に関する情報の固定効果メタアナリシス

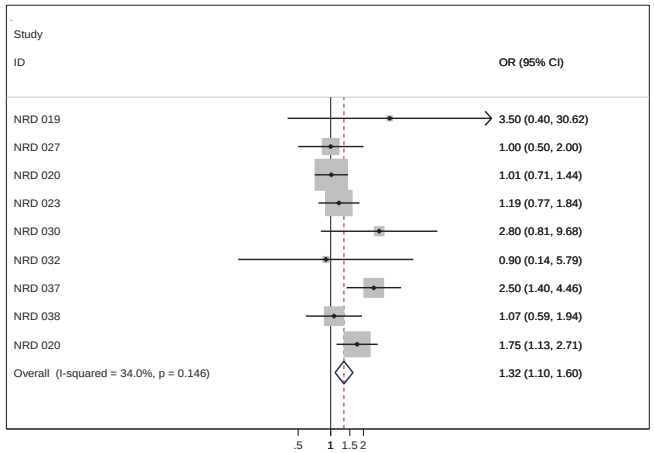


Figure 30: Fixed-effects meta-analysis for studies with information on paraquat exposure and risk of Parkinson's disease

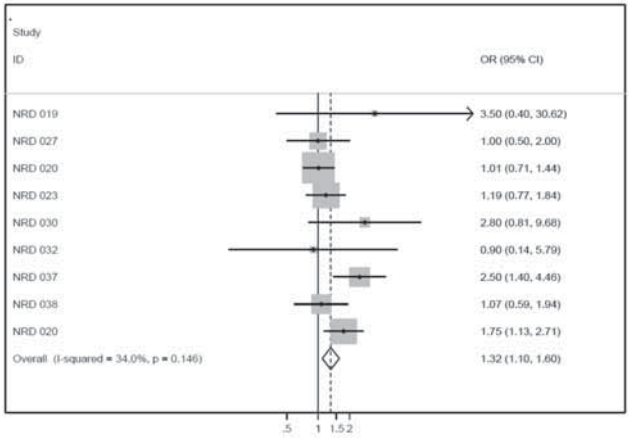


図30：パラコートばく露に関する情報とパーキンソン病リスクの固定効果メタアナリシス

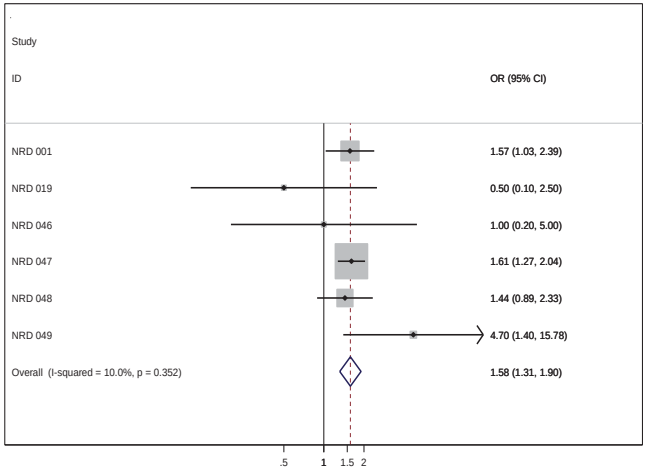


Figure 31: Fixed-effects meta-analysis for studies with information on general pesticide exposure and risk of amyotrophic lateral sclerosis

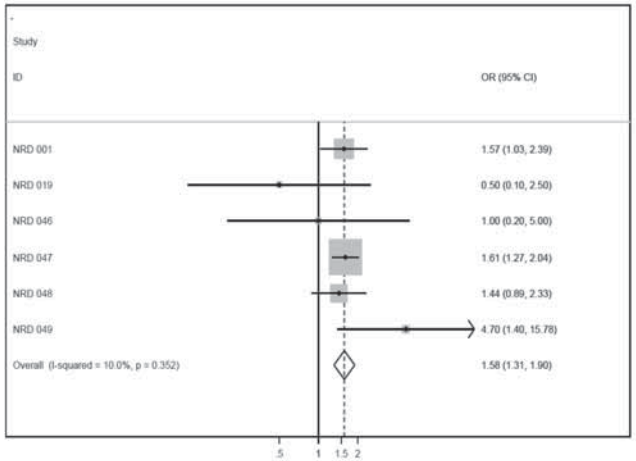


図31：農薬ばく露に関する情報と筋萎縮性側索硬化症のリスクの固定効果メタアナリシス

12. Endocrine diseases

Overall, 35 publications examined the effect of pesticide exposure on thyroid hormone dysregulation (median sample size: 226; IQR 130-453), contributing 343 separate analyses in the *data extraction database*. The main outcomes assessed were thyroxin (T4), triiodothyronine (T3) and thyroid stimulating hormone (TSH) levels. Only 3 prospective cohort studies were conducted in the field; the majority of evidence comes from retrospective case-control or cross-sectional analyses, which are prone to recall bias in exposure measurement. The sample size in the reported analyses was often small; it ranged between 27 and 16,529 participants (median 341). Here, we observed no large clusters of publications coming from large, well-known studies in the field, while the vast majority of the studies assessed environmental exposures (n=28, 80%). However, the presence of studies with information on biomarkers of exposure was more prominent here (n=29, 83%). Even though hypothyroidism, hyperthyroidism and other thyroid diseases contribute with more than 1/3 of the total analyses (n=123) the available evidence derives from Agricultural Health Study (AHS) which apparently is the largest in the field and examines the association between pesticide use and thyroid diseases in females. The study found an association between hypothyroidism and ever use of organochlorine insecticides (OR=1.2, 95% CI= 1.0-16) and fungicides (OR=1.4, 95% CI= 1.1-1.8). However, the results should be interpreted with caution due to borderline significance levels and absence of type-I error corrections due to multiple comparisons. Other studies in the field assessing several thyroid hormone levels are quite smaller and provide contradictory results. As seen with other outcomes, the diversity of the exposure definition is remarkable and poses special challenges to data synthesis. Due to heterogeneity of data and different analyses, effect sizes and metrics provided, statistical synthesis of the data (meta-analysis) was not performed.

12. 内分泌疾患

全体では、35の出版物で農薬ばく露が甲状腺ホルモン調節障害に及ぼす影響が調査され（中央値サンプルサイズ226；IQR 130-453）、データ抽出データベースでは343の個別の分析が行われた。評価された主な影響は、サイロキシン（T4）、トリヨードサイロニン（T3）、甲状腺刺激ホルモン（TSH）レベルであった。この分野で実施された前向きコホート研究は3件のみであり、エビデンスの大部分は後ろ向き症例対照または横断分析によるものであるが、これらはばく露測定においてリコールバイアスがかかりやすい。報告されている分析におけるサンプルサイズはしばしば小さく、参加者数は27～16,529人（中央値341人）であった。ここでは、この分野でよく知られた大規模な研究からの出版物の大きなクラスタは観察されず、大多数の研究は環境ばく露を評価していた（n=28、80%）。しかし、ばく露のバイオマーカーに関する情報を有する研究の存在は、ここではより多数であった(n=29、83%)。甲状腺機能低下症、甲状腺機能亢進症、その他の甲状腺疾患が分析全体の1/3以上を占めているにもかかわらず（n=123）、利用可能なエビデンスは、この分野では明らかに最大規模で農薬使用と女性の甲状腺疾患との関連を調査している農業健康調査（Agricultural Health Study: AHS）に由来している。この研究では、甲状腺機能低下症と有機塩素系殺虫剤（OR=1.2、95% CI=1.0-16）及び殺菌剤（OR=1.4、95% CI=1.1-1.8）の使用歴との間に関連があることが明らかになった。しかし、この結果は、有意水準の境界線上であったことと多重比較によるタイプIの誤差補正がないため、注意して解釈されるべきである。この分野でいくつかの甲状腺ホルモンレベルを評価している他の研究は非常に小規模であり、矛盾する結果を示している。他の影響に見られるように、まちまちなばく露の定義に注目すべきであり、データ統合に特別な問題を及ぼしている。データの不均一性と異なる分析、効果量及び指標の使用のために、データの統計的統合（メタアナリシス）は行われていない。

13. Mental and psychomotor development outcomes

Overall, 32 publications examined the effect of pesticide exposure on mental and psychomotor development outcomes in pediatric populations (median sample size: 238, IQR 109-305), contributing 462 separate analyses in the *data extraction database*. Only one study was performed in a population of non-European (Asian) ancestry, while seventeen health-related outcomes were assessed with a large proportion focusing on attention-deficit hyperactivity disorder (ADHD, 6 studies, 102 analyses). As seen with other outcomes, the diversity of the exposure definition is considerable and poses special challenges to data synthesis. A large majority of the studies (23 publications, 72%) referred to prospective cohort studies, while the sample size in the reported analyses was often small; it ranged between 25 and 7,440 participants with the largest study assessing retrospectively maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. Here, we also observed clusters of publications coming from large, well-known studies in the field, such as the CHAMACOS (The Center for Health Assessment of Mothers and Children of Salinas) (5 publications), while 84% of the studies assessed environmental exposures. In addition, the presence of studies with information on biomarkers of exposure was prominent here (n=28, 88%). The different outcome categories examined are presented in Table 15 along with the number of studies contributing to each outcome category and a decision on quantitative synthesis. Due to heterogeneity of data and small number of studies identified, no statistical synthesis of the data (meta-analysis) was performed for any outcome.

13.1. Mental and psychomotor development outcomes with few studies

With the exception of mental and psychomotor development and Attention-deficit hyperactivity disorder (ADHD), for all the remaining assessed outcomes included in Table 15, too few studies are available to allow synthesis of evidence for each outcome alone; these outcomes comprise a variety of captured information ranging from well-defined clinical entities yet with too few studies, such as autism, or pervasive developmental disorder, as well as a vast number of outcomes representing neurodevelopmental endo-phenotypes such as communication, fine and gross motor development or expressive language development. Our systematic review did not identify any previously published meta-analyses on these outcomes to allow for comparisons with previously published evidence (prior to 2006). Generally the results on these outcomes were of small effect and not statistically significant with few exceptions. Given the large number of analyses and the small number of studies and sample sizes, these results need cautious interpretation and, based on these data, there is no evidence to suggest a robust association between pesticide exposure and these outcomes.

13.2. Attention-deficit hyperactivity disorder (ADHD)

Six studies assessed the association between pesticide exposure and ADHD with a sample size ranging from 278 to 2,539 participants, contributing 102 separate extracted comparisons in the database. Three studies were cohorts, all assessed environmental exposure and in all the exposure was assessed through a biomarker. General organophosphate exposure was assessed in three studies, DDT exposure in two studies, while trans-nonachlor, hexachlorobenzene, and 2,4,6-Trichlorophenol (TCP) were assessed in one study each. Thus, no single pesticide and related biomarker was assessed in more than 4 studies using comparable outcome definitions or the same comparison unit, thus a quantitative synthesis was not performed. The largest study in the field is a National Health and Nutrition Examination Survey (NHANES) report (ID 17) used data from the 1999-2004 NHANES to evaluate the association between urinary trichlorophenols (TCPs) and parent-reported ADHD among 2546 children aged 6-15 years. The authors report that children with low levels (<3.58 mg/g) and high levels

13. 精神及び精神運動発達影響

全体では、32の出版物が小児集団における精神及び精神運動発達影響に対する農薬ばく露の影響を調査しており（サンプルサイズ中央値：238、IQR 109-305）、データ抽出データベースでは462の個別の分析が行われた。非ヨーロッパ系（アジア系）の集団を対象とした研究は1件のみであり、注意欠陥多動性障害（ADHD、6件、102件の分析）を中心に17件の健康関連影響が評価されていた。他の影響に見られるように、ばく露の定義はかなりまちまちであり、データ統合に特別な問題をもたらしている。大多数の研究（23の論文、72%）は前向きコホート研究を参考にしているが、報告されている分析におけるサンプルサイズはしばしば小さく、25～7,440人の範囲で、最大のものはカリフォルニア・セントラルバレーの小児における農薬散布付近の母親の居住と自閉症スペクトラム障害の後ろ向き研究であった。ここで、我々はまた、CHAMACOS（サリナスの母と小児の健康評価センター）（5出版物）などの大規模な、この分野でよく知られた研究から来ている出版物のクラスタを観察したが、研究の84%が環境ばく露を評価していた。さらに、ばく露のバイオマーカーに関する情報を有する研究の存在がここでは多数であった（n=28、88%）。調査したさまざまな影響カテゴリーを、各カテゴリーに寄与した研究の数と定量的統合の決定とともに表15に示す。データの不均一性と同定された研究数が少なかったため、どの影響についてもデータの統計的統合（メタアナリシス）は行われなかった。

13.1. 研究が少ない精神及び精神運動発達影響

精神及び精神運動発達影響と注意欠陥多動性障害（ADHD）を除いて、表15に記載の影響はすべて、それぞれの影響だけでエビデンスを総合的に判断するには、利用可能な研究が少なすぎる。これらの影響は、自閉症や広汎性発達障害のように研究数が少ないが適切に定義された臨床所見から、コミュニケーション、微細及び粗大な運動発達、または表現的言語発達などの神経発達の中間形質を表す多数の影響まで収集されたさまざまな情報で構成されている。我々のシステマティックレビューでは、2006年以前に発表されたエビデンスとの比較を可能にするために、これらの影響に関する以前に発表されたメタアナリシスは確認しなかった。一般的に、これらの影響に関する結果は影響が小さく、統計的に有意ではなかったが、少数の例外はあった。分析数が多く、研究数やサンプル数が少ないことを考えると、これらの結果は慎重に解釈する必要があり、これらのデータに基づいて、農薬ばく露とこれらの影響との間に妥当な関連を示唆するエビデンスはない。

13.2. 注意欠陥多動性障害（ADHD）

6件の研究では、278人から2,539人の参加者のサンプルサイズで農薬ばく露とADHDとの関連を評価し、データベースに102件の別個に抽出された比較を提供した。3つの研究はコホートであり、すべての研究は環境ばく露を評価し、すべての研究でばく露はバイオマーカーを介して評価された。一般的な有機リン剤へのばく露は3つの研究で、DDTへのばく露は2つの研究で評価され、trans-ノナクロル、ヘキサクロロベンゼン、2,4,6-トリクロロフェノール（TCP）はそれぞれ1つの研究で評価された。このように、同等の影響の定義または同一の比較単位を用いた 4 つ以上の研究では、単一の農薬と関連するバイオマーカーは評価されておらず、定量的な統合は行われなかった。この分野で最大の研究は、国民健康・栄養調査（NHANES）の報告書（ID 17）で、1999年から2004年のNHANESのデータを使用して、6歳から15歳の小児2546人の間で尿中トリクロロフェノール（TCPs）と親が報告したADHDとの関連を評価し

(>3.58 mg/g) of urinary 2,4,6-Trichlorophenol (TCP) had a higher risk of parent-reported ADHD compared to children with levels below the limit of detection (OR 1.54, 95% CI 0.97 to 2.43 and OR 1.77, 95% CI 1.18 to 2.66, respectively; p for trend=0.006) after adjusting for covariates.

Our systematic review did not identify any previously published meta-analyses on ADHD to allow for comparisons with previously published evidence (prior to 2006). Generally the results on ADHD were of small effect and not statistically significant with few exceptions. Thus, given the large number of analyses these results need cautious interpretation and, based on these data, there is no evidence to suggest association between pesticide exposure and ADHD.

13.3. Neurodevelopment

Thirty-one studies assessed the association between pesticide exposure and aspects of neurodevelopment with a sample size ranging from 25 to 1,041 contributing 325 separate extracted comparisons in the database. Only one study assessed neurodevelopmental aspects in Asian children; all the rest pertained to populations of European ancestry. Seventy-four percent of the studies were cohort studies and, in 27 studies the exposure was assessed through a biomarker. A large variety of individual pesticides were assessed with the general category of organophosphate pesticides being assessed more frequently (Table 16). No single pesticide and related biomarker was assessed in more than 4 studies using comparable outcome definitions or the same comparison unit, thus a quantitative synthesis was not performed. Actually, the assessment of neurodevelopment, as seen for cognitive function, is another typical example of a general outcome category where the multiplicity and complexity of the 35 tools and sub-tools used (Table 17) renders the attempt to systematically and quantitatively synthesize the results of the published literature fruitless.

The largest study in the field is a Collaborative Perinatal Project report (ID MPD 029) assessing in-utero exposure to dichlorodiphenyltrichloroethane and cognitive development among infants and school-aged children. The authors report that although levels of DDT and DDE were relatively high in this population (median DDT concentration, 8.9 g/L; DDE, 24.5 g/L), neither were related to Mental or Psychomotor Development scores on the Bayley Scales nor to Full-Scale Intelligence Quotient at 7 years of age.

Our systematic review did not identify any previously published meta-analyses on these outcomes to allow for comparisons with previously published evidence (prior to 2006). Generally the results on neurodevelopmental outcomes were of small effect and not statistically significant with few exceptions. Thus, given the large number of analyses these results need cautious interpretation and, based on these data, there is no evidence to suggest association between pesticide exposure and these outcomes.

Table 15: Summary of studies and mental and psychomotor development outcomes

Outcome group	N analyses
Attention Deficit Hyperactivity Disorder (ADHD)	102
Autism	2

ている。著者らの報告によると、尿中の2,4,6-トリクロロフェノール（TCP）の濃度が低値（3.58 mg/g未満）及び高値（3.58 mg/g以上）の小児は、検出限界値未満の小児に比べて、親に報告されたADHDのリスクが高かった（OR 1.54、95%CI 0.97～2.43、OR 1.77、95%CI 1.18～2.66、それぞれpはトレンド=0.006）。

我々のシステマティックレビューでは、以前に発表されたエビデンス（2006年以前）との比較を可能にするために、ADHDに関する以前に発表されたメタアナリシスは確認しなかった。一般的にADHDに関する結果は効果が小さく、少数の例外を除いて統計的に有意ではなかった。したがって、多数の分析を考慮すると、これらの結果は慎重な解釈が必要であり、これらのデータに基づいて、農薬ばく露とADHDとの関連を示唆するエビデンスはない。

13.3. 神経発達

31件の研究が農薬ばく露と神経発達の関連を評価しており、サンプルサイズは25～1,041で、データベースには325件の個別比較が掲載されている。アジア系の小児の神経発達を評価した研究は1件のみであり、その他の研究はすべてヨーロッパ系の集団を対象としたものであった。研究の74%はコホート研究で、27の研究ではバイオマーカーを用いてばく露が評価されていた。個々の農薬の評価は多種多様で、有機リン系農薬一般というカテゴリーがより頻繁に評価されている（表16）。比較可能な影響の定義または同一の比較単位を用いた 4 件以上の研究では、単一の農薬と関連するバイオマーカーの評価は行われていないため、定量的な統合は行われていない。実際、神経発達の評価は、認知機能に見られるように一般的な影響カテゴリーのもう一つの典型的な例であり、使用されている 35 のツールとサブツールの多様性と複雑性（表 17）は、公表されている文献の結果を体系的かつ定量的に統合しようとする試みを無意味なものにしている。

この分野で最大の研究は、Collaborative Perinatal Projectの報告書（ID MPD 029）であり、ジクロロジフェニルトリクロロエタンへの胎内ばく露と乳児及び学童期の小児の認知発達を評価している。著者らの報告によると、この集団では DDT と DDE の濃度は比較的高かったが（DDT 濃度中央値 8.9 g/L、DDE 24.5 g/L）、7歳時のベイリー尺度の精神・精神運動発達スコアやフルスケール知能指数のいずれにも関連していなかった。

我々のシステマティックレビューでは、2006年以前に発表されたエビデンスとの比較を可能にするために、これらの結果に関する過去に発表されたメタアナリシスは確認しなかった。一般的に、神経発達の影響に関する結果は、ほとんどの例外を除いて効果が小さく、統計的に有意ではなかった。したがって、多くの分析が行われたことを考えると、これらの結果は慎重に解釈する必要があり、これらのデータに基づいて、農薬ばく露とこれらの影響との関連を示唆するエビデンスはない。

Intelligence Quotient (IQ)	13
Learning disability	4
Cognitive disorders	20
Mental and psychomotor development	318
Pervasive developmental disorder	3

Table 16: Pesticides assessed in neurodevelopmental aspects

Pesticide assessed	N analyses
DDT	81
Chlordecone	5
Chlorpyrifos	8
Hexachlorobenzene (HCB)	5
Insecticides	6
Malathion	8
Mirex	13
Organochlorine pesticides	2
Organophosphate and carbamate pesticide	7
Organophosphate pesticides	115
Pesticides	80
Piperonyl butoxide	1

表 15：研究の概要と精神及び精神運動発達影響

影響	分析数
注意欠陥多動性障害（ADHD）	102
自閉症	2
知能指数	13
学習障害	4
認知障害	20
精神・精神運動発達	318
広汎性発達障害	3

表 16：神経発達の観点で評価された農薬

評価した農薬	分析数
DDT	81
クロルデコン	5
クロルピリホス	8
ヘキサクロロベンゼン（ＨＣＢ）	5
殺虫剤	6
マラチオン	8
マイレックス	13
有機塩素系農薬	2
有機リン系・カーバメート系殺虫剤	7
有機リン系農薬	115
農薬	80
ピペロニルブトキシド	1

Table 17: Outcome definitions and tools used in the 31 studies assessing neurodevelopment

Outcome definition / Tool used
Accuracy, impulse control
Ages and Stages Questionnaire
Behavioral Assessment and Research System (BARS)
Bayley Psychomotor Development Index Scales for Infants
Bayley Mental Development Index Scales for Infants
Beery-Buktenica VMI developmental test
Benton Visual Retention Test (BVRT)
Box test
Brazelton neonatal behavioral assessment
Brunet-Lezine scale of psychomotor development
Children's Memory Scale
combining the Picture
Completion, Codin
Continuous Performance Test (CPT)
Digit Span
Fagan test of infant intelligence (FTII)
Finger Tapping Task
Gesell Developmental Schedules
Graham–Rosenblith test
Griffiths Mental Developmental Scale
Hit reaction time
Large-pellet test
McCarthy Scales of Children's Abilities
Mullen Scales of Early Learning: AGS Ed
Performance on Continuous Performance Test (CPT)
Raven Test
Santa Ana Form Board
Score in Lincoln-Oseretsky Motor
Small-pellet test
Stanford-Binet Copying Test
Teller visual Acuity Card (TAC) test
Trail Making
University of California Berkeley Preferential Looking Test
Wechsler Intelligence Scale for children
Wisconsin Card Sorting Test

表 17：神経発達を評価する 31 の研究で使用された影響の定義とツール

影響の定義・使用ツール
正確性、衝動制御［Accuracy, impulse control］
年齢・段階別の質問紙［Ages and Stages Questionnaire］
行動評価研究システム［Behavioral Assessment and Research System (BARS)］
乳幼児のためのベイリー精神運動発達指数尺度［Bayley Psychomotor Development Index Scales for Infants］
乳幼児のためのベイリー精神発達指数尺度［Bayley Mental Development Index Scales for Infants］
ベアリーブクテニカ VMI 発達検査［Beery-Buktenica VMI developmental test］
ベントン視覚記銘検査［Benton Visual Retention Test (BVRT)］
ボックステスト［Box test］
ブラゼルトン新生児行動評価［Brazelton neonatal behavioral assessmen］
ブルネ・レジン精神運動発達尺度［Brunet-Lezine scale of psychomotor development］
小児の記憶力尺度［Children's Memory Scale］
イメージ連結［Combining the Picture］
完成、Codin［Completion, Codin］
持続的パフォーマンステスト［Continuous Performance Test (CPT)］
数列暗唱［Digit Span］
ファーガンテスト(乳児知能)［Fagan test of infant intelligence (FTII)］
フィンガータッピングタスク［Finger Tapping Task］
ゲゼル発達スケジュール［Gesell Developmental Schedules］
グラハムローゼンブリット検査［Graham-Rosenblith test］
グリフィス精神発達尺度［Griffiths Mental Developmental Scale］
ヒット反応時間［Hit reaction time］
大型ペレット検査［Large-pellet test］
マッカーシーの小児能力尺度［McCarthy Scales of Children's Abilities］
早期学習の Mullen スケール：AGS Ed［Mullen Scales of Early Learning: AGS Ed］
持続的パフォーマンス検査（CPT）のパフォーマンス［Performance on Continuous Performance Test］
レーヴン検査［Raven Test］
Santa Ana Form Board
Lincoln-Oseretsky Motor スコア［Score in Lincoln-Oseretsky Motor］
小型ペレット検査［Small-pellet test］
スタンフォードビネーコピー検査［Stanford-Binet Copying Test］
テラー視力カード（TAC）検査［Teller visual Acuity Card (TAC) test］
トレイルメイキング［Trail Making］
カリフォルニア大学バークレー校の選好注視テスト［University of California Berkeley Preferential Looking Test］
ウェクスラー小児知能検査［Wechsler Intelligence Scale for children］
ウィスコンシンカード分類テスト［Wisconsin Card Sorting Test］

14. Respiratory diseases

Overall, 29 publications examined the effect of pesticide exposure on respiratory outcomes (median sample size: 249, IQR 126-1728), contributing 399 separate analyses in the *data extraction database*. Sixty-seven percent came from Europe and America, while ten health-related outcomes were assessed with a large proportion focusing on asthma (N=9). As seen with other outcomes, the diversity of the exposure definition is considerable and poses special challenges to data synthesis. Only 6 out of the 29 publications referred to prospective cohort studies and 12 were cross-sectional studies. The sample size in the reported analyses was often small; it ranged between 35 and 47,756 participants with the largest study being the Singapore Chinese Health Study. Here, we also observed large clusters of publications coming from large, well-known studies in the field, such as the AHS (6 publications), while 17 studies (68%) assessed occupational exposures. In addition, the presence of studies with information on biomarkers of exposure was less prominent here (N=8, 34%) while 1 study assessed occupational exposure through JEM. The different outcome categories examined are presented in Table 18 along with the number of studies contributing to each outcome category and a decision on quantitative synthesis. Due to heterogeneity of data and small number of studies identified, statistical synthesis of the data (meta-analysis) was only performed for asthma.

14.1. Respiratory outcomes with few studies

With the exception of asthma, for all the remaining assessed outcomes included in Table 18, too few studies are available to allow synthesis of evidence for each outcome alone; these outcomes comprise a variety of captured information ranging from well-defined clinical entities yet with too few studies, such as idiopathic pulmonary fibrosis, or sarcoidosis, as well as a numbers of biomarkers such as forced expiratory volume (FEV). Our systematic review did not identify any previously published meta-analyses on these outcomes to allow for comparisons with previously published evidence (prior to 2006). Generally the results on these outcomes were of small effect and not statistically significant with few exceptions. Given the large number of analyses and the fact that most of the results come from the Agricultural Health Study (AHS), these results need cautious interpretation and, based on these data, there is no evidence to suggest a robust association between pesticide exposure and these outcomes.

14.2. Asthma

Nine studies assessed the association between pesticide exposure and asthma with a median sample size of 402 (IQR 127-724), contributing 196 separate extracted comparisons in the database. More than half of the studies were cross-sectional and in more than two-thirds of the studies, the exposure was assessed through a questionnaire. A large variety of individual pesticides were assessed with DDT, paraquat and chlorpyrifos being assessed more frequently. With the exception of DDT, chlorpyrifos and paraquat (Table 19), no other single pesticide and related biomarker was assessed in more than 4 studies using the same comparison unit, thus a quantitative synthesis was not performed.

When we attempted to investigate the association between exposure to DDT and asthma across the 5 available studies, the observed effect was statistically significant without indications of heterogeneity (OR 1.29, 95% CI 1.14 – 1.45, I^2 0%) (Figure 32). We then attempted to investigate the association between exposure to paraquat and asthma across the 6 available studies and the observed effect was not statistically significant with indications of heterogeneity (OR=1.40, 95%CI=0.95–2.06, I^2=53%) (Figure 33). We finally attempted to investigate the association between exposure to chlorpyrifos and

14. 呼吸器疾患

全体では、29の出版物が呼吸器影響に対する農薬ばく露の効果を調査しており（サンプルサイズ中央値：249、IQR 126-1728）、データ抽出データベースでは399の個別の分析が行われた。そのうち67%はヨーロッパとアメリカからのもので、10の健康関連影響が評価されており、その中でも特に喘息に焦点を当てた影響が多かった（N=9）。他の影響に見られるように、ばく露の定義はかなりまちまちであり、データ統合に特別な問題をもたらしている。29の出版物のうち、前向きコホート研究に言及しているのは6件のみで、12件は横断研究であった。報告された分析におけるサンプルサイズはしばしば小さく、35～47,756人の範囲であり、最大の研究はSingapore Chinese Health Studyであった。ここでは、AHS（6件）のようなこの分野でよく知られた大規模な研究からの出版物の大規模なクラスタも観察され、17件（68%）の研究が職業的ばく露を評価していた。さらに、ばく露のバイオマーカーに関する情報を持つ研究の存在は、ここではあまり目立たなかった（N=8、34%）が、1件の研究ではJEMによる職業的ばく露を評価していた。調査したさまざまな影響カテゴリーを、各カテゴリーに寄与した研究の数と定量的統合の決定とともに表 18 に示した。データの不均一性と同定された研究数が少ないため、データの統計的統合（メタアナリシス）は喘息についてのみ実施した。

14.1. 研究数が少ない呼吸器影響

これらの影響は、特発性肺線維症やサルコイドーシス、努力性呼気量（FEV）などの多数のバイオマーカーに加えて、研究数が少なすぎるが、明確に定義された臨床所見まで、様々な情報を収集したもので構成されている。我々のシステマティックレビューでは、以前に発表されたエビデンス（2006年以前）との比較を可能にするために、これらの影響に関する以前に発表されたメタアナリシスは確認しなかった。一般的に、これらの影響に関する結果は効果が小さく、統計的に有意ではなかったが、少数の例外を除いては有意であった。分析数が多く、結果のほとんどが農業健康調査（Agricultural Health Study: AHS）からのものであることを考えると、これらの結果は慎重に解釈する必要があり、これらのデータに基づいて、農薬ばく露とこれらの結果との間に妥当な関連を示唆するエビデンスはない。

14.2. 喘息

9件の研究が農薬ばく露と喘息との関連を評価しており、サンプルサイズの中央値は402（IQR 127-724）で、データベースには196件の比較が抽出されている。半数以上の研究が横断的に行われ、3分の2以上の研究ではばく露は質問紙で評価されていた。個々の農薬の評価は多岐にわたり、DDT、パラコート、クロルピリホスがより頻繁に評価されている。DDT、クロルピリホス、パラコートを除いて（表 19）、同じ比較単位を用いた 4 件以上の研究では、他の単一の農薬と関連するバイオマーカーは評価されておらず、定量的な統合は行われていない。

利用可能な 5 つの研究で DDT へのばく露と喘息との関連を調査しようとしたところ、観察された影響は不均一性を示すことなく統計的に有意であった（OR 1.29、95%CI 1.14～1.45、I2 0%）（図 32）。次に、利用可能な6つの研究について、パラコートへのばく露と喘息との関連を調査しようとしたが、観察された効果は、不均一性を示すもので統計的に有意ではなかった（OR=1.40, 95%CI=0.95-2.06, I2=53%）（図33）。最後に、利用可能な5つの研究でクロルピリホスへのばく露と喘息との関連を調査しようとしたが、観察された効果は、不均一性を示し統計的に有意ではなかった（OR=1.03、95%CI=0.82-1.28、I2=0%）（図34）。メタアナリシスの結果は主にAHSによるものであること、また、男女別、アレルギー性・非アレルギー性喘息別に報告されているため、４つがAHSに属していることに注意が必要である。また、メタアナリシスの結果は2006年以降に発表されたデータに限定されていることも認めている。したがって、DDTについては、これらの農薬へのばく露と喘息との間に統計的に有意な中等度の関連を示唆する最近のエビデンスがあると結論付けたが、クロルピリホスとパラコートについてはそうではない。

asthma across the 5 available studies and the observed effect was not statistically significant without indications of heterogeneity (OR= 1.03, 95% CI= 0.82–1.28, I^2=0%) (Figure 34). We caution that the meta-analyses results are largely driven by the AHS; in the meta-analyses 4 entries belong to the AHS as the results were separately reported for men and women and for allergic and non-allergic asthma. We also acknowledge that the results of the meta-analyses are restricted to data published after 2006. We thus conclude that for DDT, but not for chlorpyrifos and paraquat, there is recent evidence to suggest a statistically significant, moderate association between exposure to this pesticides and asthma.

Table 18: Summary of studies and outcomes in the field of respiratory medicine (N/A: not available)

Outcome Group	N studies	Meta-analysis performed	Previous published meta-analysis
Cough	2	No	N/A
Breathlessness	1	No	N/A
Cough/Phlegm	2	No	N/A
Volume that has been exhaled at the end of the first second of forced expiration (FEV_1)	1	No	N/A
FEV_1 / Forced vital capacity (FVC)	2	No	N/A
Asthma	9	Yes	N/A
Chronic bronchitis	5	No	N/A
Hypersensitivity pneumonitis	2	No	N/A
Lower respiratory tract infection	2	No	N/A
Sarcoidosis	1	No	N/A
Wheeze	2	No	N/A

表 18：呼吸器医学の研究と影響のまとめ（N/A：なし）

影響	研究数	メタアナリシス実施	以前に発表されたメタアナリシス
咳	2	No	N/A
息苦しさ	1	No	N/A
咳・痰	2	No	N/A
1 秒量(FEV1)	1	No	N/A
FEV1 / 努力性肺活量（FVC）	2	No	N/A
喘息	9	Yes	N/A
慢性気管支炎	5	No	N/A
過敏性肺炎	2	No	N/A
下気道感染症	2	No	N/A
サルコイドーシス	1	No	N/A
異常呼吸音	2	No	N/A

Table 19: Characteristics of the associations eligible for meta-analysis

ID	Year	Location	Study design	Exposure type	Exposure assessment	Comparison	Adjustment	Sample size
DDT								
RESP_002	2006	Europe	Cohort	Environmental	Biomarker	Yes/no	+++	402
RESP_004	2008	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	936
RESP_004	2008	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	946
RESP_006	2009	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	4391
RESP_006	2009	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	4468
Paraquat								
RESP_019	2009	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	134
RESP_022	2012	Asia	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	125
RESP_004	2008	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	292
RESP_004	2008	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	294
RESP_006	2009	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	3096
RESP_006	2009	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	3108
Chlorpyrifos								
RESP_019	2009	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	134
RESP_004	2008	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	1017
RESP_004	2008	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	1019
RESP_006	2009	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	2174
RESP_006	2009	America	Cross-sectional	Occupational	Questionnaire	Yes/no	+++	2199

表 19：メタアナリシスの対象となる関連付けの特徴

ID	年	場所	研究デザイン	ばく露タイプ	ばく露評価	比較	調整	サンプルサイズ
DDT								
RESP_002	2006	ヨーロッパ	コホート	環境	バイオマーカー	Yes/no	+++	402
RESP_004	2008	アメリカ	横断	職業	質問紙	Yes/no	+++	936
RESP_004	2008	アメリカ	横断	職業	質問紙	Yes/no	+++	946
RESP_006	2009	アメリカ	横断	職業	質問紙	Yes/no	+++	4391
RESP_006	2009	アメリカ	横断	職業	質問紙	Yes/no	+++	4468
パラコート								
RESP_019	2009	アメリカ	横断	職業	質問紙	Yes/no	+++	134
RESP_022	2012	アジア	横断	職業	質問紙	Yes/no	+++	125
RESP_004	2008	アメリカ	横断	職業	質問紙	Yes/no	+++	292
RESP_004	2008	アメリカ	横断	職業	質問紙	Yes/no	+++	294
RESP_006	2009	アメリカ	横断	職業	質問紙	Yes/no	+++	3096
RESP_006	2009	アメリカ	横断	職業	質問紙	Yes/no	+++	3108
クロルピリホス								
RESP_019	2009	アメリカ	横断	職業	質問紙	Yes/no	+++	134
RESP_004	2008	アメリカ	横断	職業	質問紙	Yes/no	+++	1017
RESP_004	2008	アメリカ	横断	職業	質問紙	Yes/no	+++	1019
RESP_006	2009	アメリカ	横断	職業	質問紙	Yes/no	+++	2174
RESP_006	2009	アメリカ	横断	職業	質問紙	Yes/no	+++	2199

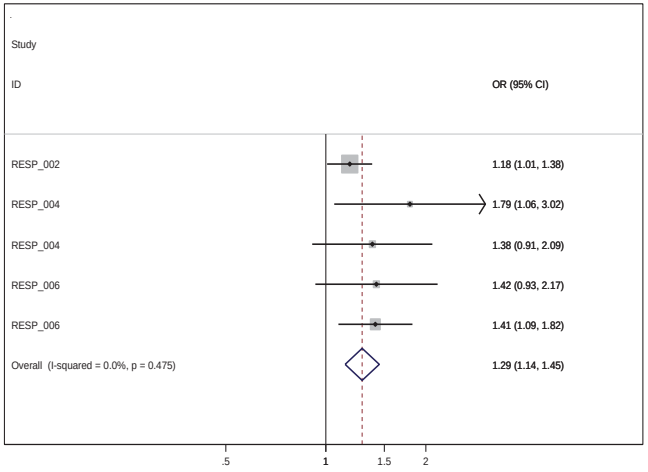


Figure 32: Fixed-effects meta-analysis for studies with information on DDT exposure and risk of any type of asthma (Studies 6 and 10 refer to Agricultural Health Study publications)

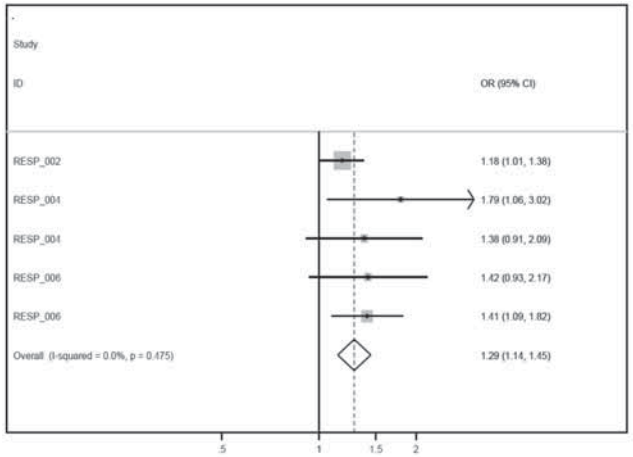


図 32：DDT ばく露に関する情報と喘息のリスクの固定効果メタアナリシス（研究 6 と 10 は農業健康研究の出版物を参照）

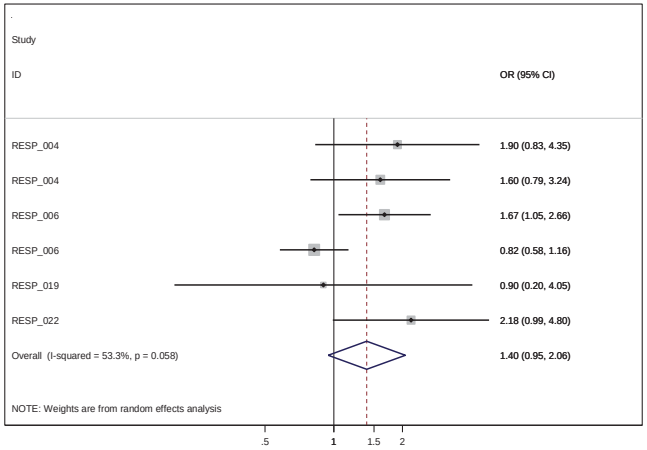


Figure 33: Random-effects meta-analysis for studies with information on paraquat exposure and risk of any type of asthma (Studies 6 and 10 refer to Agricultural Health Study publications)

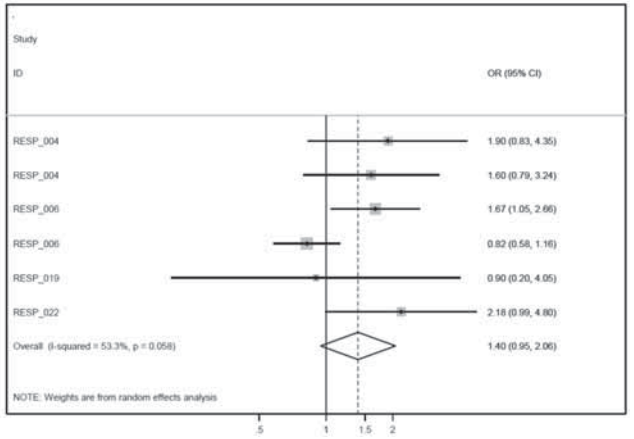


図 33：パラコートばく露に関する情報と喘息のリスクのランダム効果メタアナリシス（研究 6 と 10 は農業健康研究の出版物を参照）

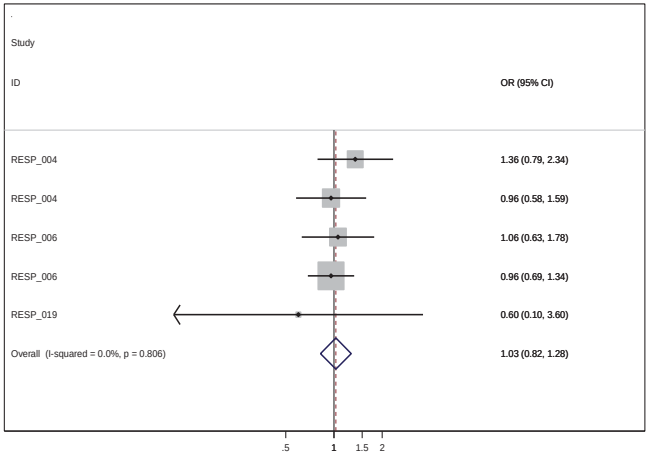


Figure 34: Fixed-effects meta-analysis for studies with information on chlorpyrifos exposure and risk of any type of asthma (Studies 6 and 10 refer to Agricultural Health Study publications)

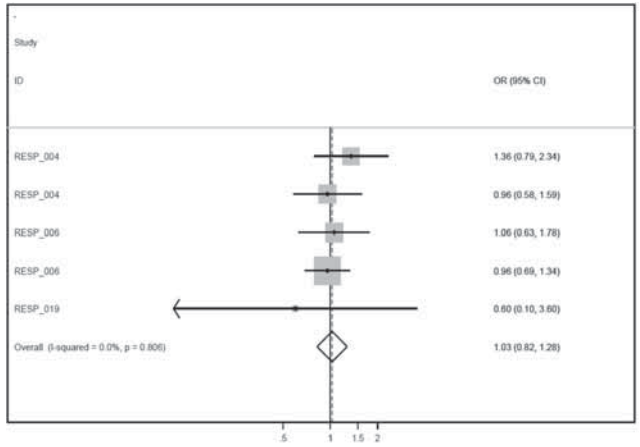


図 34：クロルピリホスばく露に関する情報と喘息のリスクの固定効果メタアナリシス（研究 6 と 10 は農業健康研究の出版物を参照）

15. Neuropsychiatric diseases

Overall, 15 publications examined the effect of pesticide exposure on neuropsychiatric outcomes in adult populations (median sample size: 596, IQR 158-12,263), contributing 358 separate analyses in the *data extraction database*. Three-quarters came from Europe and America, while 17 health-related outcomes were assessed with a large proportion focusing on cognitive function (9 studies, 246 analyses). As seen with other outcomes, the diversity of the exposure definition is considerable and poses special challenges to data synthesis. Only 2 out of the 15 publications referred to prospective cohort studies and 60% of the publications were cross-sectional studies. The sample size in the reported analyses was often small; it ranged between 66 and 112,683 participants with the largest study being a retrospective American study. Here, we also observed clusters of publications coming from large, well-known studies in the field, such as the Agricultural Health Study (AHS) (4 publications), while all but one study assessed occupational exposures. In addition, the presence of studies with information on biomarkers of exposure was far less prominent here (n=2, 13%). The different outcome categories examined are presented in Table 20, along with the number of studies contributing to each outcome category and a decision on quantitative synthesis. Due to heterogeneity of data and small number of studies identified, no statistical synthesis of the data (meta-analysis) was performed for any outcome.

15.1. Cognitive function

Nine studies assessed the association between pesticide exposure and cognitive function with a median sample size of 80 (IQR 141-205), contributing 246 separate extracted comparisons in the database. All but one of the studies were cross-sectional and, in seven studies the exposure was assessed through a questionnaire. A large variety of individual pesticides were assessed with the general category of organophosphate pesticides being assessed more frequently. No single pesticide and related biomarker was assessed in more than 4 studies using comparable outcome definitions or the same comparison unit, thus a quantitative synthesis was not performed. Actually, the assessment of cognitive function is a typical example of a general outcome category where the multiplicity and complexity of the 62 tools and sub-tools used in the 15 available studies (Table 21) renders the attempt to systematically and quantitatively synthesize the results of the published literature fruitless.

The largest study in the field is an AHS report (ID NPD 014) assessing potential associations between long-term pesticide use and neurobehavioral function, with relevant tests administered to licensed pesticide applicators. The authors report that “test performance was associated with lifetime days of use of some pesticides”. Ethoprop was significantly associated with reduced performance on a test of motor speed and visual scanning. Malathion was significantly associated with poor performance on a test of visual scanning and processing. Conversely, we observed significantly better test performance for five organophosphate pesticides. Specifically, chlorpyrifos, coumaphos, parathion, phorate, and tetrachlorvinphos were associated with better verbal learning and memory; coumaphos was associated with better performance on a test of motor speed and visual scanning; and parathion was associated with better performance on a test of sustained attention. Overall, we found no consistent evidence of an association between organophosphate pesticide use and adverse test performance among this older sample of pesticide applicators. Potential reasons for these mostly null results include a true absence of effect as well as possible selective participation by healthier applicators.

Our systematic review did not identify any previously published meta-analyses on these outcomes to allow for comparisons with previously published evidence (prior to 2006). Generally the results on neuropsychiatric outcomes were of small effect and not statistically significant with few exceptions.

15. 神経精神疾患

全体では、15の出版物が成人集団の神経精神影響に対する農薬ばく露の影響を調査しており（サンプルサイズ中央値：596、IQR158-12263）、データ抽出データベースでは358の個別の分析が行われている。4分の3はヨーロッパとアメリカの研究者であり、17の健康関連影響が評価され、大部分が認知機能に焦点を当てていた（9研究、246の分析）。他の影響に見られるように、ばく露の定義はかなりまちまちであり、データ統合に特別な問題を与えている。15の出版物のうち、前向きコホート研究に言及しているのは2件のみで、出版物の60%は横断研究であった。報告された分析におけるサンプルサイズはしばしば小さく、66～112,683人の範囲であり、最大の研究は米国の後ろ向き研究であった。ここでは、農業健康調査（Agricultural Health Study、AHS）（4件）のようなこの分野でよく知られた大規模な研究からの出版物のクラスタも観察されたが、1件を除いてすべての研究が職業ばく露を評価していた。さらに、ばく露のバイオマーカーに関する情報を有する研究の存在は、ここではあまり目立たなかった（n=2、13%）。調査したさまざまな影響カテゴリーを、各カテゴリーに寄与した研究の数と定量的統合の決定とともに表20に示した。データの不均一性と同定された研究数が少ないため、どの影響についてもデータの統計的統合（メタアナリシス）は行われていない。

15.1. 認知機能

9件の研究が農薬ばく露と認知機能との関連を評価しており、サンプルサイズの中央値は80（IQR 141-205）で、データベースには246件の比較が抽出されている。1件を除くすべての研究が横断的で、7件の研究では質問紙でばく露が評価されていた。個々の農薬の評価は多種多様で、有機リン系農薬の一般的なカテゴリーがより頻繁に評価されていた。比較可能な影響の定義や同じ比較単位を用いた4件以上の研究では、単一の農薬と関連するバイオマーカーの評価は行われておらず、定量的な統合は行われていない。実際、認知機能の評価は一般的な影響カテゴリーの典型的な例であり、利用可能な 15の研究（表21）で使用された62のツールとサブツールの多様性と複雑性のため、公表されている文献の結果を体系的かつ定量的に統合する試みは実りのないものとなっている。

この分野で最大の研究は、農薬の長期使用と神経行動機能との間の潜在的な関連を評価したAHSの報告書（ID NPD 014）であり、農薬散布者にこれらに関連する検査を行っている。著者らは、「検査結果は一部の農薬の生涯使用日数と関連していた」と報告している。エトプロプは、運動速度と視覚走査のテストのパフォーマンス低下と有意に関連していた。マラチオンは、視覚的走査と処理のテストのパフォーマンス低下と有意に関連していた。逆に、5種類の有機リン系農薬では、検査結果の有意な改善が観察された。具体的には、クロルピリホス、クマホス、パラチオン、ホレート、テトラクロルビンホスは言語学習と記憶力の向上と関連しており、クマホスは運動速度と視覚走査のテストの成績向上と関連しており、パラチオンは持続注意力のテストの成績向上と関連していました。全体的に、有機リン系農薬の使用とテスト成績低下との間には、この高齢の農薬使用者のサンプルでは一貫した関連のエビデンスは見られなかった。これらのほとんどが無効な結果となった理由としては、真の効果がないことや、より健康的な農薬使用者が選択的に参加している可能性が考えられる。

我々のシステマティックレビューでは、以前に発表されたエビデンス（2006年以前）との比較を可能にするために、これらの結果に関する以前に発表されたメタアナリシスは確認しなかった。一般的に、神経精神影響に関する結果は効果が小さく、統計的に有意ではなかったが、いくつかの例外を除いて

Thus, given the large number of analyses these results need cautious interpretation and, based on these data, there is no evidence to suggest association between pesticide exposure and these outcomes.

15.2. Neuropsychiatric outcomes with few studies

With the exception of cognitive function, for all the remaining assessed outcomes included in Table 20, too few studies are available to allow synthesis of evidence for each outcome alone; these outcomes comprise a variety of captured information ranging from well-defined clinical entities yet with too few studies, such as depression, or obsessive-compulsive disorder, as well as a numbers of outcomes representing neuropsychiatric endo-phenotypes such as hostility or orientation disorders. Our systematic review did not identify any previously published meta-analyses on these outcomes to allow for comparisons with previously published evidence (prior to 2006). Generally the results on these outcomes were of small effect and not statistically significant with few exceptions. Given the large number of analyses and the fact that a number of the results come from the AHS, these results need cautious interpretation and, based on these data, there is no evidence to suggest a robust association between pesticide exposure and these outcomes.

Table 20: Summary of studies and neuropsychiatric outcomes

Outcome group	N studies
Anxiety	3
Attention and calculation disorders	1
Cognitive function	9
Depression	4
Electroencephalographic (EEG) state	1
Hostility	1
Interpersonal sensitivity diosrder	1
Learning disability	1
Nausea	1
Neuropsychiatric symptoms	3
Obsessive-compulsive disorder	1
Orientation disorders	1
Paranoid ideation	1
Psychotisism	1
Rapid Eye Movement (REM) Sleep Behavior Disorders (RBD)	1
Somatization	1
Suicide commitment	3

は有意であった。

したがって、多数の分析を考慮すると、これらの結果は慎重に解釈する必要があり、これらのデータに基づいて、農薬ばく露とこれらの影響との関連を示唆するエビデンスはない。

15.2. 研究数が少ない神経精神影響

これらの影響は、うつや強迫性障害のような明確に定義されているが研究数が少なすぎる臨床所見から、また敵意や見当識障害のような神経精神医学的な中間形質を表す影響も多数含まれている。我々のシステマティックレビューでは、以前に発表されたエビデンス（2006 年以前）との比較を可能にするために、これらの影響に関する以前に発表されたメタアナリシスは確認しなかった。一般的に、これらの影響に関する結果は効果が小さく、統計的に有意ではなかった（少数の例外を除く）。分析の数が多く、結果の多くが AHS からのものであることを考えると、これらの結果は慎重に解釈する必要があり、これらのデータに基づいて、農薬ばく露とこれらの結果との間の妥当な関連を示唆するエビデンスはない。

表 20：研究と神経精神影響のまとめ

影響	研究数
不安	3
注意力・計算障害	1
認知機能	9
うつ	4
脳波（EEG）の状態	1
敵意	1
対人感受性障害	1
学習障害	1
吐き気	1
神経精神症状	3
強迫性障害	1
見当識障害	1
被害妄想的なイデオロギー	1
精神病傾向	1
REM 睡眠行動障害（RBD）	1
身体化	1
自殺	3

Table 21: Outcome definitions and tools used in the 15 studies assessing cognitive function (BARS: Behavioral Assessment and Research System, AVLT:Auditory Verbal Learning Test, BVFT: Benton Visual Form Discrimination Test CALCALP: California Computerised Assessment Package Manual, WAIS: Wechsler Adult Intelligence Scale, WMS: Wechsler Memory Scale)

Outcome definition / Tool used	
% Correct rejects (BARS)	Selective attention latency (BARS)
% Hits (BARS)	Selective attention trials (BARS)
Recall (AVLT)	Sequences A test performance (seconds)
Recognition (AVLT)	Sequences B test performance (seconds)
Total recall (AVLT)	Serial digit learning task (BARS)
Benton Visual Form Discrimination Test (BVFT)	Serial Digit Learning Test
Block design test	Simple Reaction Time Test (ms)
CALCAP choice test	Spatial span test
Continuous Performance Test Score (m/s)	Stroop test
Counting errors	Summary index (BARS)
Digit span backward task (BARS)	Symbol Digit Substitution Test (s)
Digit span forward task (BARS)	Symbol-digit latency task (BARS)
Digit-Symbol test score (seconds)	Symptom Checklist 90 revised (SCL-90-R)
False alarm latency (BARS)	Trails B test
Fine motor control test	Verbal fluency test
Finger tapping (preferred hand) (BARS)	WAIS-III picture arrangement test
Finger tapping , dominant hand (BARS)	WAIS-III arithmetic test
Finger tapping, (nonpreferred hand) (BARS)	WAIS-III comprehension test
Finger tapping, alternating hand (BARS)	WAIS-III digit span test
Graded naming test	WAIS-III digit symbol test
Grooved pegboard, dominant hand score	WAIS-III full scale IQ
Hit latency (BARS)	WAIS-III graded-naming test
Match-Sample (BARS)	WAIS-III similarities test
N100 latency (ms)	WAIS-III vocabulary test
N200 latency (ms)	WMS-III auditory delayed memory test
P200 latency (ms)	WMS-III auditory immediate memory test
P300 amplitude (μv), Cz	WMS-III auditory recognition test
P300 latency (ms)	WMS-III letter-number test
Progressive ratio (BARS)	WMS-III visual delayed memory test
Reaction time latency a (BARS)	WMS-III visual immediate test
Reaction time latency a (BARS)	Selective attention interstimulus interval (BARS)

表 21：認知機能を評価する 15 の研究で使用された影響の定義とツール（BARS. 行動評価研究システム、AVLT:Auditory Verbal Learning Test、BVFT:Benton Visual Form Discrimination Test CALCALP:California Computerised Assessment Package Manual、WAIS:Wechsler Adult Intelligence Scale、WMS:Wechsler Memory Scale）

影響の定義・使用ツール	
正解率（BARS）[% Correct rejects]	選択的注意潜時（BARS）[Selective attention latency]
ヒット数（BARS）[% Hits]	選択的注意試験（BARS）[Selective attention trials]
リコール（AVLT）[Recall]	シーケンス A テスト性能（秒）[Sequences A test performance]
認識（AVLT）[Recognition]	シーケンス B テスト性能（秒）[Sequences B test performance]
トータルリコール（AVLT）[Total recall]	シリアルディジット学習タスク（BARS）[Serial digit learning task]
ベントン視覚形態判別テスト（BVFT）[Benton Visual Form Discrimination Test]	シリアルデジット学習テスト [Serial Digit Learning Test]
ブロックデザイン（積み木問題）[Block design test]	単純反応時間試験（ms）[Simple Reaction Time Test]
ＣＡＬＣＡＰ選択テスト [CALCAP choice test]	空間スパンテスト [Spatial span test]
連続性能試験スコア（m/s）[Continuous Performance Test Score]	ストループテスト [Stroop test]
カウントエラー [Counting errors]	サマリーインデックス（BARS）[Summary index]
数列暗唱逆唱（BARS）[Digit span backward task]	記号桁置換試験 [Symbol Digit Substitution Test]
数列暗唱順唱（BARS）[Digit span forward task]	記号桁遅延タスク（BARS）[Symbol-digit latency task]
符号問題のスコア（秒）[Digit-Symbol test score]	症状チェックリスト 90 改訂版（SCL-90-R）[Symptom Checklist 90 revised]
誤報待ち時間（BARS）[False alarm latency]	トレイルズ B テスト [Trails B test]
微細運動制御試験 [Fine motor control test]	言語流暢性テスト [Verbal fluency test]
フィンガータッピング（利き手）（BARS）[Finger tapping]	WAIS-Ⅲ絵画配列 [WAIS-III picture arrangement test]
フィンガータッピング、利き手（BARS）[Finger tapping, dominant hand]	WAIS-Ⅲ計算問題 [WAIS-III arithmetic test]
フィンガータッピング、（非利き手）（BARS）[Finger tapping]	WAIS-Ⅲ理解力 [WAIS-III comprehension test]
フィンガータッピング、交互に手を動かす（BARS）[Finger tapping, alternating hand]	WAIS-Ⅲ数列暗唱 [WAIS-III digit span test]
グレーデッドネーミングテスト [Graded naming test]	WAIS-Ⅲ符号問題 [WAIS-III digit symbol test]
溝付きのペグボード、支配的な手のスコア [Grooved pegboard, dominant hand score]	WAIS-Ⅲフルスケール IQ [WAIS-III full scale IQ]
ヒット潜時（BARS）[Hit latency]	WAIS-Ⅲ段階的命名試験 [WAIS-III graded-naming test]
マッチサンプル（BARS）[Match-Sample]	WAIS-Ⅲ類似 [WAIS-III similarities test]
N100 潜時（ms）[N100 latency]	WAIS-Ⅲ語彙 [WAIS-III vocabulary test]
N200 潜時（ms）[N200 latency]	WMS-Ⅲ 聴覚遅延記憶 [WMS-III auditory delayed memory test]
P200 潜時（ms）[P200 latency]	WMS-Ⅲ聴覚即時記憶 [WMS-III auditory immediate memory test]
P300 振幅（μv）, Cz [P300 amplitude]	WMS-Ⅲ聴覚認識 [WMS-III auditory recognition test]
P300 の潜時（ms）[P300 latency]	WMS-Ⅲ文字・数字配列決定 [WMS-III letter-number test]
進歩率（BARS）[Progressive ratio]	WMS-Ⅲ視覚的遅延記憶 [WMS-III visual delayed memory test]
反応時間潜時 a（BARS）[Reaction time latency a]	WMS-Ⅲ視覚即時試験 [WMS-III visual immediate test]
反応時間潜時 a（BARS）[Reaction time latency a]	選択的注意間刺激間隔（BARS）[Selective attention interstimulus interval]

16. Diabetes

Overall, 23 publications examined the effect of pesticide exposure on diabetes related outcomes (median sample size: 430; IQR 192-1721), contributing 125 separate analyses in the *data extraction database*. Four health-related outcomes were assessed with a large proportion focusing on type 1 diabetes (n=93, 74%) whereas 18 analyses focused on type 2 diabetes. The rest of the outcomes assessed was prediabetes (n=10), gestational diabetes (n=2) and other glucose and insulin related outcomes (n=2). Only one prospective cohort study was performed; the large majority was cross-sectional designs (n=15), whereas 3 studies were case-controls and 4 studies used a nested case-controls. The large majority of the studies was conducted in America (n=15, 65%) whereas 7 studies where Europeans and only one Asian. Here, we did not observe large clusters of publications coming from large, well-known studies in the field, such as the AHS. Only three study assessed occupational exposures the rest examined environmental exposures (n=19) or both (n=1). In addition, the presence of studies with information on biomarkers of exposure was limited to 9 studies, whereas 10 studies included information both on questionnaire and biomarkers. The different outcome categories examined are presented in Table 22 along with the number of studies contributing to each outcome category. For the pesticides accessed meta-analysis was feasible for DDE and DDT exposure and type 1 diabetes and DDE exposure and type 2 diabetes.

16.1. Type 1 diabetes

Thirteen studies assessed the effect of pesticides on type 1 diabetes (median sample size: 309, IQR: 159-398) and a meta-analysis of ORs was feasible for DDE and DDT exposure. For DDE, 9 studies contributed a median sample size of 202, IQR=142-334. We were not able to include a prospective study that reported a (significant) Incidence Rate Ratio (IRR) of 7.1 and compared the highest vs. the lowest tertile of exposure with DDE. The computed summary OR was 1.90 (95% CI: 1.25-2.86) for the DDE exposure using random effects models. Moderate heterogeneity was observed (I^2=49%). For DDT, 6 studies had available data for synthesis (median sample size: 577, IQR: 272-2163) providing a summary effect of 1.76 (95% CI: 1.20-2.59) with very large heterogeneity observed ((I^2=76%). Main source of heterogeneity is the different exposure levels used for the calculations of the effect estimates. Even though there is evidence from the random effects meta-analysis that an increased risk for type 1 diabetes exists, however the findings should be interpreted with caution due to the heterogeneity that was observed.

16.2. Type 2 diabetes

Four studies were eligible for the assessment of the DDE exposure and risk for type 2 diabetes (median sample size: 471, IQR=292-642). The summary OR derived from those studies was 1.30 (95% CI: 1.13-1.48). No heterogeneity was observed, however the summary results is driven by a case-control study that reported an effect size OR=1.30 (95% CI=1.11-1.52). Even though, there is evidence suggesting that DDE exposure is a risk factor for developing type 2 diabetes, this is based on small studies.

16. 糖尿病

全体として、糖尿病関連影響に対する農薬ばく露の効果を調査した論文は23編（サンプルサイズ中央値：430、IQR 192-1721）で、データ抽出データベースには125の個別の分析結果が掲載されていた。4つの健康関連影響が評価されており、1型糖尿病（n=93、74%）に大きな割合を占めていたのに対し、18の分析では2型糖尿病に焦点が当てられていた。評価されたその他の影響は、前糖尿病（n=10）、妊娠糖尿病（n=2）、その他のグルコース及びインスリン関連影響（n=2）であった。前向きコホート研究は1件のみで、大多数は横断的デザイン（n=15）であったが、3件は症例対照、4件はコホート内症例対照を使用した研究であった。大多数の研究はアメリカで行われており（n=15、65%）、7研究はヨーロッパ人であり、アジア人は1研究のみであった。ここでは、AHSのような分野でよく知られた大規模な研究からの出版物の大規模なクラスターは観察されなかった。3つの研究のみが職業ばく露を評価し、残りは環境ばく露（n=19）またはその両方（n=1）を調査した。さらに、ばく露のバイオマーカーに関する情報がある研究は9件に限られていたが、10件の研究では質問紙とバイオマーカーの両方の情報が含まれていた。調査した異なる影響カテゴリーを、各カテゴリーに寄与した研究の数とともに表 22 に示す。DDE と DDT ばく露と 1 型糖尿病、DDE ばく露と 2 型糖尿病についてはメタアナリシスが可能であった。

16.1. 1型糖尿病

1型糖尿病に対する農薬の影響を評価した研究は 3 件あり（サンプルサイズ中央値 309、IQR：159-398）、DDE と DDT ばく露については OR のメタアナリシスが可能であった。DDEについては、9件の研究がサンプルサイズ中央値202、IQR=142-334であった。我々は、（有意な）罹患率比（IRR）7.1を示し、DDE被曝の最上位層と最下位層を比較した前向き研究を含めることができなかった。計算された要約ORは、ランダム効果モデルを用いたDDEばく露で1.90（95%CI：1.25-2.86）であった。中等度の不均一性が観察された（I2=49%）。DDTに関しては、6件の研究が統合に利用可能なデータを持っていた（サンプルサイズ中央値：577、IQR：27-2-2163）ため、1.76（95%CI：1.20-2.59）の要約効果が得られ、非常に大きな不均一性が観察された（I2=76%）。不均一性の主な原因は、効果推定値の計算に使用された異なるばく露レベルである。ランダム効果メタアナリシスでは、1型糖尿病リスクの増加が存在するというエビデンスがあるとはいえ、観察された不均一性のため、この結果は慎重に解釈されるべきである。

16.2. 2型糖尿病

DDEばく露と2型糖尿病リスクを評価するために4件の研究が対象となった（サンプルサイズ中央値：471、IQR=292-642）。これらの研究から得られた要約ORは1.30（95%CI：1.13-1.48）であった。不均一性は観察されなかったが、要約結果は、効果量OR=1.30（95%CI=1.11-1.52）を報告した症例対照研究に牽引されている。DDEばく露が2型糖尿病発症のリスク因子であることを示唆するエビデンスはあるが、これは小規模な研究に基づくものである。

Table 22: Summary of studies identified per outcome subgroup with more than 4 studies (NA: not available)

Outcome	N studies	Meta-analysis done	Previous meta-analysis result
Type 1 diabetes	13	Yes	NA
Type 2 diabetes	6	Yes	NA
Gestational diabetes	2	No	NA
Insulin/ Glucose tolerance	2	No	NA

表 22：4 研究以上のサブグループごとに確認された研究の概要（NA：利用不可）

影響	研究数	メタアナリシス実施	前回のメタアナリシス結果
1 型糖尿病	13	Yes	NA
2 型糖尿病	6	Yes	NA
妊娠糖尿病	2	No	NA
インスリン・グルコース耐性	2	No	NA

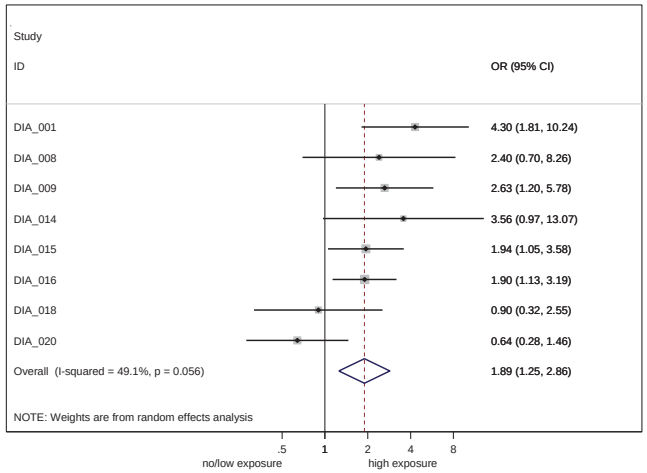


Figure 35: Summary odds ratio (OR) for the association between DDE exposure and type 1 diabetes

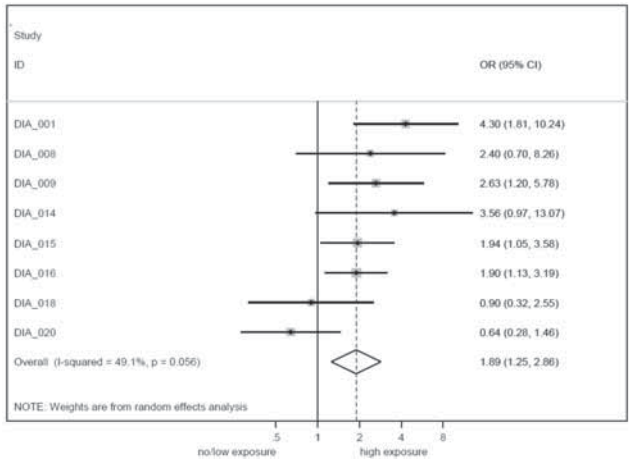


図35：DDEばく露と1型糖尿病との関連のサマリーオッズ比（OR）

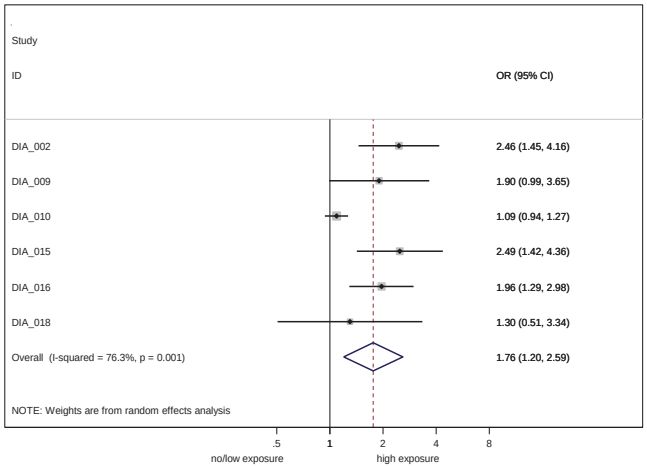


Figure 36: Summary odds ratio (OR) for the association between DDT exposure and type 1 diabetes

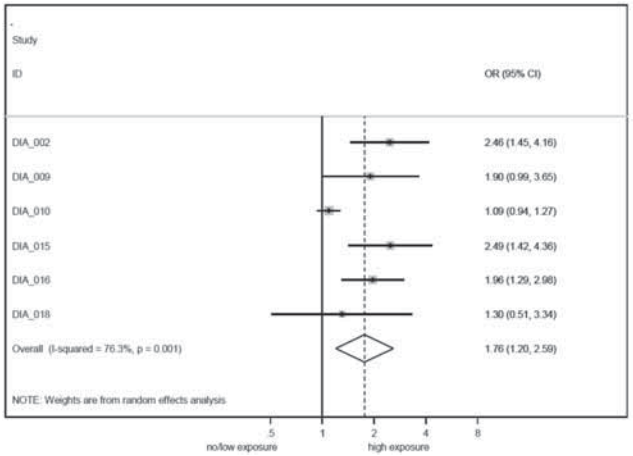


図36：DDTばく露と1型糖尿病との関連のサマリーオッズ比（OR）

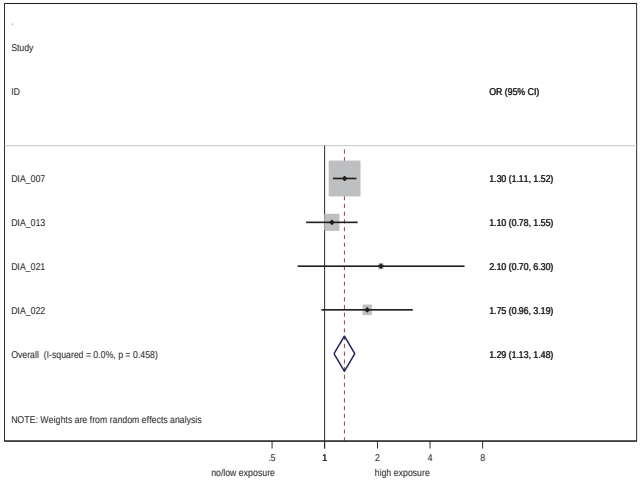


Figure 37: Summary odds ratio (OR) for the association between DDE exposure and type 2 diabetes

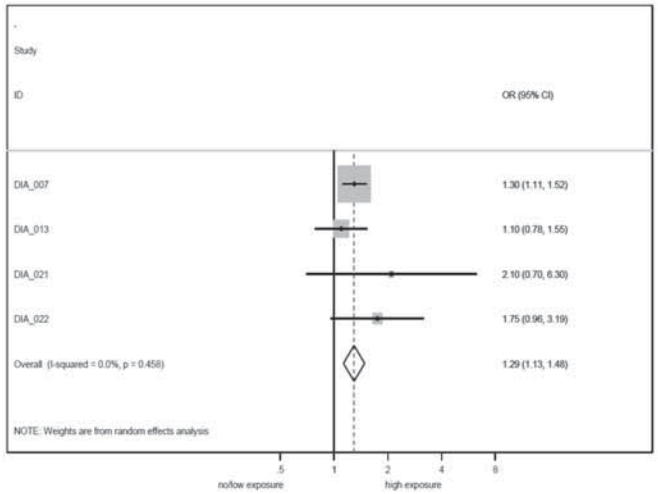


図37：DDEばく露と2型糖尿病との関連のサマリーオッズ比（OR）

17. Cardiovascular diseases

This section includes hard cardiovascular outcomes (myocardial infraction, stroke etc.), cardiovascular risk factors (lipids, blood pressure) and other cardiometabolic outcomes (metabolic syndrome and obesity). No previous meta-analysis has been identified for any of these traits. The evidence collected in this systematic review provides weak suggestions of associations in particular regarding cardiometabolic risk factors and organochlorines; however, other classes of pesticides were not studied and even results on organochlorines were limited and require prospective replication.

17.1. Hard cardiovascular outcomes

Five studies examined hard cardiovascular outcomes including myocardial infarction (ID CVD 005, ID CVD 006), peripheral arterial disease (PAD) (ID CVD 007), stroke (ID CVD 008), and composite cardiovascular disease (ID CVD 009). The Agricultural Health Study (AHS) contributed two prospective analyses (ID CVD 005, ID CVD 006) and National Health and Nutrition Examination Survey (NHANES) other two cross-sectional analyses (ID CVD 007, ID CVD 009). Studies on myocardial infarction (ID CVD 005, ID CVD 006) showed no evidence of an association between having used pesticides, individually or by class, and myocardial infarction mortality among men in the AHS. Similarly, among women of AHS, no overall association with pesticide use and myocardial infarction was seen. Six of 27 individual pesticides evaluated were significantly associated with nonfatal myocardial infarction among women (ID CVD 006), including chlorpyrifos, coumaphos, carbofuran, metalaxyl, pendimethalin, and trifluralin, which all had relatively high odds ratios (>1.7) but also high probability of false positive due to multiple testing.

Another prospective study (8) examined 21 persistent organic pollutants (POPs) in relation to stroke. After adjusting for known stroke risk factors, most polychlorinated biphenyls (PCBs) with 4, 5, or 6 chlorine atoms, p,p′-DDE, trans-nonachlor, and octachlorodibenzo-p-dioxin significantly predicted the risk of stroke. Nonetheless, results need replication from future studies. Peripheral arterial disease (PAD) and composite cardiovascular disease were studied in the cross-sectional NHANES cohort in relation to POPs. Compared with subjects without PAD, those with PAD had significantly higher concentrations of organochlorine pesticides but associations were not seen among non-obese participants. For composite cardiovascular disease, significant associations were observed for chlordane only. These findings need to be carefully interpreted because of the cross-sectional design and use of self-reported cardiovascular disease.

Overall, evidence for associations between pesticide exposure and cardiovascular outcomes is weak and mainly concentrated on organochlorine pesticides.

17.2. Cardiovascular risk factors

17.2.1. Blood pressure

Five studies examined associations between pesticides and blood pressure (ID CVD 002, ID CVD 003, ID CVD 004, ID CVD 010, ID CVD 011). All but one study (ID CVD 011) had cross-sectional

17. 循環器疾患

重篤な心血管影響（心筋梗塞、脳卒中など）、心血管リスク因子（脂質、血圧）、その他の心血管影響（メタボリックシンドローム、肥満）を含む。これらのいずれについても、これまでのメタアナリシスは同定されていない。この系統的レビューで収集されたエビデンスは、特に心血管リスク因子と有機塩素に関する関連を弱く示唆しているが、他のクラスの農薬は研究されておらず、有機塩素に関する結果でさえ限られており、前向き研究の反復が必要である。

17.1. 重篤な心血管影響

心筋梗塞（ID CVD 005、ID CVD 006）、末梢動脈疾患（PAD）（ID CVD 007）、脳卒中（ID CVD 008）、複合心血管疾患（ID CVD 009）を含む5つの研究が重篤な心血管影響を調査した。Agricultural Health Study(AHS)は2つの前向き分析(ID CVD 005、ID CVD 006)、National Health and Nutrition Examination Survey（NHANES）は他の2つの横断分析（ID CVD 007、ID CVD 009）を提供している。心筋梗塞に関する研究（ID CVD 005、ID CVD 006）では、AHSの男性の心筋梗塞死亡率と農薬使用（個人またはクラス別）との関連を示すエビデンスは示されなかった。同様に、AHSの女性では、農薬の使用と心筋梗塞との全体的な関連は認められなかった。評価された27種類の農薬のうち、クロルピリホス、クマホス、カルボフラン、メタラキシル、ペンディメタリン、トリフラリンを含む6種類の農薬が女性の非致死的心筋梗塞と有意に関連し（ID CVD 006）、いずれも比較的高いオッズ比（1.7以上）を示したが、複数回の検査による偽陽性の確率も高かった。

別の前向き研究（8）では、脳卒中との関連で21種類の残留性有機汚染物質（POPs）を調査した。既知の脳卒中リスク因子を調整した後、塩素原子が4、5、または6個のポリ塩化ビフェニル（PCB）、p、p′-DDE、トランスノナクロル及びオクタクロロジベンゾ-p-ジオキシンのほとんどが脳卒中のリスクを有意に予測した。にもかかわらず、結果は今後の研究で再現する必要がある。末梢動脈疾患（PAD）及び複合心血管疾患が、横断的なNHANESコホートでPOPsとの関連で研究された。PADのない被験者と比較して、PADのある被験者では有機塩素系殺虫剤の濃度が有意に高かったが、肥満でない被験者では関連は認められなかった。複合心血管疾患については、クロルデンのみに有意な関連が観察された。横断的なデザインと自己申告による心血管疾患のため、これらの所見は慎重に解釈する必要がある。

全体的に、農薬ばく露と心血管影響との間の関連エビデンスは弱く、主に有機塩素系農薬に集中している。

17.2. 心血管リスク因子

17.2.1. 血圧

5件の研究で農薬と血圧の関連が調査された（ID CVD 002、ID CVD 003、ID CVD 004、ID CVD 010、ID CVD 011）。1件の研究（ID CVD 011）では、横断的な研究が行われていた。

designs. All effect sizes were very small and not suggestive of an association between pesticide exposure and blood pressure.

17.2.2. Metabolic syndrome components

Nine studies examined components of metabolic syndrome in relation to pesticide exposure including lipids levels, glucose and insulin levels. All but one study examined exposure to organochlorine pesticides and significant associations for some classes and lipid levels or glucose levels were observed. Highest quality evidence comes from the prospective Coronary Artery Risk Development in Young Adults (CARDIA) Study (ID CVD 016). In CARDIA, p,p'-DDE most consistently predicted higher triglycerides, and homeostasis model assessment value for insulin resistance (HOMA–IR) and lower High Density Lipoprotein (HDL)-cholesterol at year 20 after adjusting for various confounders. Oxychlordane, trans-nonachlor, and hexachlorobenzene also significantly predicted higher triglycerides. Finally, a case-control study in China, examined differences in glucose regulation in participants highly exposed to pyrethroids (occupational exposure). An indication of increased risk for abnormal glucose regulation was noted for exposure to pyrethroids (OR = 1.48, 95%CI = 1.24–1.77) (ID CVD 021). However, these results need external replication in other populations as the study is retrospective and residual confounding cannot be excluded.

17.2.3. Subclinical atherosclerosis

The population-based Prospective Investigation of the Vasculature in Uppsala Seniors examined in a cross-sectional study, whether POP levels were related to subclinical atherosclerosis. Circulating levels of PCBs were associated with atherosclerotic plaques and echogenicity of the intima-media complex independent of cardiovascular risk factors, but associations need to be confirmed in prospective studies.

17.3. Metabolic syndrome and obesity

Three studies (ID CVD 010, ID CVD 011) examined associations between organochlorine exposure and prevalence of metabolic syndrome. In National Health and Nutrition Examination Survey (NHANES) (ID CVD 010) significant association between organochlorine exposure and prevalence of Metabolic Syndrome was reported with ORs of 1.0, 1.5, 2.3 and 5.3 across organochlorine pesticide quartiles (p for trend <0.01). In the other case-control study (ID CVD 011) significant associations were noted for heptachlor only.

Overall, 12 cross-sectional studies examined associations between pesticide exposure and measures of body fatness or obesity. Also, 10 out of 12 studies examined associations between organochlorines and obesity or body fatness; evidence around other pesticide classes was scarce. Three studies (ID CVD 012, ID CVD 013, ID CVD 014) only presented correlation analysis with measures of body fatness. The remaining studies have shown some significant associations between waist circumference, Body Mass Index (BMI) and organochlorines (DDT and chlordane) but the evidence is limited to cross-sectional analysis and results are only suggestive of an association.

すべての効果量は非常に小さく、農薬ばく露と血圧との関連を示唆するものではなかった。

17.2.2. メタボリックシンドロームの構成要素

9件の研究では、脂質レベル、グルコース、インスリンレベルを含む農薬ばく露に関連したメタボリックシンドロームの構成要素が調査された。1件を除くすべての研究で有機塩素系農薬へのばく露が調査され、いくつかのクラスと脂質レベルまたはグルコースレベルとの有意な関連が観察された。最も質の高いエビデンスは、前向きCARDIA（Coronary Artery Risk Development in Young Adults）研究（ID CVD 016）から得られている。CARDIAでは、様々な交絡因子を調整した後、20年目にp,p'-DDEが最も一貫してトリグリセリド、インスリン抵抗性のホメオスタシスモデル評価値（HOMA-IR）及び高密度リポ蛋白（HDL）コレステロールの低下を予測していた。また、オキシクロルデン、トランスノナクロル、ヘキサクロロベンゼンもトリグリセリドの上昇を有意に予測した。最後に、中国で行われた症例対照研究では、ピレスロイド（職業ばく露）に高度にばく露された参加者のグルコース調節の違いが調査された。その結果、ピレスロイドにばく露されると異常なグルコース調節のリスクが高まることが示された（OR = 1.48、95%CI = 1.24-1.77）（ID CVD 021）。しかし、この研究は後ろ向きであり、残留交絡因子を除外できないため、これらの結果は他の集団で外部で再現の必要がある。

17.2.3. 無症候性アテローム性動脈硬化症

集団ベースの Prospective Investigation of the Vasculature in Uppsala Seniors（ウプサラ高齢者の血管系に関する前向き調査）では、POPのレベルが無症候性アテローム性動脈硬化症と関連しているかどうかを横断研究で調査した。循環中のPCBレベルは、心血管リスク因子とは無関係に、アテローム性動脈硬化性斑点と内膜複合体の超音波反射性と関連していたが、関連は前向き研究で確認する必要がある。

17.3. メタボリックシンドロームと肥満

3件の研究（ID CVD 010、ID CVD 011）で有機塩素ばく露とメタボリックシンドローム罹患率との関連を調査した。国民健康・栄養調査（NHANES）（ID CVD 010）では、有機塩素系農薬の四分位間のORが1.0、1.5、2.3、5.3であり、有機塩素ばく露とメタボリックシンドロームの罹患率との間に有意な関連が報告された（傾向＜0.01の場合はp）。他の症例対照研究（ID CVD 011）では、ヘプタクロルのみで有意な関連が認められた。

全体として、12件の横断研究で農薬ばく露と体脂肪率または肥満度の測定値との関連が調査された。また、12件中10件の研究では有機塩素系農薬と肥満または体脂肪率との関連が調査されていたが、他のクラスの農薬についてはエビデンスが乏しかった。3件の研究（ID CVD 012、ID CVD 013、ID CVD 014）では、体脂肪率の測定値との相関分析のみが示された。残りの研究では、ウエスト周囲長、体格指数（BMI）、有機塩素系農薬（DDTとクロルデン）との間に何らかの有意な関連が示されているが、エビデンスは横断的な分析に限られており、結果は関連を示唆するものに過ぎない。

18. Mortality

Overall, 11 publications examined the effect of pesticide exposure on mortality (median sample size: 1,986), contributing 318 separate analyses in the *data extraction database*. This section consists of a heterogeneous group of publications, which assessed associations between pesticides and all cause mortality of major mortality outcomes. Despite the fact that these studies were large, they were of modest quality and they are not very informative as they test a wide range of diseases simultaneously without corrections for multiple testing. The results do not show any apparent trend of pesticide exposure with overall mortality.

18. 死亡率

全体では 11 の論文が農薬ばく露の死亡率への影響を調査し（サンプルサイズ中央値：1,986）、データ抽出データベースでは 318 の個別分析が行われた。このセクションは、農薬と主要な死因との関連を評価した異種の出版物群で構成されている。これらの研究は大規模なものであったにもかかわらず、質は中等度であり、多重検定の補正を行わずに種々の疾患を同時に検定しているため、あまり有益ではなかった。結果は、農薬ばく露と死亡との明らかな傾向を示していない。

19. Immune/ Autoimmune diseases

Overall, 10 publications examined the effect of pesticide exposure on immune disorders (median sample size: 196, IQR 81-476), contributing 67 separate analyses in the *data extraction database*. Sixty studies were conducted in America, 3 in Europe and one study was Asian. Various health related outcomes including arthritis, osteoarthritis, rheumatoid arthritis and an extensive list of various antibodies, cytokines etc. as summarized in Table 23. Seven out of the 10 publications referred to prospective cohort studies whereas 2 studies were cross-sectional and only one was case-control. The sample size in the reported analyses was rather small; it ranged between 19 and 532 participants with the largest study being the Carolina Lupus Study. Half of the studies assess occupational exposures and information on biomarkers of exposure was available in 2 studies whereas 4 studies used both biomarkers and questionnaires. As seen with other outcomes, the diversity of the exposure definition and the outcomes assessed are extensive and poses special challenges to data synthesis. No single outcome was assessed in more than two studies therefore synthesis of the data was not feasible for the field of immune disorders.

Table 23: Health outcomes assessed in the field of immune disorders

Health outcome	
Antinuclear antibodies	Interleukin-4 (IL-4)
Arthritis	Interleukin-13 (IL-13)
Complement components C3, C4	Immunologic effects
Eosinophils	Leucocyte counts
Erythrocyte counts	Lymphocyte levels
Glycoproteins	Neutrophils
Hematocrit/Hemoglobin	Natural Killers (NK) cells
Interferon-γ (IFN-γ)	Osteoarthritis
Immunoglobulin 1 (IgG1)	Rheumatoid arthritis
Immunoglobulin 4 (IgG4)	Systematic Lupus
Immunoglobulin M (IgM)	

19. 免疫疾患/自己免疫疾患

全体では、農薬ばく露が免疫障害に及ぼす影響を調査した論文は 10（サンプルサイズ中央値 196、IQR 81-476）で、データ抽出データベースでは 67 の個別の分析が行われた。60の研究はアメリカで実施され、3つの研究はヨーロッパで実施され、1つの研究はアジアで実施された。関節炎、変形性関節炎、関節リウマチ、様々な抗体、サイトカインなどの広範なリストを含む様々な健康関連影響が表 23 にまとめられている。10の出版物のうち7つは前向きコホート研究に言及していたが、2つの研究は横断的であり、1つだけが症例対照であった。報告されている分析のサンプル数はかなり少なく、19～532人で、最大の研究はCarolina Lupus Studyであった。研究の半分は職業ばく露を評価しており、ばく露のバイオマーカーに関する情報は2つの研究で得られたが、4つの研究ではバイオマーカーと質問紙の両方を使用していた。他の影響に見られるように、ばく露の定義と評価された影響はまちまちであり、データ統合に特別な問題をもたらしている。2件以上の研究で単一の影響が評価されたものはなく、免疫障害の分野ではデータの統合は不可能であった。

表 23：免疫障害の分野で評価された健康影響

健康影響	
抗核抗体	インターロイキン-4（IL-4
関節炎	インターロイキン１３（ＩＬ-１３
補体成分 C3、C4	免疫学的効果
好酸球	白血球数
赤血球数	リンパ球レベル
糖タンパク質	好中球
ヘマトクリット/ヘモグロビン	ナチュラルキラー（NK）細胞
インターフェロンγ	変形性関節症
免疫グロブリン１（IgG1）	関節リウマチ
免疫グロブリン４（IgG4）	全身性エリテマトーデス
免疫グロブリンＭ（IgM）	

20. Allergic diseases

Nine studies from eight different populations reported associations between pesticide exposure and allergic disorders. Seven studies examined occupational exposure whereas two studies examined environmental exposure. Eight studies were cross-sectional investigations and therefore conclusions are prone to reverse causality and other biases. In terms of outcomes examined, five studies examined self-reported allergic rhinitis, one examined self-reported asthma and the remaining 3 examined self-reported skin irritation, contact dermatitis, food allergy, hay fever and fragrance allergies. Statistically significant results were reported by four studies on allergic rhinitis (ID ALL_003, ID ALL_004, ID ALL_005, ID ALL_006). These studies reported significant association between various pesticide classes and allergic rhinitis. In particular, the Agricultural Health Study (AHS) reported significant association between allergic rhinitis and exposure to the herbicides 2,4-Dichlorophenoxyacetic acid (2,4-D) glyphosate and petroleum oil, the insecticide diazinon and the fungicide benomyl. However, the study has many limitations and results need cautious interpretation and require replication by future prospective studies. The study is limited by its ability to distinguish allergic from non-allergic symptoms of rhinitis and to establish temporality between exposure and symptoms due to its cross-sectional design. One study with low overall quality reported high effect sizes (OR, 12.50; 95% CI, 2.00-78.05) for allergic rhinitis in greenhouse flower and ornamental plant growers with pesticide application by hand pump vs. without (ID ALL_006). Again, the study has low overall quality, concerns a heavily exposed population with definition of exposure related to the method of application rather than a chemical class. Overall, the evidence around allergic disorders and pesticide exposure is weak.

20. アレルギー疾患

8つの異なる集団における9つの研究が、農薬ばく露とアレルギー性障害との関連を報告した。7件の研究では職業ばく露が調査され、2件の研究では環境ばく露が調査された。8件の研究は横断的な調査であったため、結論は逆因果関係やその他のバイアスがかかりやすい。結果については、5件の研究が自己申告によるアレルギー性鼻炎、1件の研究が自己申告による喘息、残りの3件の研究が自己申告による皮膚刺激、接触性皮膚炎、食物アレルギー、花粉症、香料アレルギーを調査した。アレルギー性鼻炎に関する4件の研究（ID ALL_003、ID ALL_004、ID ALL_005、ID ALL_006）で統計学的に有意な結果が報告された。これらの研究では、様々な農薬クラスとアレルギー性鼻炎との間に有意な関連が報告されている。特に、Agricultural Health Study（AHS）では、アレルギー性鼻炎と除草剤である2,4-ジクロロフェノキシ酢酸（2,4-D）グリホサート及び石油油、殺虫剤であるジアジノン及び殺菌剤であるベノミルへのばく露との間に有意な関連が報告されている。しかし、この研究には多くの限界があり、結果は慎重な解釈が必要であり、将来の前向き研究での再現が必要である。この研究は、アレルギー性鼻炎と非アレルギー性鼻炎の症状を区別できているか、また、横断的なデザインのためにばく露と症状の間の時系列を示せるかという点で制限されている。全体的に質の低い1件の研究では、温室内の花卉及び観賞用植物の栽培者におけるアレルギー性鼻炎について、手押しポンプによる農薬散布と農薬散布なしの比較で高い効果量（OR、12.50；95%CI、2.00-78.05）が報告されている（ID ALL_006）。ここでも、この研究は全体的に質が低く、化学物質の種類ではなく散布方法に関連して定義された高濃度ばく露集団に関係している。全体的に、アレルギー性障害と農薬ばく露に関するエビデンスは弱い。

21. Haematological diseases

21.1. Aplastic anaemia

Three studies examined associations between pesticide exposure and aplastic anaemia; a rare hematologic condition. All studies were case-control designs and had small sample sizes (range 9-310). Two studies reported significant associations with large effect sizes but it is difficult to draw firm conclusions due to the small number of studies available and the limitations of these studies (Table 24). The other case control study (ID APL_002) did not report effect sizes but only the p value of association, which was non-significant. Further evidence is required to throw light into these suggestive results.

Table 24: Summary of results between pesticide exposure and aplastic anemia in 2 case-control studies that reported effect sizes

Study ID	Pesticide assessed	Comparison	OR	Lower 95% CI	Higher 95% CI	N cases	N controls
APL_001	Organophosphates	yes/no	2.1	1.1	4.2	21	32
APL_001	DDT	yes/no	6.7	1.5	30	5	4
APL_001	Carbamates	yes/no	7.4	1.7	31	8	3
APL_001	Paraquat	yes/no	2.3	1	5.1	12	24
APL_001	Other occupational pesticides	yes/no	1	0.4	2.2	11	32
APL_001	Any household pesticides	yes/no	1.3	0.9	1.9	64	238
APL_001	Organophosphates	yes/no	2.1	1	4.4	17	26
APL_001	Paraquat	yes/no	1.9	0.7	4.9	7	20
APL_001	Other occupational pesticides	yes/no	1.1	0.4	2.7	9	24
APL_003	Agricultural use of pesticides	yes/no	2.2	1.1	4.7	12	23
APL_003	Home use of pesticides	yes/no	1.3	0.9	1.9	70	240
APL_003	Organophosphorates	highest tertile of exposure/no exposure	3	0.9	10.1	5	7
APL_003	Pyrenthroids	highest tertile of exposure/no exposure	1.8	1	3.1	23	57
APL_003	Herbicides	yes/no	2.4	0.9	6	8	15

21.2. Haematological and biochemical alterations

Fourteen studies examined various haematological and biochemical alterations in relation to pesticide exposure. Main alterations studied were basic haematology and vitamin levels. The sample size ranged between 51 and 1,275. The quality of these studies was modest to low. Most studies reported unadjusted correlation statistics or means between haematological parameters and pesticide exposure and no effect sizes beyond the p values were reported. All studies provided cross-sectional evidence. Despite the fact than many of the reported analyses were statistically significant, results should not be interpreted at this stage due the limited evidence and modest quality associated with these data.

21. 血液疾患

21.1. 再生不良性貧血

3件の研究では、農薬ばく露と再生不良性貧血（まれな血液疾患）との関連が調査された。すべての研究は症例対照デザインであり、サンプルサイズは小さい（9～310の範囲）。2件の研究では、大きな効果量で有意な関連が報告されたが、利用可能な研究の数が少ないことと、これらの研究の限界があるため、確実な結論を出すことは難しい（表24）。もう1件の症例対照研究（ID APL_002）では、効果量は報告されていないが、関連のp値のみが報告されており、有意ではなかった。これらの示唆に富む結果を明らかにするためには、さらなるエビデンスが必要である。

表 24：効果量を報告した 2 つの症例対照研究における農薬ばく露と再生不良性貧血の結果のまとめ

Study ID	調査した農薬	比較	OR	下位 95% CI	上位 95% CI	ケース数	コントロール数
APL_001	有機リン剤	yes/no	2.1	1.1	4.2	21	32
APL_001	DDT	yes/no	6.7	1.5	30	5	4
APL_001	カーバメート	yes/no	7.4	1.7	31	8	3
APL_001	パラコート	yes/no	2.3	1	5.1	12	24
APL_001	職業的ばく露の農薬	yes/no	1	0.4	2.2	11	32
APL_001	住居用農薬	yes/no	1.3	0.9	1.9	64	238
APL_001	有機リン剤	yes/no	2.1	1	4.4	17	26
APL_001	パラコート	yes/no	1.9	0.7	4.9	7	20
APL_001	職業的ばく露の農薬	yes/no	1.1	0.4	2.7	9	24
APL_003	農業用農薬	yes/no	2.2	1.1	4.7	12	23
APL_003	住居用農薬	yes/no	1.3	0.9	1.9	70	240
APL_003	有機リン剤	高濃度ばく露／ばく露なし	3	0.9	10.1	5	7
APL_003	ピレスロイド	高濃度ばく露／ばく露なし	1.8	1	3.1	23	57
APL_003	除草剤	yes/no	2.4	0.9	6	8	15

21.2. 血液学的及び生化学的変化

14の研究では、農薬ばく露に関連した様々な血液学的及び生化学的変化を調べた。主に一般血液検査とビタミンレベルであった。サンプル数は51～1,275人であった。これらの研究の質は中等度から低度であった。ほとんどの研究では、血液学的パラメータと農薬ばく露との間の無補正相関統計値または平均値が報告されており、p値以外に効果量は報告されていない。すべての研究は横断的なエビデンスを提供している。報告された分析の多くが統計的に有意であったにもかかわらず、これらのデータに関連するエビデンスが限られており、質も中等度であるため、現段階では結果を解釈すべきではない。

22. Other outcomes

Overall, 30 publications examined the effect of pesticide exposure on other outcomes. Based on our criteria for data synthesis no meta-analysis was performed for those outcomes.

22.1. Bone diseases

Three studies examined the effect of pesticide exposure on osteoporosis including 13 different analyses. We identified two European cross-sectional studies and one Asian cohort (median sample size: 176, IQR: 153-908). All studies assess environmental exposure with information on biomarkers of exposure and all studies examined exposure to organochlorines only. Osteoporosis was assessed via ultrasound measurements and bone mineral density. The largest study of 908 women showed that p,p'-DDE was positively associated with bone mineral density, the association remained after adjustment for confounders, but the effect was weak.

22.2. Skin diseases

Six studies examined the effect of pesticide exposure on skin lesion (median sample size: 356, IQR 262-2203) including 11 analyses. Four studies used cross-sectional design. Environmental exposure was assessed in 3 studies. The definition of outcome was often skin rash or eczema. The resulst were largely not statistical significant. One prospective study (ID SKD 004) on 5,042 men from the Health Effects of Arsenic Longitudinal Study in Araihazar reported highly significant effect sizes for skin lesions and pesticide use but study also evaluated arsenic exposure and it is difficult to differentiate between the effect of each exposure.

22.3. Dental diseases

One study cross-sectional study from America including 496 participants assessed two outcomes. The study assessed environmental exposure with information of biomarkers (ID PER 001). In this study, organochlorine (OC) pesticides were strongly associated with periodontal disease.

22.4. Metabolic diseases

One European cross-sectional study assessed the effect of pesticides on metabolic diseases and specifically on levels of various prorfyrins including 8 analyses but no significant results were reported. Environmental exposure was studied using biomarkers for the assessment of exposure.

22.5. Men health

One case-control study reported association between pesticide exposure and erectile dysfunction. The study focused on organochlorine pesticides and compared 101 cases with erectile dysfunction to 234 comparable control subjects. The results were no statistically significant and do not provide evidence of an association.

22. その他の影響

全体では 30 の論文がその他の影響に対する農薬ばく露の効果を調査した。データ統合のための我々の基準に基づき、これらの影響に対するメタアナリシスは実施されなかった。

21.1. 骨疾患

農薬ばく露が骨粗鬆症に及ぼす影響を調査した研究は3件あり、13の異なる分析を行った。我々は2つのヨーロッパの横断研究と1つのアジアのコホート研究を同定した（サンプルサイズ中央値：176、IQR：153-908）。すべての研究は、ばく露のバイオマーカーに関する情報とともに環境ばく露を評価しており、すべての研究は有機塩素へのばく露のみを調査している。骨粗鬆症は超音波測定と骨密度によって評価された。908名の女性を対象とした最大の研究では、p,p'-DDEが骨密度と明確な関連を示し、交絡因子を調整した後も関連は維持されたが、効果は弱いことが示された。

22.2. 皮膚疾患

11件の分析のうち農薬ばく露が皮膚病変に及ぼす影響を調査した研究は6件（サンプルサイズ中央値356、IQR 26-2203）であった。4件の研究では横断的デザインが用いられていた。環境ばく露は3件の研究で評価された。影響の定義は多くの場合、発疹や湿疹であった。結果はほとんど統計的に有意ではなかった。1つの前向き研究（ID SKD 004）では、男性5,042人を対象としたAraihazarのヒ素の健康影響縦断研究から、皮膚病変と農薬使用について非常に有意な効果量が報告されているが、この研究ではヒ素ばく露も評価されており、それぞれのばく露の効果を区別することは困難であった。

22.3. 歯科疾患

アメリカで行われた1つの横断研究では、496人の参加者が2つの影響で評価された。この研究では、バイオマーカー（ID PER 001）の情報を用いて環境ばく露を評価した。この研究では、有機塩素系（OC）農薬は歯周病と強く関連していた。

22.4. 代謝性疾患

ヨーロッパで行われた横断研究では、農薬が代謝性疾患、特に様々なprorfyrins（誤植？）のレベルに及ぼす影響を評価し、8つの分析を行ったが、有意な結果は報告されていない。環境ばく露は、ばく露評価のためのバイオマーカーを用いて研究された。

22.5. 男性機能疾患

1件の症例対照研究では、農薬ばく露と勃起不全との関連が報告されている。この研究では有機塩素系農薬に焦点を当て、勃起不全の症例101例を234例の同等の対照群と比較した。結果は統計的に有意ではなく、関連を示すエビデンスとはならなかった。

22.6. Gynaecological diseases

In this group we included gynaecological outcomes not included in the previous outcome categories. Four studies are included in this group, three examined endometriosis and one the timing of menopause. The three studies on endometriosis (ID GYN 001, ID GYN 002, ID GYN 003) were all cross-sectional and all examined organochlorines. One out of 12 separate analyses on endometriosis and organochlorines was statistically significant; the highest tertile of aromatic fungicide was associated with a fivefold risk of endometriosis (OR = 5.3; 95% CI, 1.2–23.6) compared to the lowest tertile. This effect size is large and requires independent replication in other prospective studies.

Data from the Agricultural Health Study (AHS) was used to study associations between exposure to pesticides and age at menopause in a prospective investigation of pre-menopausal women. After control for age, smoking status, and past use of oral contraceptives, the median time to menopause increased by approximately 3 months for women who used pesticides (HR 0.87, 95% CI: 0.78, 0.97) and by approximately 5 months for women who used hormonally active pesticides (HR 0.77, 95% CI: 0.65, 0.92). Pesticide use may be associated with a later age at menopause based on these results; however results are prone to false positive bias and independent replication is needed.

22.7. Symptoms and general health

Five studies examined general health symptoms such as nausea, fatigue, dizziness, and shortness of breath. The definition of these outcomes is very hard and associated with large measurement errors. Studies were of modest to low quality and all concerned occupational exposures. Some statistically significant results were observed but are far form conclusive at this stage due to heterogeneity of data reported and the limitations associated with these studies.

22.8. Kidney diseases

Three studies examined kidney diseases including chronic kidney disease and gallstone disease. One study reported statistically significant results between DDE and DDT residues and gallstone disease.

22.9. Benign tumours

One a population-based case-control study on acoustic neuroma found no link between pesticide exposure and acoustic neuroma.

22.10. Gastrointestinal diseases

Seven studies examining associations between pesticide exposure and liver enzymes were identified. All studies were cross-sectional or case-control. One study, the National Health and Nutrition Examination Survey (NHANES), examined organochlorines, another one examined exposure to 2,4-dichlorophenoxyacetic acid (2,4-D) and paraquat and the remaining studies examined broadly defined pesticide categories. The studies were of modest and low quality and presented only the means of enzymes in exposed and unexposed participants often without adjustments. Almost all studies reported statistically significant results with higher level of liver enzymes (e.g. Gamma-glutamyltransferase (GGT), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)) in participants exposed to pesticides. However, due to the low quality of the data and the limited number of studies firm conclusions cannot be drawn and data is only suggestive of associations at this stage.

22.6. 婦人科疾患

このグループには、上述の影響カテゴリーには含まれていない婦人科学的影響が含まれている。このグループには4件の研究が含まれており、3件は子宮内膜症、1件は閉経のタイミングを調査した。子宮内膜症に関する3件の研究（ID GYN 001、ID GYN 002、ID GYN 003）はすべて横断的であり、すべて有機塩素を調査していた。子宮内膜症と有機塩素に関する12の個別分析のうち1つは統計学的に有意であった；芳香族系殺菌剤の上位3位までは、下位3位までと比較して子宮内膜症のリスクが5倍（OR = 5.3；95%CI、1.2-23.6）であった。この効果量は大きく、他の前向き研究で独立した再現が必要である。

農業健康調査（Agricultural Health Study：AHS）のデータを用いて、閉経前の女性を対象とした前向き調査において、農薬へのばく露と閉経時年齢との関連を調査した。年齢、喫煙状況、経口避妊薬の過去の使用状況をコントロールした後、閉経までの期間の中央値は、農薬を使用した女性では約3ヵ月（HR 0.87、95%CI：0.78、0.97）、ホルモン活性農薬を使用した女性では約5ヵ月（HR 0.77、95%CI：0.65、0.92）増加した。農薬の使用は、これらの結果に基づいて、閉経年齢の遅延と関連している可能性がある。しかしながら、結果は偽陽性バイアスがかかりやすく、独立した再現が必要である。

22.7. 症状及び一般的な疾患

吐き気、倦怠感、めまい、息切れなどの一般的な疾患を5つの研究で調査した。これらの結果の定義は非常に難しく、大きな測定誤差と関連している。研究の質は中等度から低度で、すべての研究が職業ばく露に関係していた。いくつかの統計的に有意な結果が観察されたが、報告されたデータの不均一性とこれらの研究に関連する限界のため、現段階では決定的な結論には程遠い。

22.8. 腎臓疾患

3つの研究では、慢性腎臓病や結石疾患などの腎臓病を調査した。1件の研究では、DDE及びDDT残留農薬と結石疾患との間に統計的に有意な結果が報告された。

22.9. 良性腫瘍

聴神経腫瘍に関する集団ベースの症例対照研究では、農薬ばく露と聴神経腫瘍との関連は認められなかった。

22.10. 消化器疾患

農薬ばく露と肝臓酵素との関連を調査した 7 件の研究が同定された。すべての研究は横断的または症例対照であった。1件の研究、国民健康・栄養調査（NHANES）では有機塩素について、もう1件の研究では2,4-ジクロロフェノキシ酢酸（2,4-D）とパラコートへのばく露について、残りの研究では広く定義された農薬のカテゴリーについて調査が行われた。これらの研究は限られた規模で質が低く、多くの場合調整なしで、被ばく露者と非ばく露者の酵素の平均値のみが提示されていた。ほとんどすべての研究で、農薬にばく露された参加者の肝臓酵素（例：γ-グルタミルトランスフェラーゼ（GGT）、アラニンアミノトランスフェラーゼ（ALT）、アスパラギン酸アミノトランスフェラーゼ（AST））のレベルが高いほど、統計的に有意な結果が報告されている。しかし、データの質の低さと研究の数が限られているため、しっかりとした結論を出すことはできず、データは現段階では関連をほのめかすだけである。

CONCLUSIONS

After an exhaustive and comprehensive search of almost 46,000 scientific publications we identified 602 publications, which examine epidemiologic associations between pesticide exposure and diverse health outcomes. The entire spectrum of health outcomes related to pesticide exposure has not been studied before. Our results show a very wide spectrum including 24 major disease categories. Few environmental exposures have been associated with such a wide range of outcomes. The most prevalent outcomes are cancers and mother and child health outcomes. But other disease categories have received considerable attention such as neurological conditions and reproductive diseases. Despite the large volume of available data and the large number (>6,000) of analyses available, firm conclusions cannot be made for the majority of the outcomes studied. This observation is disappointing especially when one accounts for the large volume of research in the area. However, this observation is in line with previous studies on environmental epidemiology and in particular on pesticides which all acknowledge that such epidemiological studies suffer from many limitations and that the heterogeneity of data is such that does not allows firm conclusions to de made.

The range of categories of pesticide studied is wide but studies very often concentrate on a broadly defined pesticide category, and it is hard to understand which pesticide the population is exposed to. Studies often examine pesticides that have already been banned in western populations and the European Union. The use of biomarkers as means of exposure assessment is infrequent but still available in almost half of the studies. In addition, cohort studies represent a minority of this literature with case control and cross-sectional studies representing an approximately equal proportion of eligible articles. Case-control and cross-sectional evidence does not allow the study of temporal relations and thus are unable to provide support regarding the causality of associations. The assessment of exposure is perhaps the most important methodological limitation of the studies. Studies used different methods for exposure assessment and assignment. Most studies were based on self-reported exposure to pesticides, defined as ever versus never use or as regular versus non-regular use. Such methods suffer from high misclassification rates and especially in the case of retrospective studies where misclassification would be differential with higher exposures reported in participants with disease (recall bias). Above all, such questionnaires might be capable of differentiating subjects with very high and very low exposure levels but are not capable of valid exposure classification across an exposure gradient thus not allowing the study of dose-response relationships. Also, the accuracy of exposure might be high for broad categories of pesticides and commonly used pesticides, but not for specific pesticides. It is important that questionnaires used for exposure assessment are validated. However, studies largely used “home- made” versions of questionnaires, sometimes not giving the information on the actual questions used to assess exposure. In addition, exposure simultaneously in multiple agents is common which may introduce further bias in the results. For example, occupational exposure to pesticides is likely to coexist with exposure to benzene, heavy metals, solvents, suspended particulate matter etc. all of which have adverse health outcomes. It is essential to account for confounding from exposure to multiple agents in order to delineate true associations but this has not been possible in the overwhelming majority of evidence assessed herein.
In addition, the evidence collected and appraised herein is likely to suffer from selective reporting and multiple testing. The studies reported a very wide range of analyses; 602 publications resulted in 6000 analyses. The amount of multiple hypothesis testing is enormous. These analyses need to be adjusted for multiple hypothesis testing else the results suffer from high false positive rate. Even when studies present only one analysis, selective reporting is always a possibility as has been shown in other epidemiological fields as well. In addition, when interpreting results one should also take into account that, especially for certain outcomes (e.g. cancers), the majority of evidence comes from single study populations and the AHS in particular.

結論

約46,000の科学出版物を網羅的かつ包括的に検索した結果、602の出版物を確認した。農薬ばく露に関連した健康影響の全領域については、これまでにも研究されたことがなかった。我々の結果は、24の主要な疾患カテゴリーを含む非常に幅広いスペクトルを示している。これほど広範囲の影響と関連した環境ばく露はこれまでほとんどなかった。最も一般的な影響は、がんと母子の健康影響である。しかし、神経疾患や生殖器疾患など、他の疾患カテゴリーにも注目が集まっている。利用可能なデータが大量にあり、利用可能な分析の数が多い（6,000件以上）にもかかわらず、研究された影響の大部分について確固たる結論を出すことはできない。この調査は、この分野の研究量の多さを考慮すると、特に残念な結果となった。しかし、この調査は環境疫学、特に農薬に関するこれまでの研究と一致しており、疫学研究には多くの限界があり、データの不均一性から確固たる結論を出すことができないことを認めている。

研究されている農薬のカテゴリーの範囲は広いが、研究は多くの場合、広く定義された農薬のカテゴリーに集中しており、集団がどの農薬にばく露されているかを理解するのは難しい。研究では、欧米の集団や欧州連合ですでに禁止されている農薬を調査することが多い。ばく露評価の手段としてバイオマーカーを使用することはほとんどないが、ほぼ半数の研究ではまだ使用可能である。さらに、コホート研究はこの文献の中では少数派であり、症例対照研究と横断研究が対象となる論文のほぼ同じ割合を占めている。症例対照研究や横断研究では、時間的関係を研究することができないため、関連の因果関係に関する裏付けを提供することができない。ばく露の評価は、おそらくこれらの研究の最も重要な方法論的限界である。研究では、ばく露の評価と割り付けに異なる方法が用いられていた。ほとんどの研究では、農薬へのばく露を、使用したことがあるかないか、あるいは定期的に使用したことがあるかないかという自己申告に基づいていた。このような方法は、高い誤分類率に悩まされ、特に後ろ向き研究の場合には、病気のある参加者で報告されたばく露量が多いほど誤分類に差が出てしまう（リコールバイアス）。とりわけ、このような質問紙は、非常に高いばく露量の被験者と非常に低いばく露量の被験者を区別することができるかもしれないが、ばく露の段階にわたって有効なばく露分類ができないため、用量反応関係の研究を行うことができない。また、幅広いカテゴリーの農薬や一般的に使用されている農薬ではばく露の精度が高いかもしれないが、特定の農薬ではそうではない。ばく露評価に使用される質問紙の妥当性が確認されていることが重要である。しかし、研究では、ほとんどの場合、質問紙の「自己流」バージョンが使用されており、ばく露評価に使用された実際の質問紙に関する情報が得られないことがある。さらに、複数の物質への同時ばく露は一般的であり、結果にさらなる偏りが生じる可能性がある。例えば、農薬への職業ばく露は、ベンゼン、重金属、溶剤、浮遊粒子状物質などへのばく露と共存している可能性が高い。真の関連を明らかにするためには、複数の物質へのばく露による交絡を考慮することが不可欠であるが、ここで評価されたエビデンスの圧倒的多数では、これは不可能であった。

さらに、ここで収集されて評価されたエビデンスは、選択的な報告と多重検定に悩まされている可能性が高い。研究は非常に広範囲の分析を報告しており、602件の論文で6000件の分析が行われていた。多重仮説検定の量は膨大である。これらの分析は多重仮説検定のために調整する必要があり、そうしないと結果は高い偽陽性率に悩まされることになる。研究が1つの分析しか行われていない場合でも、他の疫学分野でも示されているように、選択的な報告が行われる可能性は常にある。さらに、結果を解釈する際には、特に特定の影響（がんなど）については、エビデンスの大部分が単一の研究集団と特に

Beyond definition of exposure, the definition of clinical outcomes displayed large variability in eligible epidemiological studies, which can further cause the variability in results. Perhaps most important in this setting is the use of surrogate outcomes examined. Here we observed a great number of surrogate outcomes. Surrogate outcomes are biomarkers or physical measures that are generally accepted as substitutes for or predictors of specific clinical outcomes. However, many times these surrogate outcomes are unvalidated and do not meet the strict definitions of surrogate outcomes. Such outcomes can be defined as possible predictors of clinical outcomes but do not fulfil the criteria for a surrogate outcome. It is essential that the evidence around unvalidated surrogate outcomes are appraised taking into account the implicit assumptions of unvalidated surrogate outcomes.

Acknowledging these limitations we attempted to summarise the evidence retrieved in this report. An added important limitation here is the fact that this review is limited to publications after 2006. This allows us only to review recent evidence and any meta-analysis needs very cautious interpretation, as it does not include all available evidence. Results might be biased if data published after 2006 are different from earlier evidence. To this end, we also provided updated meta-analysis for major outcomes and for those that a relevant meta-analysis published after 2006 was identified. This has only been possible for childhood leukaemia and for Parkinson's disease. For both these outcomes we found significant associations between pesticide exposure and disease in line with previous evidence. Significant summary estimates have also been reported for other outcomes as summarised in Table 25 below. However, as they represent studies form 2006 onwards results should be regarded as suggestive of associations only and limitations especially regarding the heterogeneity of exposure should always been take into consideration.

AHSから得られていることも考慮に入れるべきである。

ばく露の定義以外に、臨床所見の定義は妥当な疫学研究においても大きなばらつきを示しており、これが結果のばらつきの原因となっている。おそらく、このような状況で最も重要なのは、調査された代替健康影響の使用であろう。ここでは非常に多くの代替健康影響が観察された。代替健康影響とは、特定の臨床所見の代用または予測因子として一般的に受け入れられているバイオマーカーまたは身体測定値である。しかし、多くの場合、これらの代替健康影響は検証されておらず、代替健康影響の厳密な定義を満たしていない。このような影響は、臨床所見の予測因子として定義される可能性はあるが、代替健康影響の基準を満たしていない。検証されていない代替健康影響に関するエビデンスは、検証されていない代替健康影響の暗黙の想定を考慮に入れて評価されることが不可欠である。

これらの限界を認識した上で、我々は本報告書で検索されたエビデンスを要約することを試みた。ここで追加された重要な制限は、このレビューが2006年以降の出版物に限定されているという事実である。これにより、最近のエビデンスのみをレビューすることが可能となり、メタアナリシスは利用可能なすべてのエビデンスを含んでいるわけではないため、非常に慎重な解釈が必要となる。2006年以降に発表されたデータがそれ以前のエビデンスと異なる場合、結果に偏りが生じる可能性がある。この目的のために、主要な影響及び2006年以降に発表された関連するメタアナリシスが確認されたものについては、更新されたメタアナリシスも提供した。これは小児白血病とパーキンソン病についてのみ可能である。これらの影響については、以前のエビデンスに沿って、農薬ばく露と疾患との間に有意な関連があることがわかった。有意な要約推定値は他の影響についても報告されており、以下の表25にまとめられている。しかし、これらは2006年以降の研究であるため、結果はあくまでも関連を示唆するものであり、特にばく露の不均一性に関する限界を常に考慮に入れるべきである。

Table 25: Summary of meta-analyses performed in this report

Health outcome	*N* studies	Meta-analysis result	I^2
Leukemia	6	1.26 (0.93,1.71)	59.4%
Hodgkin's Lymphoma	7	1.29 (0.81, 2.06)	81.6%
Childhood Leukemia (exposure to pesticides during pregnancy)	6	1.67 (1.25, 2.23)	81.2%
Childhood Leukemia (exposure to insecticides during pregnancy)	5	1.55 (1.14, 2.11)	65%
Childhood Leukemia (exposure to insecticides during pregnancy-update Turner 2010)	9	1.69 (1.35, 2.11)	49.8%
Childhood Leukemia (exposure to unspecified pesticides during pregnancy)	5	2.00 (1.73, 2.30)	39.6%
Childhood Leukemia (exposure to unspecified pesticides during pregnancy-update Turner 2010)	11	1.30 (1.09, 1.56)	26.5%
Childhood Leukemia (exposure to pesticides during childhood)	7	1.27 (0.96, 1.69)	61.1%
Childhood Leukemia (exposure to insecticides during childhood-update Turner 2010)	8	1.51 (1.28, 1.78)	0%
Childhood Leukemia (exposure to unspecified pesticides during childhood-update Turner 2010)	11	1.36 (1.19, 1.55)	0%
Breast Cancer (DDE exposure)	5	1.13 (0.81, 1.57)	0%
Breast Cancer	11	1.24 (1.08, 1.43)	0%
Testicular Cancer (DDE exposure)	5	1.40 (0.82, 2.39)	59.5%
Stomach Cancer	6	1.79 (1.30, 2.47)	0%
Liver Cancer	5	2.50 (1.57, 3.98)	25.4%
Cryptorchidism	8	1.19 (0.96, 1.49)	23.9%
Cryptorchidism (DDT exposure)	4	1.47 (0.98, 2.20)	51%
Hypospadias (general pesticide exposure)	6	1.01 (0.74, 1.39)	71.5%
Hypospadias (exposure to specific pesticides)	9	1 (0.84, 1.18)	65.9%
Abortion	6	1.52 (1.09, 2.13)	63.1%
Parkinson's disease	26	1.49 (1.28, 1.73)	54.6%
Parkinson's disease (DDT exposure)	5	1.01 (0.78, 1.30)	0%
Parkinson's disease (paraquat exposure)	9	1.32 (1.09, 1.60)	34.1%
Amyotrophic Lateral Sclerosis	6	1.58 (1.31, 1.90)	10%
Asthma (DDT exposure)	5	1.29 (1.14, 1.45)	0%
Asthma (paraquat exposure)	6	1.40 (0.95, 2.06)	53.3%
Asthma (chlorpyrifos exposure)	5	1.03 (0.82, 1.28)	0%
Type 1 Diabetes (DDE exposure)	8	1.89 (1.25, 2.86)	49%
Type 1 Diabetes (DDT exposure)	6	1.76 (1.20, 2.59)	76.3%
Type 2 Diabetes (DDE exposure)	4	1.29 (1.13, 1.48)	0%

表 25：本報告書で実施されたメタアナリシスの要約

健康影響	研究数	メタアナリシス結果	I^2
白血病	6	1.26（0.93, 1.71）	59.40%
ホジキンリンパ腫	7	1.29（0.81, 2.06）	81.60%
小児白血病（妊娠期の農薬ばく露）	6	1.67（1.25, 2.23）	81.20%
小児白血病（妊娠期の殺虫剤ばく露）	5	1.55（1.14, 2.11）	65%
小児白血病（妊娠期の殺虫剤ばく露-ターナー2010 年に更新）	9	1.69（1.35, 2.11）	49.80%
小児白血病（妊娠期の不特定農薬ばく露）	5	2.00（1.73, 2.30）	39.60%
小児白血病（妊娠期の不特定殺虫剤ばく露-ターナー2010 年に更新）	11	1.30（1.09, 1.56）	26.50%
小児白血病（小児期の農薬ばく露）	7	1.27（0.96, 1.69）	61.10%
小児白血病（小児期の殺虫剤ばく露-ターナー2010 年に更新）	8	1.51（1.28, 1.78）	0%
小児白血病（小児期の不特定殺虫剤ばく露-ターナー2010 年に更新）	11	1.36（1.19, 1.55）	0%
乳がん（DDE ばく露）	5	1.13（0.81, 1.57）	0%
乳がん	11	1.24（1.08, 1.43）	0%
精巣がん（DDE ばく露）	5	1.40（0.82, 2.39）	59.50%
胃がん	6	1.79（1.30, 2.47）	0%
肝臓がん	5	2.50（1.57, 3.98）	25.40%
停留精巣	8	1.19（0.96, 1.49）	23.90%
停留精巣（DDT ばく露）	4	1.47（0.98, 2.20）	51%
尿道下裂（一般的な農薬ばく露）	6	1.01（0.74, 1.39）	71.50%
尿道下裂（特定の農薬ばく露）	9	1（0.84, 1.18）	65.90%
流産	6	1.52（1.09, 2.13）	63.10%
パーキンソン病	26	1.49（1.28, 1.73）	54.60%
パーキンソン病（DDT ばく露）	5	1.01（0.78, 1.30）	0%
パーキンソン病（パラコートばく露）	9	1.32（1.09, 1.60）	34.10%
筋萎縮性側索硬化症	6	1.58（1.31, 1.90）	10%
喘息（DDT ばく露）	5	1.29（1.14, 1.45）	0%
喘息（パラコートばく露）	6	1.40（0.95, 2.06）	53.30%
喘息（クロルピリホスばく露）	5	1.03（0.82, 1.28）	0%
1 型糖尿病（DDE ばく露）	8	1.89（1.25, 2.86）	49%
1 型糖尿病（DDT ばく露）	6	1.76（1.20, 2.59）	76.30%
2 型糖尿病（DDE ばく露）	4	1.29（1.13, 1.48）	0%

RECOMMENDATIONS

As discussed above, the extensive evidence gathered for this report highlights that there is immense amount of information available on pesticide exposure and health outcomes from epidemiological studies. Nonetheless, the quality of this evidence is usually low and many biases are likely to affect the results to an extent that firm conclusions cannot be made. Childhood cancers and Parkinson's disease are the two outcomes for which a corresponding meta-analysis after 2006 was found and for which data are consistent to show an increased risk associated with pesticide exposure. Nonetheless, the exposure needs to be studies further in order to disentangle the effect of specific pesticide classes or even individual pesticides. Effects on other outcomes, such as endocrine disorders, asthma and allergies, diabetes and obesity, are showing increased risk and should be explored further. This report concentrated on examining separately health outcomes. An alternative approach would be to look for pesticide classes, subclasses or even individual pesticides across a range of outcomes. These approaches could highlight whether a pesticide class has a particular detrimental effect across a variety of disease endpoints. Finally, exposure epidemiology has long suffered from exposure measurement and definition and in particular for pesticides this has always been exceptionally difficult to assess and define. Technological advances now enable us to measure in a large scale and agnostic way biomarkers of exposure using high throughput technologies of omics. For example, metabolomic analysis offers a way to capture a whole range of environmental exposures with minimal measurement error and ability to specify the exposure. These approaches are now being developed and are likely to offer much clearer view on the associations between environmental exposures, including dietary exposures, and health outcomes.

推奨事項

上述したように、本報告書のために収集された広範なエビデンスは、疫学研究から得られる農薬ばく露と健康影響に関する膨大な量の情報があることを浮き彫りにしている。しかし、これらのエビデンスの質は通常低く、多くのバイアスが結果に影響を与え、確固とした結論を出すことができない可能性が高い。小児がんとパーキンソン病は、2006 年以降に対応するメタアナリシスが行われた 2 つの影響であり、農薬ばく露に関連したリスクの増加を示すデータが一貫している。しかし、特定の農薬クラスや個々の農薬の影響を切り離すためには、ばく露の研究をさらに進める必要がある。内分泌疾患、喘息、アレルギー、糖尿病、肥満などの他の影響への影響はリスクの増加を示しており、さらに調査が必要である。本報告書では、健康影響を個別に調査することに集中した。別のアプローチとしては、農薬のクラス、サブクラス、あるいは個々の農薬でさえも、さまざまな影響にわたって調べることであろう。これらのアプローチにより、ある農薬クラスが様々な疾患エンドポイントにおいて特定の有害な影響を及ぼすかどうかを明らかにすることができる。最後に、ばく露疫学は長い間、ばく露の測定と定義に悩まされてきたが、特に農薬については、これは常に評価と定義が非常に困難であった。技術的な進歩により、オミクスのハイスループット技術を用いて、大規模かつ断定的でない方法でばく露のバイオマーカーを測定することが可能になった。例えば、メタボローム分析は、最小限の測定誤差とばく露を特定する能力で、環境ばく露の全範囲を捕捉する方法を提供している。これらのアプローチは現在開発が進められており、食事ばく露を含む環境ばく露と健康影響との関連について、より明確な見解を提供してくれる可能性が高い。

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APPENDICES

APPENDIX I. EXTENDED SEARCH ALGORITHM IN MEDLINE

Pesticid* OR Pesticide OR pest control OR "pest control" OR (Chemosteril* OR Chemosterilant OR Fungicid* OR fungicide OR Fungicide, Industrial OR Herbicid* OR Herbicide OR Defoliant* OR Defoliant, Chemical OR Insect Repellent*OR Insect Repellent OR Insecticid* OR Insecticide OR Molluscacid* OR Molluscacide OR Pesticide Synergist* OR Pesticide Synergist OR Rodenticid* OR Rodenticide OR organochlor* OR organochloride OR organochlorine OR chlorocarbon OR chlorinated hydrocarbon OR chlorinated solvent OR organophosphat* OR organophosphate OR carbamat* OR carbamate OR pyrethroid* OR pyrethroid) OR (1,2-dibromo-3-chloropropane OR 1,3-dichloro-1-propene OR 1-(4-ethynylphenyl)-4-propyl-2,6,7-trioxabicyclo(2.2.2)octane OR 1-Methyl-4-phenylpyridiniumOR 2,4,5-Trichlorophenoxyacetic Acid OR 2,4-Dichlorophenoxyacetic AcidOR 2-dichlorobenzeneOR 2-Methyl-4-chlorophenoxyacetic Acid OR 2-methyl-4-chlorophenoxyacetic acid dicamba herbicide solution OR 2-phenylphenol OR 3,5,6-trichloro-2-pyridinolOR 4"-epiacetylamino-4"-deoxyavermectin B1 OR 4-dichlorobenzeneOR abamectin OR acephate OR acetochlor OR acifluorfen ORAgent OrangeOR alachlor OR Aldicarb OR Aldrin OR Allethrin OR allosamidin OR alpha-Chlorohydrin OR alpha-naphthyl thiourea OR alpha-naphthylphthalamic acid OR aluminum phosphide OR aminocarb OR amitrazOR AnabasineOR arsenic acidOR Atrazine OR avermectinOR azadirachtin OR AzinphosmethylOR Bacillus thuringiensis protoxinOR bendiocarbOR BenomylOR bentazoneOR benthiocarbOR benzyl benzoate OR bialaphos OR binB protein Bacillus sphaericus OR bioallethrinOR bioresmethrin OR bis(tri-n-butyltin)oxideOR boric acid OR bromacil OR bromadiolone OR bromfenacoumOR bullatacinOR butachlorOR butyl phosphorotrithioate OR Cacodylic Acid OR captafol OR CaptanOR Carbaryl OR Carbofuran OR CarboxinOR Chloranil OR ChlordanOR ChlordeconeOR Chlorfenvinphos OR chlorocresol OR chlorophacinoneOR ChlorphenamidineOR Chlorpropham OR Chlorpyrifos OR chlorsulfuronOR chlortoluronOR cismethrinOR closantel OR CoumaphosOR crotamiton OR cyanazine OR cyclonite OR cyfluthrinOR cyhalothrinOR cyhexatinOR cypermethrinOR cyromazineOR cythioateOR daminozideOR decamethrinOR DEETOR dexon (fungicide)OR diallyl trisulfideOR Diazinon OR Dicamba OR dichlobanilOR Dichlorodiphenyl DichloroethyleneOR DichlorodiphenyldichloroethaneOR dichlorodiphenyltrichloroethane OR DDT OR Dichlorvos OR Dicofol OR dieldrin OR difenacoumOR DimethoateOR dimethyl 4,4'-o-phenylene bis (3-thioallophanate) with carbamic acid ethylene bis (dithio)-mangenese zinc complexOR dimethyl 4-phthalateOR dimethyl phthalateOR Dinitrophenols OR dinosebOR diphenylOR DiquatOR DisulfotonOR DiuronOR doramectin OR EndosulfanOR EndrinOR ethionOR Ethylmercuric Chloride OR Ethylmercury Compounds OR famophos OR fenarimol OR FenitrothionOR fenoxycarb OR fenpropimorphOR Fenthion OR fenvalerate OR fipronil OR fluazifop OR fluazifop-butyl OR fluoroacetic acid OR fluphenacur OR fluridoneOR fluvalinate OR folpet OR FonofosOR glyphosateOR hedolit OR Hempa OR HeptachlorOR Heptachlor Epoxide OR heptenophosOR HexachlorobenzeneOR hexachlorobutadiene OR hexazinoneOR hydramethylnonOR imazalilOR imidaclopridOR insecticidal crystal protein Bacillus ThuringiensisOR iprodioneOR isofenphosOR isoproturonOR IvermectinOR jasplakinolideOR LeptophosOR linaloolOR LindaneOR Linuron ORmalachite greenOR malaoxonOR MalathionOR Maleic HydrazideOR mancozebOR ManebOR mecarzoleOR mecopropOR metalaxylOR metaldehydeOR methamidophosOR methidathionOR MethiocarbOR MethomylOR MethoxychlorOR methyl demetonOR methyl isothiocyanateOR Methyl ParathionOR methylbromfenvinphosOR methyldithiocarbamateOR methyllycaconitineOR metolachlorOR metribuzinOR MevinphosOR milbemycinOR molinateOR Monocrotophos OR monomethylarsonic acidOR N,N-diethylphenylacetamide OR N-(3,5-dichlorophenyl)succinimideOR N-bromoacetamideOR n-hexanalOR Naled OR neem oilOR neosaxitoxinOR Niclosamide OR nitrofenOR nonachlor OR norbormideOR norflurazoneOR nornicotine OR octamethyl pyrophosphoramideOR oryzalinOR

付録

付録 I. MEDLINE における拡張検索アルゴリズム

Pesticid* OR Pesticide OR pest control OR "pest control" OR (Chemosteril* OR Chemosterilant OR Fungicid* OR fungicide OR Fungicide, Industrial OR Herbicid* OR Herbicide OR Defoliant* OR Defoliant, Chemical OR Insect Repellent*OR Insect Repellent OR Insecticid* OR Insecticide OR Molluscacid* OR Molluscacide OR Pesticide Synergist* OR Pesticide Synergist OR Rodenticid* OR Rodenticide OR organochlor* OR organochloride OR organochlorine OR chlorocarbon OR chlorinated hydrocarbon OR chlorinated solvent OR organophosphat* OR organophosphate OR carbamat* OR carbamate OR pyrethroid* OR pyrethroid) OR (1,2-dibromo-3-chloropropane OR 1,3- dichloro-1-propene OR 1-(4-ethynylphenyl)-4-propyl-2,6,7-trioxabicyclo(2.2.2)octane OR 1-Methyl- 4-phenylpyridiniumOR 2,4,5-Trichlorophenoxyacetic Acid OR 2,4-Dichlorophenoxyacetic AcidOR 2- dichlorobenzeneOR 2-Methyl-4-chlorophenoxyacetic Acid OR 2-methyl-4-chlorophenoxyacetic acid dicamba herbicide solution OR 2-phenylphenol OR 3,5,6-trichloro-2-pyridinolOR 4''-epiacetylamino- 4''-deoxyavermectin B1 OR 4-dichlorobenzeneOR abamectin OR acephate OR acetochlor OR acifluorfen ORAgent OrangeOR alachlor OR Aldicarb OR Aldrin OR Allethrin OR allosamidin OR alpha-Chlorohydrin OR alpha-naphthyl thiourea OR alpha-naphthylphthalamic acid OR aluminum phosphide OR aminocarb OR amitrazOR AnabasineOR arsenic acidOR Atrazine OR avermectinOR azadirachtin OR AzinphosmethylOR Bacillus thuringiensis protoxinOR bendiocarbOR BenomylOR bentazoneOR benthiocarbOR benzyl benzoate OR bialaphos OR binB protein Bacillus sphaericus OR bioallethrinOR bioresmethrin OR bis(tri-n-butyltin)oxideOR boric acid OR bromacil OR bromadiolone OR bromfenacoumOR bullatacinOR butachlorOR butyl phosphorotrithioate OR Cacodylic Acid OR captafol OR CaptanOR Carbaryl OR Carbofuran OR CarboxinOR Chloranil OR ChlordanOR ChlordeconeOR Chlorfenvinphos OR chlorocresol OR chlorophacinoneOR ChlorphenamidineOR Chlorpropham OR Chlorpyrifos OR chlorsulfuronOR chlortoluronOR cismethrinOR closantel OR CoumaphosOR crotamiton OR cyanazine OR cyclonite OR cyfluthrinOR cyhalothrinOR cyhexatinOR cypermethrinOR cyromazineOR cythioateOR daminozideOR decamethrinOR DEETOR dexon (fungicide)OR diallyl trisulfideOR Diazinon OR Dicamba OR dichlobanilOR Dichlorodiphenyl DichloroethyleneOR DichlorodiphenyldichloroethaneOR dichlorodiphenyltrichloroethane OR DDT OR Dichlorvos OR Dicofol OR dieldrin OR difenacoumOR DimethoateOR dimethyl 4,4'-o-phenylene bis (3-thioallophanate) with carbamic acid ethylene bis (dithio)-mangenese zinc complexOR dimethyl 4-phthalateOR dimethyl phthalateOR Dinitrophenols OR dinosebOR diphenylOR DiquatOR DisulfotonOR DiuronOR doramectin OR EndosulfanOR EndrinOR ethionOR Ethylmercuric Chloride OR Ethylmercury Compounds OR famophos OR fenarimol OR FenitrothionOR fenoxycarb OR fenpropimorphOR Fenthion OR fenvalerate OR fipronil OR fluazifop OR fluazifop-butyl OR fluoroacetic acid OR fluphenacur OR fluridoneOR fluvalinate OR folpet OR FonofosOR glyphosateOR hedolit OR Hempa OR HeptachlorOR Heptachlor Epoxide OR heptenophosOR HexachlorobenzeneOR hexachlorobutadiene OR hexazinoneOR hydramethylnonOR imazalilOR imidaclopridOR insecticidal crystal protein Bacillus ThuringiensisOR iprodioneOR isofenphosOR isoproturonOR IvermectinOR jasplakinolideOR LeptophosOR linaloolOR LindaneOR Linuron ORmalachite greenOR malaoxonOR MalathionOR Maleic HydrazideOR mancozebOR ManebOR mecarzoleOR mecopropOR metalaxylOR metaldehydeOR methamidophosOR methidathionOR MethiocarbOR MethomylOR MethoxychlorOR methyl demetonOR methyl isothiocyanateOR Methyl ParathionOR methylbromfenvinphosOR methyldithiocarbamateOR methyllycaconitineOR metolachlorOR metribuzinOR MevinphosOR milbemycinOR molinateOR Monocrotophos OR monomethylarsonic acidOR N,N- diethylphenylacetamide OR N-(3,5-dichlorophenyl)succinimideOR N-bromoacetamideOR n- hexanalOR Naled OR neem oilOR neosaxitoxinOR Niclosamide OR nitrofenOR nonachlor OR norbormideOR norflurazoneOR nornicotine OR octamethyl pyrophosphoramideOR oryzalinOR ParaoxonOR ParaquatOR ParathionOR

ParaoxonOR ParaquatOR ParathionOR pendimethalin OR pentachlorobenzeneOR PentachlorophenolOR PermethrinOR phenothrinOR phenthoateOR phentin acetate OR Phenylmercuric Acetate OR phenylmercuric nitrate, basicOR Phenylmercury CompoundsOR Phenylphosphonothioic Acid 2-Ethyl 2-(4-Nitrophenyl) EsterOR Phorate OR phosaloneOR PhosmetOR PhosphamidonOR phosphineOR phosphinothricinOR phoxim OR Picloram OR Piperonyl ButoxideOR pirimicarbOR pirimiphos methylOR precocene IIOR prochlorazOR procymidoneOR profenofosOR PrometryneOR propachlorOR PropanilOR PropoxurOR PyrethrinsOR pyriminil OR quinalphos OR quintozene OR RotenoneOR S,S'-(2-(dimethylamino)-1,3-propanediyl)thiosulfuric acid ester OR SimazineOR sodium chlorateOR spinosadOR sulfamic acidOR sulfometuron methyl OR tebufenozideOR TemefosOR terbutryneOR terbutylazineOR terthienyl OR tetrachloroisophthalonitrileOR TetrachlorvinphosOR tetramethrinOR thallium sulfate OR ThiophanateOR ThiramOR ToxapheneOR triadimefon OR Triallate OR TrichlorfonOR triclopyrOR triflumuron OR Trifluralin OR vinclozolin OR Warfarin OR zinc phosphide OR Zineb OR Ziram)

(LIMITS: HUMAN, 1/1/2006 - 1/10/2012)

pendimethalin OR pentachlorobenzeneOR PentachlorophenolOR PermethrinOR phenothrinOR phenthoateOR phentin acetate OR Phenylmercuric Acetate OR phenylmercuric nitrate, basicOR Phenylmercury CompoundsOR Phenylphosphonothioic Acid 2-Ethyl 2-(4-Nitrophenyl) EsterOR Phorate OR phosaloneOR PhosmetOR PhosphamidonOR phosphineOR phosphinothricinOR phoxim OR Picloram OR Piperonyl ButoxideOR pirimicarbOR pirimiphos methylOR precocene IIOR prochlorazOR procymidoneOR profenofosOR PrometryneOR propachlorOR PropanilOR PropoxurOR PyrethrinsOR pyriminil OR quinalphos OR quintozene OR RotenoneOR S,S'-(2-(dimethylamino)-1,3-propanediyl)thiosulfuric acid ester OR SimazineOR sodium chlorateOR spinosadOR sulfamic acidOR sulfometuron methyl OR tebufenozideOR TemefosOR terbutryneOR terbutylazineOR terthienyl OR tetrachloroisophthalonitrileOR TetrachlorvinphosOR tetramethrinOR thallium sulfate OR ThiophanateOR ThiramOR ToxapheneOR triadimefon OR Triallate OR TrichlorfonOR triclopyrOR triflumuron OR Trifluralin OR vinclozolin OR Warfarin OR zinc phosphide OR Zineb OR Ziram)

(LIMITS: HUMAN, 1/1/2006 - 1/10/2012)

APPENDIX II. EXPLANATIONS TO THE DATA EXTRACTION DATABASE

Study ID	This is the unique ID of the study given sequentially for each study major outcome
PUBMED_ID	This is the PUBMED ID of the study (if not available ID in EMBASE was provided and when this was not available the title of the study was provided)
First author	First author's last name
Journal	Journal in which the study was published
Year	Year of publication
Country	Country where the study was conducted
Location (continent)	Continent where the study was conducted
Recruitment period	Period during which the study participants were recruited
Exposure Period (preconception, infancy, childhood, adulthood, pregnancy)	Growth period in which the pesticide exposure occurred (preconception, pregnancy, infancy, childhood, adolescence, adulthood)
Follow-up period	Follow-up calendar period for prospective/ retrospective studies
Follow-up duration (maximum)	Maximum follow-up period in years for prospective/ retrospective studies
Follow-up duration (years) (median/mean)	Mean or median follow-up period in years for prospective/ retrospective studies
Study type (cohort, nested case-control, case-control, cross-sectional)	The epidemiological study design: cohort, nested case-control, case-control, cross-sectional
Cohort name	The name of the epidemiological study
Age (years) (range/mean/median..)	The age of the population studied (preference is to provide the mean or meadian age, when not available the range is given). Data is presented in years unless otherwise stated.
Gender (% male)	Percentage of males in study population
Active substance assessed	Pesticide assessed in the study as defined/named in the study
Active substance category	Chemical or functional pesticide category in which the pesticide is classified
Authorisation status	Pesticide active substances authorized within EU (06/09/2013). Yes/No/NA (NA=not applicable)
Biomarker name	The name of the biomarker of exposure to pesticide (if measured)
Control definition	Definition of the control group in case-control studies
Pesticide co-exposure (measured)	Did the study provided information on other co-exposed pesticides? (yes, no)
Population characteristics	Description of the population examined (gender, location, disease status)
Type of exposure (occupational, environmental, both)	What is the source of exposure to pesticides: occupational (if the exposure is related to a specific occupational activity); environmental (if the exposure is not related to any

付録 II. データ抽出データベースの説明

Study ID	これは、研究の主要な影響ごとに順次与えられる研究の固有 ID である。
PUBMED _ID	これがその研究の PUBMED ID である（EMBASE の ID が提供されていない場合に PUBMED ID が提供され、PUBMED ID が提供されていない場合は研究のタイトルが提供された）。
筆頭著者	筆頭著者の姓
ジャーナル	研究が掲載された雑誌
年	出版年
国	研究実施国
場所（大陸）	研究実施大陸
募集期間	研究参加者を募集した期間
ばく露期間（妊娠前、乳児期、小児期、成人期、妊娠期）	農薬ばく露が発生した発育期（妊娠前、妊娠期、乳児期、小児期、思春期、成人期）
追跡期間	前向き/後ろ向き研究の追跡予定期間
追跡期間（最大）	前向き/後ろ向き研究の最大追跡期間は年単位である。
追跡期間(年)(中央値/平均値)	前向き/後ろ向き研究の平均または中央値の追跡期間（年）。
研究の種類（コホート、コホート内症例対照、症例対照、横断的）	疫学研究のデザイン：コホート、コホート内症例対照、症例対照、横断的
コホート名	疫学研究の名称
年齢(年)（範囲/平均/中央値...）	調査対象となった集団の年齢（平均年齢または中央値年齢を提示することを好む。データは、別段の記載がない限り、年単位で表示される。
性別(男性の割合)	調査対象集団における男性の割合
評価された有効成分	試験で定義・命名された試験で評価された農薬
有効成分のカテゴリー	農薬が分類されている化学的または機能的な農薬の分類
認可状況	EU 域内で認可された農薬有効成分(2013/09/06) Yes/No/NA（NA=該当なし）
バイオマーカー名	農薬ばく露のバイオマーカー名（測定した場合）
対照定義	症例対照研究における対照群の定義
農薬の共ばく露（測定値）	その研究では、他の共ばく露農薬に関する情報を提供したか？(はい、いいえ)
集団の特徴	調査した集団の説明（性別、場所、病状）
ばく露の種類（職業的、環境的、両方）	農薬へのばく露源は何か：職業的（ばく露が特定の職業活動に関連している場合）；環境的（ばく露がいかなる職業活動にも関連していない場合（例えば、住居内での農薬使用、ガーデニングでの農薬使用、ガーデニングに関連したばく露など）；両方（職業ばく露と環境ばく露の両方が存在する場合）。
ばく露評価の種類（直接ばく露についての質問紙／バイオマーカー／居住履歴／職歴／JEM／専門家評価／環境 odeling 誤植と思われる	農薬ばく露の測定方法：直接ばく露についての質問紙（面接または自己記入）；体液中のバイオマーカーの測定；居住歴；職業歴；職業ばく露マトリックス（JEM）。

	occupational activity (e.g. domestic use of pesticides, use of pesticides in gardening, exposure related to gardening etc.); both (when both occupation and environmental exposure is present).
Type of exposure assessment (direct exposure questionnaire/ biomarker/residential history/occupational history/ JEM/ expert evaluation/ environmental odeling)	Means of measuring pesticide exposure: direct exposure questionnaire (interview or self-administered); measurement of biomarker in biological fluids; residential history; occupational history; Job Exposure Matrix (JEM)
Exposure definition	Definition of exposure as described in the study
Questionnaire type	Questionnaire type (interview or self administrated) (for studies which assessed exposure through questionnaires, else state n/a)
Measurement of biomarker (whole blood, plasma, urine, breast milk, placenta, nails, hair, saliva, adipose tissue)	Body fluid or tissue in which the biomarker was measured (whole blood, plasma, urine, breast milk, placenta, nails, hair, saliva, adipose tissue etc.)
Assay type	Type of biochemical assay used for biomarker measurement
Exposure duration	Duration of exposure to pesticides in years (when available)
Pediatric exposure type (mother, father, child, combinations)	For studies on child outcomes, describe means of exposure through self-exposure or parental exposure (mother, father, child, combinations)
Pediatric exposure time (preconception, pregnancy, combination)	For studies on child outcomes, was parental exposure during preconception, pregnancy or combinations?
Health outcome	Health outcome as described in the study
Outcome definition	Health outcome definition used in the study
Disease category	Disease category
Effect estimate type (RR, OR, HR, beta, MD, SMD)	Type of effect estimate for the assessment of pesticide and health outcome relationship (RR, OR, HR, beta, MD, SMD)
Effect (binary, continuous)	Effect estimated on a binary or continuous manner (binary, continuous)
Comparison unit (yes/no, unit increase, ...)	The definition of comparison for the calculation of the effect size (yes/no, unit increase etc.)
Effect estimate	Value of effect estimate
SE/SD effect stimate	Standard error/Standard deviation of effect estimate
Lower 95% CI	Lower 95% confidence interval of the effect estimate
Higher 95% CI	Higher 95% confidence interval of the effect estimate
Adjustment for	Confounders/ variables for which the effect estimate was adjusted for
Controls matched for	Variables for which controls were matched to cases (case control studies only)
Sample size	Total number of participants
N cases	Number of cases

ばく露の定義	研究に記載されているばく露の定義
質問紙の種類	質問紙の種類（面接または自己管理）（質問紙を用いてばく露を評価した研究の場合、そうでない場合は該当なし）
バイオマーカーの測定（全血、血漿、尿、母乳、胎盤、爪、毛髪、唾液、脂肪組織）	バイオマーカーが測定された体液または組織（全血、血漿、尿、母乳、胎盤、爪、毛髪、唾液、脂肪組織など）
アッセイタイプ	バイオマーカー測定に使用した生化学的アッセイの種類
ばく露期間	年単位での農薬ばく露期間（入手可能な場合）
小児ばく露タイプ（母、父、小児、組合わせ）	小児の影響に関する研究については、自己ばく露または親のばく露（母親、父親、小児、組合わせ）を通じたばく露手段を記述
小児ばく露時期（妊娠前、妊娠期、両方）	小児の影響に関する研究では、親のばく露は妊娠前、妊娠期、または両方の期間に行われたか？
健康影響	研究に記載されている通りの健康影響
影響の定義	研究で使用された健康影響の定義
疾患カテゴリ	疾患カテゴリ
効果推定タイプ（RR、OR、HR、β、MD、SMD）	農薬と健康影響の関係を評価するための効果推定値の種類（RR, OR, HR, β, MD, SMD）
効果（2 変数、連続変数）	2 変数法または連続変数法で推定された効果（2 変数、連続変数）
比較単位（はい／いいえ、単位増加、...	効果量を算出するための比較の定義（はい／いいえ、単位増加など）
効果推定	効果推定値
SE/SD 効果推定	効果推定値の標準誤差・標準偏差
95% CI の下限	効果推定値の 95%信頼区間の下限
95% CI の上限	効果推定値の 95%信頼区間の上限
調整	効果推定値の交絡因子/変数の調整
マッチした対照	対照の変数を症例にマッチさせた（症例対照研究のみ）
サンプルサイズ	参加者総数
N 症例	症例数
N 対照	対照数
統計的手法	効果量の計算に用いられる統計的手法
試験デザイン（前向き、後ろ向き、混合、横断）	研究デザインの前向き型または後ろ向き型（前向き、後ろ向き、混合、横断）
包含/除外の基準の明記（はい、一部、いいえ）	研究参加者（母集団）の説明は詳細に行われていましたか？(はい/一部/いいえ)
著者による検出力の言及（はい、いいえ）	著者らは、統計分析の前または後に論文で検出力について言及しているか？(はい/いいえ)
ばく露レベル（高、中、低）の詳細記述	農薬ばく露の定義でばく露レベル（高、中、低）の詳細記述
ばく露量の妥当な測定 ：(バイオマーカー(有)；小規模区域の生態学的測定、職種、質問紙(一部)；大規模区域の生態学的測定に基づいた(無))	ばく露量の測定は妥当であったか：バイオマーカー（はい）；小規模区域の生態学的測定、職種、質問紙（一部）；大規模区域の生態学的測定に基づいた（いいえ）
ばく露量の測定は特定のものであったか？はい；より広範で化学的に関連したグループに基づく（一部）；多様な化学的及び毒	ばく露量の測定は特定のものであったか？（はい）；より広範で化学的に関連したグループに基づく（一部）；多様な化学的及び毒性学的特性の広範なグループ化に基づく（いいえ）

N controls	Number of controls
Statistical method	Statistical method used to calculate the effect size
Study design (prospective, retrospective, mixed, cross-sectional)	Prospective or retrospective type of study design (prospective, retrospective, mixed, cross-sectional)
Inclusion/exclusion criteria clearly stated (yes, partially, no)	Was the description of study participants (population) inclusion and exclusion criteria detailed? (yes/partially/no)
Authors mention power calculations (yes, no)	Do the authors mention power calculations in the manuscript preceding or proceeding their statistical analysis (yes/no)
Level of detail in describing exposure (high, medium, low)	Level of detail in which the definition of exposure to pesticides is provided (high/medium/low)
Robust measurement of exposure. (biomarker (yes); small area ecological measures, job titles, questionnaire (partial); was based on large area ecological measures (no)	Was the measurement of exposure robust: biomarker (yes); small area ecological measures, job titles, questionnaire (partial); was based on large area ecological measures (no)
Were measures of exposure specific? Yes; based on broader, chemically-related groups (partial); based on broad groupings of diverse chemical and toxicological properties (no)	Were measures of exposure specific? (yes); based on broader, chemically-related groups (partial); based on broad groupings of diverse chemical and toxicological properties (no)
Attempt to balance the allocation between the groups (e.g., through stratification, matching)	Was an attempt to balance the allocation between the groups in case-control studies either through stratification or matching (yes/no)?
Adjustment performed for potential confounders (yes, some, no)	Was the effect size adjusted for potential confounders (yes, some, no)?
Assessors blinded to exposure status (for cohort studies)	Were the assessors blinded to exposure status in cohort studies (yes/no/;n/a:not available or not applicable when studies are not cohorts)?
Outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Were the outcomes assessed using valid and reliable measures implemented consistently across all study participants (yes/no)
Sample size (top [991], middle, bottom quartiles[104])	The size of the sample
Was source of funding acknowledged	Do the authors acknowledge any possible source of funding (yes/no)
Rough quality assessment	Rough quality assessment taking into account the data in all other columns of the quality assessment of data extraction form
COMMENTS	Any comments related to the study that help interpretation of the data extracted

性学的特性の広範なグループに基づく（いいえ）	
グループ間の配分のバランスを図る（層別化、マッチングなど）	症例対照研究では、層別化またはマッチングによってグループ間の配分のバランスをとる試みが行われたか？（はい/いいえ）
潜在的な交絡因子の調整を行った（はい、いくつか、いいえ）	潜在的な交絡因子について効果量を調整したか？（はい、いくつか、いいえ）
ばく露状況を盲検化された評価者（コホート研究の場合）	コホート研究では、評価者はばく露状況を盲検化されていたか？（はい/いいえ/;n/a:コホート研究でない場合は、成果なし、または該当なし）
影響は、すべての研究参加者に一貫して実施された有効かつ信頼性のある測定を用いて評価されたか？	影響は、すべての研究参加者に一貫して実施された有効で信頼性のある測定を用いて評価されたか？（はい/いいえ）
サンプルサイズ（四分位数の上部[991]、中間部、下部[104]）	サンプルの大きさ
資金源の承認	著者は、資金調達の可能性があることを認めているか（はい/いいえ）
大まかな品質評価	データ抽出フォームの品質評価の他のすべての列のデータを考慮した大まかな品質評価
コメント	抽出されたデータの解釈に役立つ研究に関するコメント

APPENDIX III. REFERENCES TO THE DATA EXTRACTION DATABASE

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GLOSSARY AND ABBREVIATIONS

AHS: Agricultural Health Study

Beta estimate: coefficient of linear regression

Bias: A systemic inaccuracy in data due to the characteristics of the process employed in the creation, collection, manipulation and presentation of the data or due to faulty sample design of the estimating technique

Biomarker: A measurable substance or characteristic in the human body that can be used to monitor the presence of a chemical in the body, biological responses, or adverse health effects. Biomarkers of exposure are used to assess the amount of a chemical that is present within the body.

Blinded outcome assessment: Individuals who assess the exposure are blinded to the health outcome status of the participants.

CARDIA: The "Coronary Artery Risk Development In Young Adults" study, a multi-center, population-based study.

Case-control study: A type of observational study in which two existing groups differing in outcome are identified and compared on the basis of some supposed causal attribute. Case-control studies are retrospective, as the exposure status is assessed retrospectively.

Case reports: Detailed reports of the symptoms, signs, diagnosis, treatment, and follow-up of individual patients.

Case series: descriptive study that tracks patients with a known exposure given similar treatment or examines their medical records for exposure and outcome. These studies lack control groups.

Center-specific analysis: Analysis per centre in studies, which have participants, recruited from more than one centre.

CHAMACOS: The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS). A prospective birth cohort aimed at studying the association of pesticides and other environmental agents on the health of pregnant women and their children living in the Salinas Valley, California.

CI: Confidence Interval

Cohort study: A longitudinal/prospective study, which analyses risk factors and follows a group of people who do not have the disease until participants develop the disease(s) of interest

Confounders: Extraneous variables in a statistical model that correlate (positively or negatively) with both the dependent variable (exposure) and the independent variable (outcome)

Cross-sectional study: A study that involves observation of all of participants at one specific point in time, exposure and outcome are measured in the same time point.

Ecological study: Studies in which the unit of observation is the population or community. Disease rates and exposures are measured in each of a series of populations and their relation is examined.

用語解説と略語

AHS：農業健康調査

ベータ推定値: 線形回帰の係数

バイアス：データの作成、収集、操作及び表示に採用されたプロセスの特性に起因する、または推定手法の誤ったサンプルデザインに起因する、データの体系的な不正確さ。

バイオマーカー：体内の化学物質の存在、生物学的反応、または健康への有害影響を監視するために使用できる、人体内の測定可能な物質または特性。ばく露のバイオマーカーは、体内に存在する化学物質の量を評価するために使用される。

盲検影響評価：ばく露を評価する個人は、参加者の健康状態を盲検化する。

CARDIA（カーディア）：″Coronary Artery Risk Development In Young Adults（若年成人の冠状動脈リスク発症）″研究、多施設、集団ベースの研究。

症例対照研究（Case-control study）：観察研究の一種で、結果の異なる２つの既存のグループを特定し、何らかの因果関係に基づいて比較する研究。症例対照研究は、ばく露状況を後ろ向きに評価する後ろ向き研究である。

症例報告：個々の患者の症状、徴候、診断、治療、経過観察の詳細な報告。

症例集積：同様の治療を受けたばく露が知られている患者を追跡したり、ばく露と影響について医療記録を調べたりする記述研究。これらの研究には対照群がない。

センターごとの分析：複数のセンターから募集した参加者がいる研究におけるセンターごとの分析。

CHAMACOS（チャマコス）：Center for the Health Assessment of Mothers and Children of Salinas（CHAMACOS）。カリフォルニア州サリナスバレーに住む妊婦とその子供の健康に及ぼす農薬やその他の環境要因の関連を調べることを目的とした前向き出生コホート。

CI：信頼区間

コホート研究：リスク因子を分析し、調査対象疾患を発症するまで疾患を持たない人のグループを追跡調査する縦断的/前向き研究。

交絡因子（Confounders）：従属変数（ばく露）と独立変数（影響）の両方と相関する（正または負の）統計モデルの外部変数。

横断研究：ある特定の時点での参加者全員の観察を行い、ばく露と影響を同じ時点で測定する研究。

生態学的研究：観察の単位が集団または共同体である研究。疾病率とばく露が各集団集積で測定され、それらの関係が調査される。

効果（２変数/連続変数）：影響は２変数法（二項対立、例：がん（はい/いいえ））または連続変数法（例：収縮期血圧（120㎜Hg））である。

効果推定値/サイズ：関連の強さの尺度

ESCALE：全国登録ベースの症例対照研究「Etude sur les cancers de l'enfant」試験

ファンネルプロット：システマティックレビューやメタアナリシスにおける出版バイアスの有無を確認するために設計されたグラフ

不均一性：メタアナリシスは、類似した研究のグループから複合的な効果を推定するために使用される。しかし、治療効果の個々の推定値は偶然によって変動する；ある程度の変動は予想され

Effect (binary/continuous): Outcome is binary (dichotomous, e.g. cancer (yes/no)) or continuous (e.g. systolic blood pressure (120mmHg)).

Effect estimate/ size: A measure of the strength of association

ESCALE: The “Etude sur les cancers de l'enfant” study, a national registry-based case-control study

Funnel plots: graph designed to check the existence of publication bias in systematic reviews and meta-analyses

Heterogeneity: meta-analysis is used to estimate a combined effect from a group of similar studies. However, the individual estimates of treatment effect will vary by chance; some variation is expected. The question is whether there is more variation than would be expected by chance alone. When this excessive variation occurs, it is called heterogeneity

HR: Hazard Ratio

I^2: measure of the consistency between trials in a meta-analysis, it is a measurement of heterogeneity and takes values form 0 (no heterogeneity) to 1 (extreme heterogeneity)

INUENDO: “INUENDO—Biopersistent organochlorines in diet and human fertility Epidemiological studies of time to pregnancy and semen uality in nuit and European populations , a European pro ect on fertility that was supported by the European Commission to the 5th Framework Programme Quality of Life and Management of Living Resources, Key Action 4 on Environment and Health (Contract no. QLK4-CT-2001-00202) (http://www.inuendo.dk).

IRR: Incidence rate ratio

IQR: Interquartile Range

JEM :Job Exposure Matrix

MD: Mean Difference

Meta-analysis: The process or technique of synthesizing research results by using various statistical methods to retrieve, select, and combine results from previous separate but related studies.

Multiple testing: Testing many hypotheses, which are not a priori defined or based on a priori hypothesis.

Misclassification: Bias in an estimate arising from measurement error

Multivariable models: Statistical models with more than one dependent variable. These models typically adjust for a number of confounders the analysis of interest.

Nested case-control study: In a nested case-control study, cases of a disease that occur in a defined cohort are identified and, for each, a specified number of matched controls is selected from among those in the cohort who have not developed the disease by the time of disease occurrence in the case

NHANES: National Health and Nutrition Examination Survey

る。問題は、偶然だけで予想される以上の変動があるかどうかである。このような過度の変動が生じる場合、それは不均一性と呼ばれる。

HR: ハザード比（Hazard Ratio）

I^2 : メタアナリシスにおける試験間の一貫性の尺度で、不均一性の測定であり、0（不均一性なし）から 1（極端な不均一性）までの値をとる。

INUENDO: ″INUENDO-食品中の生物持続性有機塩素化合物とヒト生殖能、イヌイットと欧州の集団における妊娠までの期間と精液の質の疫学研究″、欧州委員会（the 5th Framework Programme Quality of Life and Management of Living Resources, Key Action 4 on Environment and Health（Contract no. QLK4-CT-2001-00202）（契約番号：QLK4-CT-2001-00202）（http://www.inuendo.dk））の支援を受けた不妊に関する欧州のプロジェクト。

IRR:発生率比

IQR:四分位間範囲

JEM:職業ばく露マトリックス

MD:平均差

メタアナリシス（Meta-analysis）：様々な統計的手法を用いて研究結果を統合し、以前の別々ではあるが関連のある研究の結果を検索、選択、結合するプロセスまたは技術。

Multiple testing（多重検定）：先験的に定義されていない、または先験的仮説に基づいていない、多くの仮説を検定すること。

誤分類：測定誤差に起因する推定値のバイアス

多変量モデル：1 つ以上の従属変数を持つ統計モデル。これらのモデルは通常、調査対象の分析の交絡因子の数を調整する。

コホート内症例対照研究：コホート内症例対照研究では、定義されたコホート内で発生した疾患の症例が同定され、各症例の疾患発生時までに疾患を発症していないコホート内の患者の中から、指定された数のマッチした対照が選択される。

NHANES：米国国民健康栄養調査

観察研究：観察研究とは、被験者に対する治療の効果について推論を行うもので、被験者を治療群と対照群に割り当てるのは研究者の管理外である。

OR：オッズ比

統合効果推定値：メタアナリシスの要約した効果推定値、メタアナリシスの結果

POPs：残留性有機汚染物質

前向き研究（Prospective study）：ある影響に影響を及ぼす可能性のある要因に基づいて個人（コホート）のグループを選択する疫学研究

出版バイアス（Publication bias）：研究者、編集者、製薬会社が、陽性（すなわち有意な知見を示す）の実験結果の報告を、陰性（すなわち帰無仮説を支持する）または結論の出ない結果とは異なる扱いをする傾向から生じたバイアス。

回想バイアス（Recall bias）： 過去の出来事や経験の記憶に対する回想の正確さや完全さの違いによるシステマティックエラー。

残存交絡：残存交絡因子は、交絡因子が分析で十分に調整されていない場合に発生する（通常、交絡

Observational study: an observational study draws inferences about the possible effect of a treatment on subjects, where the assignment of subjects into a treated group versus a control group is outside the control of the investigator

OR: Odds ratio

Pooled effect estimate: Summary effect estimate of the meta-analysis, the result of meta-analysis

POPs: Persistent Organic Pollutants

Prospective study: An epidemiologic study in which the groups of individuals (cohorts) are selected on the bases of factors that are to be examined for possible effects on some outcome

Publication bias: Bias arisen from the tendency for researchers, editors, and pharmaceutical companies to handle the reporting of experimental results that are *positive* (i.e. showing a significant finding) differently from results that are negative (i.e. supporting the null hypothesis) or inconclusive.

Recall bias: Systematic errors due to differences in accuracy or completeness of recall to memory of past events or experiences.

Residual confounding: Residual confounding occurs when a confounder has not been adequately adjusted for in the analysis (usually because the confounder is not known)

Retrospective study: an epidemiologic study in which participating individuals are classified as either having some outcome (cases) or lacking it (controls); the outcome may be a specific disease, and the persons' histories are examined for specific factors that might be associated with that outcome

Reverse causality: Reverse causality refers to the direction of cause-and-effect, it is not known whether the exposure has led to the outcome or the outcome has led to the exposure.

RR: Relative Risk

Narrative review: An article written to consider the critical points of current knowledge including substantive findings, as well as theoretical and methodological contributions to a particular topic

SD: Standard Deviation

SE: Standard Error

Surrogate outcome: A laboratory measurement or physical sign that is used in trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the exposure
Systematic reviews: Reviews of the evidence on a clearly formulated question that use systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyse data from the studies that are included in the review

Type-I error: The incorrect rejection of a true null hypothesis

UFW: United Farm Workers

因子が知られていないため)。

後ろ向き研究：参加した個人を何らかの影響あり（症例）と影響なし（対照）に分類する疫学研究で、影響は特定の疾患である可能性があり、その影響と関連する可能性のある特定の因子について、その人の病歴を調べる。

逆因果関係：逆因果関係とは、因果関係の方向性のことで、ばく露が影響につながったのか、影響がばく露につながったのかはわからない。

RR：相対リスク

ナラティブ・レビュー（Narrative review）：実質的な知見や、特定のトピックに対する理論的・方法論的な貢献を含めて、現在の知識の重要な点を調査するために書かれた論文

SD：標準偏差

SE：標準誤差

代替健康影響（surrogate outcome）：患者がどのように感じているか、機能しているか、または生存しているかを直接測定するものや、ばく露の影響を予測することが期待されるものである臨床的に意味のあるエンドポイントの代わりに試験で使用される測定値または物理的徴候。

システマティックレビュー：関連する主要研究を特定、選択、批判的に評価し、レビューに含まれる研究からデータを抽出、分析するために、体系的かつ明示的な方法を用いて、明確に定式化された問題に関するエビデンスのレビュー。

第一種の誤り：真の帰無仮説の誤った棄却

UFW: 米国農場労働者（United Farm Workers）