REVIEW ARTICLE

SEX HORMONE LEVELS IN RURAL WORKERS EXPOSED TO PESTICIDES: A SYSTEMATIC REVIEW WITH META-ANALYSIS

Jaciara Pinheiro de Souza[1]; Cristiani Isabel Banderó Walker[2]
Murilo de Jesus Porto[3]; Jeferson de Menezes Souza[4]
Liz Oliveira dos Santos[5]; Maria de Fátima Santana de Souza Guerra[6]
André Lacerda Braga Teles[7]

Highlights: (1) Exposure to pesticides led to decreased levels of testosterone and prolactin. (2) While for SHBG there was a significant increase. (3) There was no significant evidence of alteration in FSH and LH hormone levels.

http://dx.doi.org/10.21527/2176-7114.2025.50.16289

How to cite:
Souza JP, Walker CIB, Porto M de J, Souza J de M, dos Santos LO, Guerra M de FS de S. et al. Sex hormone levels in rural workers exposed to pesticides: a systematic review with meta-analysis. Rev. Contexto & Saúde. 2025;25(50):e16289

[1] Universidade Federal de Sergipe (UFS). São Cristovão/SE, Brasil. http://orcid.org/0000-0002-4056-974X
[2] Universidade Federal de Sergipe (UFS). São Cristovão/SE, Brasil. https://orcid.org/0000-0001-6219-2325
[3] Universidade Federal da Bahia (UFBA). Salvador/BA, Brasil. https://orcid.org/0000-0003-2339-8173
[4] Universidade Estadual de Feira de Santana (UEFS). Feira de Santana/BA, Brasil. https://orcid.org/0000-0001-7688-8606
[5] Universidade Federal do Recôncavo da Bahia (UFRB). Feira de Santana/BA, Brasil. https://orcid.org/0000-0003-2064-2097
[6] Universidade Estadual da Bahia (UNEB). Salvador/BA, Brasil. https://orcid.org/0000-0002-2760-8230
[7] Universidade Estadual da Bahia (UNEB). Salvador/BA, Brasil. https://orcid.org/0000-0001-7884-2177

SEX HORMONE LEVELS IN RURAL WORKERS EXPOSED TO PESTICIDES: A SYSTEMATIC REVIEW WITH META-ANALYSIS

ABSTRACT

The present study aims to analyze the excitatory and/or inhibitory effects of pesticide exposure on the production of male sex hormones in rural populations. The protocol for this systematic review was previously registered in PROSPERO (CRD42022354863) and follows the guidelines recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The research question addressed was: Does pesticides exposure cause excitatory and/or inhibitory effects on the production of sex hormones? The literature search was conducted from July 1 to July 17, 2023, in the following databases: Public Medline (PubMed), Latin American and Caribbean Literature in Health Sciences (LILACS), Science Direct, and Scientific Electronic Library (Scielo). The results indicate that pesticides exposure was associated with a significant decrease in testosterone levels (mean difference: -1.60, 95% CI: -2.47 to -0.72) and prolactin levels (mean difference: -1.28, 95 %: CI -2.19 to -0.37). In constrast, there was significant increase in Sex Hormone Binding Globulin (SHBG) levels (mean difference: 4.24, 95% CI: 1.54 to 6.93). No significant changes were observed in the levels of Follicle Stimulating Hormone (FSH) (mean difference: 0.98, 95% CI: 0.74 to 1.21) and Luteinizing Hormone (LH, mean difference: 0.44; 95% CI: 0.25 to 0.64) between the groups studied. In conclusion, evidence suggests that pesticide exposure may alter the production of various sex hormones. Specifically, individuals exposed to pesticides tend to exhibit lower levels of testosterone and prolactin, while SHBG levels are increased compared to those without exposure.

Keywords: Sex hormones; Pesticide; Endocrine disruptors.

NÍVEIS DE HORMÔNIOS SEXUAIS EM TRABALHADORES RURAIS EXPOSTOS A AGROTÓXICOS: UMA REVISÃO SISTEMÁTICA COM META-ANÁLISE

RESUMO

O presente estudo tem como objetivo mensurar os efeitos excitatórios e/ou inibitórios sobre a produção de hormônios sexuais masculinos em populações rurais expostas a agrotóxicos. Assim, o protocolo para esta revisão sistemática foi previamente registrado no PROSPERO (CRD42022354863) e segue as recomendações do protocolo Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Apresenta a questão central: a exposição a agrotóxicos causa efeitos excitatórios e/ou inibitórios sobre a produção de hormônios sexuais?. A busca de publicações foi realizada no período de 1º a 17 de julho de 2023, nas bases de dados Public Medline (PubMed), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Science Direct e Scientific Electronic Library -Scielo. Como resultado, observa-se que a exposição a agrotóxicos foi associada a uma diminuição nos níveis de testosterona (-1,60, IC 95%: -2,47 a -0,72) e prolactina (-1,28, IC 95%: -2,19 a -0,37), enquanto para SHBG houve um aumento significativo (4,24, IC 95%: 1,54 a 6,93). Não houve evidência significativa de alteração nos níveis do hormônio FSH (0,98, IC 95%: 0,74 a 1,21) e LH (0,44; IC 95%: 0,25 a 0,64) entre os grupos estudados. Em conclusão, sugere-se que alterações no padrão fisiológico dos hormônios sexuais nesta população estudada estejam acontecendo, mas de forma discreta, uma vez que todos os estudos mostram resultados dentro do padrão de normalidade estabelecido pelo laboratório Hermes, com exceção da prolactina, que apresentou níveis elevados, na maioria dos estudos selecionados, para ambos os grupos (controle e exposto).

Palavras-Chave: Hormônios sexuais; Agrotóxicos; Desreguladores endócrinos.

INTRODUCTION

The high global demand for food has led to an exorbitant increase in the pesticide use, specially in Brazil, where consumption increased from approximately 162,000 tons of active ingredient in 2000 to 620,000 tons in 2019, a roughly 280% increase [(1,2)]. According to FAOSTAT [(3)], Brazil is the second largest consumer of pesticides in the world, by planted area.

Although pesticides are primarily used for pest control and to boost large-scale productivity, their use has several negative implications, mainly for the health of workers involved in this process [(4)].

In vitro and *in vivo* research indicates that a variety of pesticides, included organophosphates, carbamates, synthetic pyrethroids, different herbicides, and fungicides, can act as chemical disruptors that directly interfere with the production of sex hormones [(5-12)]. In humans, studies on pesticide exposure have demonstrated changes in the functioning of the hypothalamic-pituitary-gonadal axis [(13-16)] and correlation with the emergence of the reproductive system disorders such as infertility and cancers of prostate, testis, breast and ovary [17].

Experimental studies have also clearly shown (anti) estrogenic and/or (anti) androgenic activities associated with the toxicity of certain pesticides [12, 18-19]. However, these findings are not always reproducible in human research due to several limiting factors. According to Ye and Liu [12], the exposure doses used in animal experiments often exceed those experencied by humans, and the duration of exposure in animals is generally much shorter. Another limiting factor is the heterogeneity in human research results, which arises from variations in pesticide exposure patterns and the simultaneous use of multiple products, making it difficult to understand the changes that occur in sex hormones [16].

In this context, studies focusing on human subjects have produced conflicting results when analyzing hormonal levels in rural populations exposed to pesticides, with some studies reporting negative (inhibitory) associations, others positive (stimulatory) associations, and some finding no association at all [16, 20].

Therefore, although pesticide exposure may alter reproductive hormone levels, the extent to which this occurs in humans is not yet well understood in the literature [16]. Thus, the present review and meta-analysis aims to measure the excitatory and/or inhibitory effects of persticide exposure on the production of male sex hormones in rural populations.

METHODS

Protocol and registration

The protocol of this systematic review was previously registered in the PROSPERO database (CRD42022354863) and follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) l [21-23].

Search strategy and Data extraction

The search was conducted from July 1, 2023 to July 17, 2023, in the databases Public Medline (PubMed), Latin American and Caribbean Literature in Health Sciences

(LILACS), Science Direct and Scientific Electronic Library (Scielo). The objective was to identify studies that reported on the dosage of sex hormones in rural populations exposed to pesticides, with no restriction on the year of publication. In addition, other studies were consulted from the SaberAberto database, the institutional repository of the State University of Bahia-UNEB.

The search was conducted using Health Sciences Descriptors combined research in English with the following terms: “sex hormones AND pesticides AND rural workers AND occupation”; “sex hormones AND pesticides AND toxicology AND occupational”; “Sex hormones AND pesticides”.

This systematic review is based on the following question: Does pesticide exposure cause excitatory and/or inhibitory effects on the production of sex hormones? Using the PICO strategy (P: male rural workers who work in rural areas; I: exposure to pesticides. C: male rural workers not exposed to pesticides, O: quantitative changes in sex hormone levels, including testosterone, prolactin, Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), estradiol, and Sex Hormone Binding Globulin (SHBG), assessed through measures of central tendency and variability.

Study Selection

Sstudies were selected by reading the titles and abstracts. When the studies met the eligibility criteria, each study was read in full. The authors rigorously constructed the data extraction instrument, ensuring a meticulous detailing of the information extracted from the primary articles. The selection was carried out independently by two reviewers, and in cases of divergence, a third reviewer was consulted. The information recorded for each selected study was: (i) study identification data (name of authors, year of publication, journal); (ii) study population (occupation of the population; sex; sample size; participant selection strategies; country of origin); (iii) type of exposure (type of pesticide and form of exposure); (iv) hormones analyzed in each study and (v) results (mean and standard deviation of each hormone in the exposed and unexposed groups).

Elebility criteria

Articles, dissertations, and theses resulting from original research that included analyzes of sex hormone levels in male participants exposed to pesticides were included. There was no restriction regarding the year of publication and time of exposure to the pesticide. Works written in Portuguese, English and Spanish were selected. Systematic reviews were excluded from this study; overview; scope review; meta-analyses; editorials; case reports; studies that did not present inclusion and exclusion criteria for sample selection; exposed population not classified as rural; studies with missing data (e.g. did not present mean and standard deviation for hormone levels).

Quality analyses

Two researchers used the Newcastle-Ottawa Scale (NOS) [24] in order to evaluate the quality of the studies included in this meta-analysis research. The scale is based on the “star system” where the included studies are evaluated according to three concepts: selection of study group participants, group comparability and exposure.

Analysis

Qualitative data were tabulated in Microsoft® Office Word version 2019 in a table created by the authors themselves, covering the following variables: age group; minimum exposure time; types of pesticides; type of exposure (occupational and/or environmental); kind of study; analytical method employed; analyzed hormones.

Quantitative data on mean and standard deviation of hormonal levels were tabulated in Microsoft® Office Excel version 2019. As the works have different measurement units, the data were converted into standardized measures according to the International System of Units (SI), as available at Unitslab website [25]. Therefore, the measurement units for hormonal levels were standardized for the present work as follows: Testosterone expressed in nmol/L;Luteinizing hormone-LH expressed in mU/ml; Follicle Stimulating Hormone-FSH expressed in mUI/Ml; Prolactin- PRL expressed in mU/ml; Sex Hormone-Binding Globulin-SHBG expressed in nnmol/L.

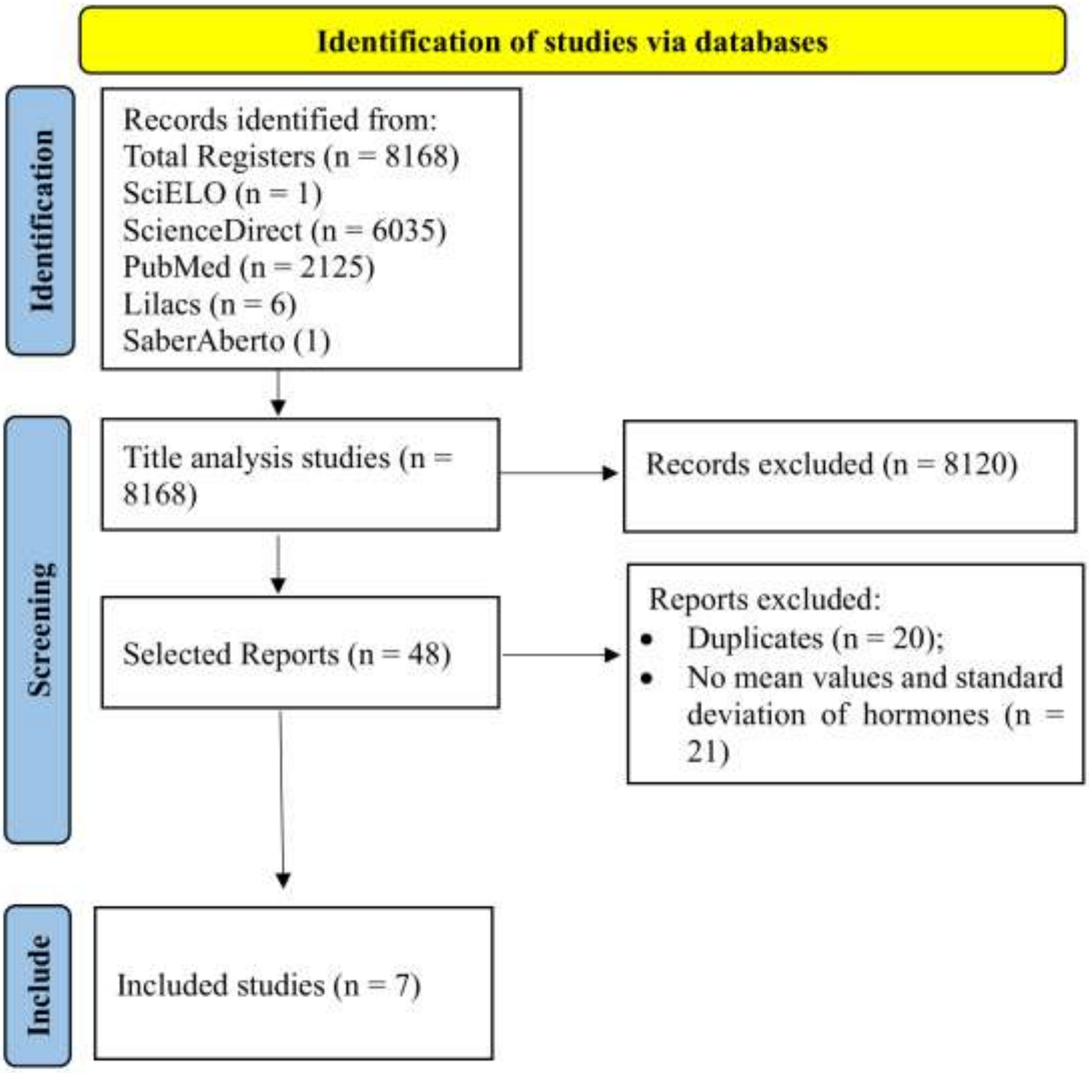
Data are presented as mean and standard deviation (SD) for independent groups. Then, the data were exported and analyzed by the REVMAN 5.4 software [26]. Due to the observed heterogeneity, a fixed effects meta-analysis was performed and confidence intervals were estimated. The I-squared (I^2) was analyzed to assess the heterogeneity magnitude among the selected works, with I^2 > 50% and >75% being considered substantial and considerable heterogeneity, respectively. Significant heterogeneity among studies were considered when Chi-square (X^2) had p<0.10.

We adopted as reference values considered normal for each hormone; the values proposed by the Instituto Hermes Pardini laboratory. The bias analysis of the included studies was carried out considering the Newcastle-Ottawa School (NOS). The scale is based on the "star system" where the included studies are evaluated according to three concepts: selection of study group participants, comparability of groups and exposure ([24]). The included articles ranged from 4 to 9 stars, that is, showing a good quality of the searched parameters.

RESULTS

The search in the databases returned a total of 8,168 documents, of which 8,120 were excluded after reading the titles because they did not meet the eligibility criteria. The abstracts of 48 articles were read, 20 being excluded because they were duplicates. Subsequently, 28 articles were read in full, of which 21 were eliminated. Therefore, seven works were selected in this review (Figure 1).

Figure 1 – Studies identified by searching the databases



The publications included cover the years 2006 to 2022, comprising participants aged 18 to 73, with many interviewees exposed for more than 1 year to different types of pesticides. The main form of exposure was occupational and the collection of biological samples from the studies was carried out at a single moment, constituting cross-sectional studies. It was found that most of the works (3 studies) were developed in Brazil. In addition, hormonal measurements were taken using different techniques such as immunoradiometric assay (IRMA); radioimmunoassay (RIA); Electrochemiluminescence immunoassay; Enzyme-linked immunosorbent assay (ELISA) (Table 1)

Table 1 - Characteristics of the studies included in the systematic review on the effects of pesticides on sex hormones.

Reference	Country	Age group	Minimum exposure time	Types of pesticides	Type of exposure	Kind of study	Analyzed hormones and analytical method employed
Yucra et al. (2006)	Peru	20-60 years	2 years	Organophosphate	Occupational	Cross-sectional study	FSH and LH were measured by IRMA. Testosterone and estradiol were determined by RIA.
Hernández et al. (2009)	Cuba	20-50 years	1 year	Pesticides in geal	Occupational	Cross-sectional study	FSH, LH and prolactina were determined by IRMA
Manfo et al. (2010)	Cameroon	18-59 years	5 years	Pesticides in geal	Occupational	Cross-sectional study	FSH, LH, SHBG and testosterone were determined by RIA
Celik-Ozenci et al. (2012)	Turkey	25-39 years	5 years	Abamectine	Occupational	Cross-sectional study	FSH, LH and testosterone were determined by ELISA
Cremonese (2014)	Brazil	18-69 years	<2 years	Pesticides in geal	Occupational and environmental	Cross-sectional study	FSH, LH, SHBG, prolactina and testosterone were determined by ELISA
Cremonese et al. (2017)	Brazil	18-23 years	<2 years	Pesticides in geal	Occupational and environmental	Cross-sectional study	FSH, LH, SHBG, prolactina and testosterone were determined by ELISA
Souza et al. (2022)	Brazil	20-73 years	>2 years	Pesticides in geal	Occupational	Cross-sectional study	FSH, LH, SHBG and testosterone were determined by ELISA

Regarding the methodological quality and risk of bias of the selected studies, it was found that six studies had good methodological quality and only one work was classified as “poor quality”, as it did not score in the exposure criteria (Table 2). Additionally, the studies showed great heterogeneity (Figure 2).

Figure 2 - Funnel Plot on the risk of bias

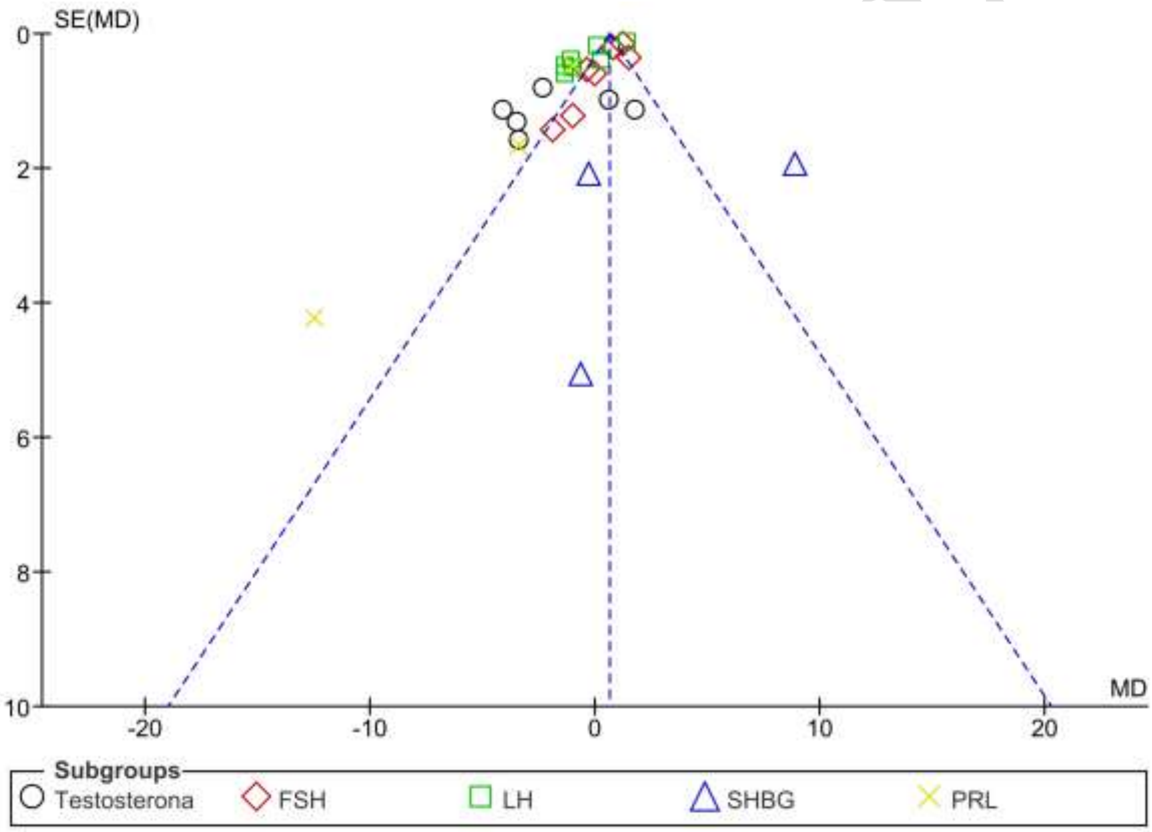


Table 2. Newcastle-Ottawa Quality Rating Scale (NOS) for the studies included in the meta-analysis

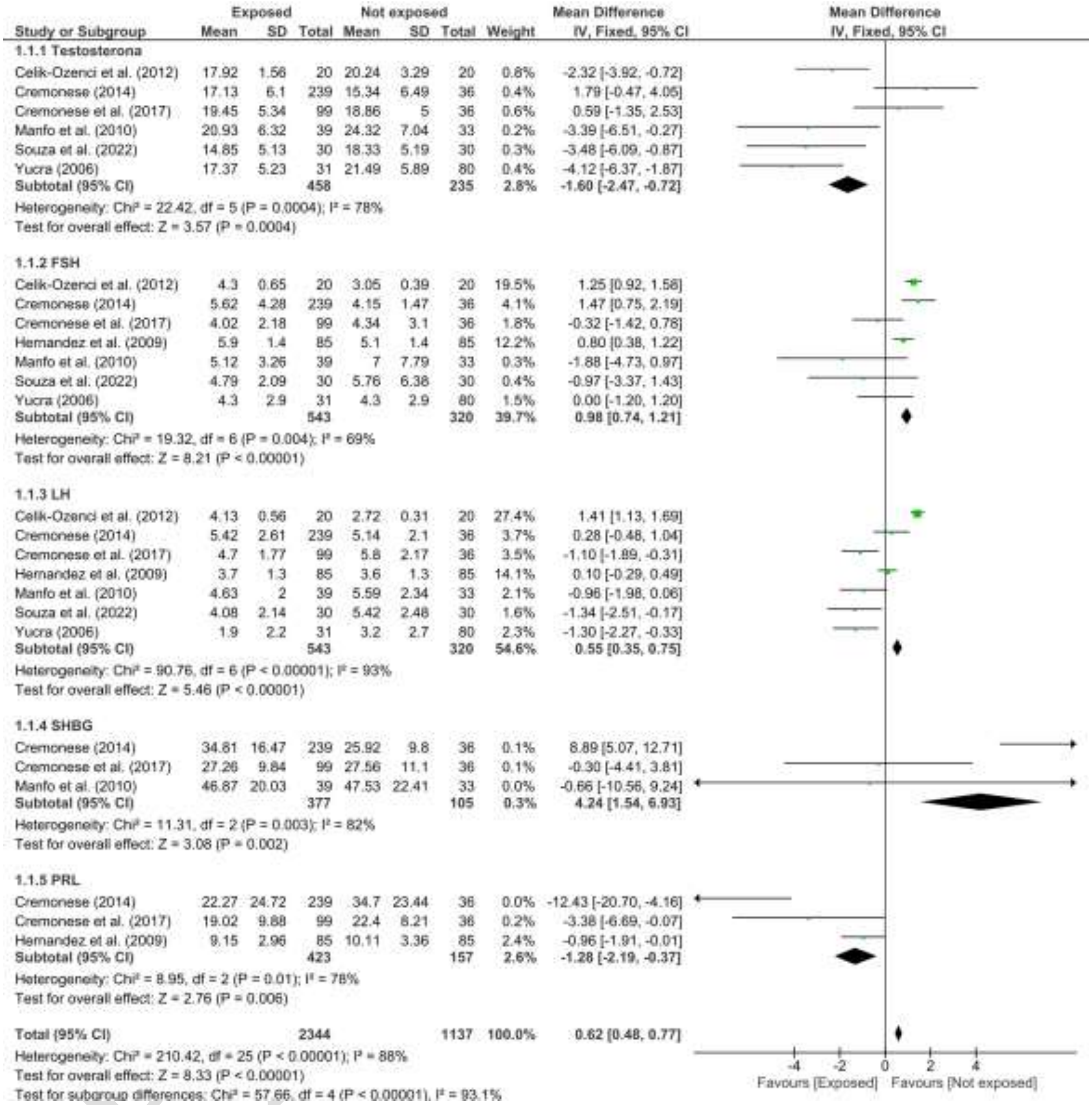
	Criterion	Yucra et al. (2006)	Hernández et al. (2009)	Manfo et al. (2010)	Celik-Ozenci et al. (2012)	Cremonese (2014)	Cremonese et al. (2017)	Souza et al. (2022)
Selection	The case definition is adequate with independente validation	*	*	*	*	*	*	*
	Consecutive or obviosly representative series of cases	*	*	*	*	*	*	*
	Community controls	*		*	*	*	*	*
Comparability	Controls with no history of disease (endpoint)	*		*	*	*	*	*
	Cases and controls with comparable ages	*	*	*			*	*
	Cases and controls with comparability on any other factors	*	*	*	*	*	*	*
Exposure	Ascertainment of exposure using secure records (eg surgical records) or structured interviews with blinding to case/control statuses	*			*	*	*	
	Ascertainment of exposure using the same method for cases and controls	*			*	*	*	*
	Ascertainment of exposure with non-response rate for both groups	*		*		*	*	*
	Score	**9**	**4**	**7**	**7**	**8**	**9**	**8**

The hormonal levels of the groups (exposed and not exposed to pesticides) were summarized in Table 3. It was found that all studies recorded hormonal levels within the reference range considered normal for testosterone, FSH, LH and SHBG in both groups. However, changes in prolactin were recorded in participants in two studies, both in the control and exposed groups (Table 3).

It was found that adding the number of participants from all studies, the group exposed to pesticides comprised a sample of 543 people, while the unexposed group comprised 320 individuals. To seek generalizations about the influence of pesticides on hormone production, we analyzed separately each hormone portrayed in the seven studies selected in the review. In this context, the meta-analysis showed that there is a statistical difference between people exposed and not exposed to pesticides for all hormones analyzed (Figure 3).

It is possible to verify that data on testosterone was available in their studies, and that exposure was associated with a decrease in testosterone levels. Additionally, all seven articles analyzed the influence of pesticides on the levels of follicle-stimulating hormone and luteinizing hormone, showing that the levels of both hormones are favored by the unexposed group. When it comes to SHBG, there is a significant difference between the two groups, favoring the unexposed group. Furthermore, there is a difference between the exposed and unexposed groups in relation to prolactin levels, with a tendency for the hormone to decrease among the exposed population (Figure 3).

Figure 3 - Forest plot showing hormone levels in people exposed to pesticides.



Analysis of the table below shows that the study findings result in average hormonal levels within the normal range established by the Hermes Pardine laboratory, except for the hormone prolactin. This would be a positive point for the workers surveyed, however, there is a pattern of distance between the averages of the exposed group and the control group for the hormones testosterone, SHBG and prolactin, something that is not repeated for the hormones FSH and LH.

Table 3 - Average values of hormone levels and comparison with reference values considered normal. **Legend:** exposed group (Exp); unexposed group (NExp); Follicle Stimulating Hormone (FSH); Luteinizing Hormone (LH); Sex Hormone Binding Globulin (SHBG); Prolactin (PRL); hormone not analyzed in the study (--)

Hormones [Ref: mínimo – máximo]	Yucra et al. (2006)		Hernández et al. (2009)		Manfo et al. (2010)		Celik-Ozenci et al. (2012)		Cremonese (2014)		Cremonese et al. (2017)		Souza et al. (2022)	
	Exp	NExp	Exp	NExp	Exp	NExp	Exp	NExp	Exp	NExp	Exp	NExp	Exp	NExp
Testosterone [8.66 a 33.42 nMol/L]	17.37 ±5.23	21.49 ±5.89	--	--	20.93 ±6.32	24.32 ±7.04	17.92 ±1.56	20.24 ±3.29	17.13 ±6.10	15.34 ±6.49	19.45 ±5.34	18.86 ±5.0	14.85 ±5.13	18.33 ±5.19
FSH [0.2 a 10.5 mUI/mL]	4.3 ±2.9	4.3 ±2.9	5.9 ±1.4	5.1 ±1.4	5.12 ±3.26	7.0 ±7.79	4.3 ±0.65	3.05 ±0.39	5.62 ±4.28	4.15 ±1.47	4.02 ±2.18	4.34 ±3.1	4.79 ±2.18	5.76 ±6.38
LH [0.2 a 10 mUI/mL]	1.9 ±2.2	3.2 ±2.7	3.7 ±1.3	3.6 ±1.3	4.63 ±2.0	5.59 ±2.34	4.13 ±0.56	2.72 ±0.31	5.42 ±2.61	5.14 ±2.1	4.70 ±1.77	5.8 ±2.17	3.06 ±1.55	6.32 ±2.16
SHBG [13 a 71 nMol/L]	--	--	--	--	46.87 ±20.03	47.53 ±22.41	--	--	--	--	27.26 ±9.84	27.56 ±11.1	--	--
PRL [0.6 a 17 ng/mL]	--	--	9.15 ±3.26	10.11 ±3.36	--	--	--	--	22.27 ±24.72	34.7 ±23.44	19.02 ±9.88	22.40 ±8.21		--

DISCUSSION

This meta-analysis covers studies published between 2006 and 2022, which together include a total sample size of 863 participants (exposed group: n = 543; control group: n = 320). In general, participants' ages range from 18 to 73 years across all studies that compared age between the exposed and control groups, except Celik-Ozenci et al. [(27)]. This is particularly important because, according Cunha, Moura e Reis[(28)], hormone levels vary according to certain age groups.

All selected studies employed a cross-sectional design, with biological samples collected at a single point in time. According to Souza el al [(16)], this may be a limitation, as it does not characterize the inhibitory or inductive profiles of hormonal actions relative to the variations in exposure that occur throughout periods of high, medium, and low pesticide use during the year.

Additionally, although the studies measured hormone levels using different assays—such as IRMA, RIA, and electrochemiluminescence immunoassay—they are all based on the same fundamental principle: the immunoassay method, which involves an in vitro immunological reaction between antigen and antibody [(29)]. Because most immunoassay techniques use this basic principle, the hormone dosage methods are similar, which supports the accuracy of the data presented in this meta-analysis.

In all selected studies, the subjects were rural workers occupationally exposed to pesticides, including sprayers, farmers, and others. However, it is important to note that although all individuals working in rural areas are occupationally exposed, studies indicate that pesticide applicators—who handle, mix, and apply these toxic substances directly—are most affected and more likely to develop hormonal disorders (30,16).

Only the study by Yucra et al. (31) selected a sample consisting of 31 pesticide sprayers (with at least two years of exposure) and 80 non-exposed men, and it observed that serum testosterone and LH levels were significantly lower in the exposed group compared to those not exposed to organophosphate (OP) pesticides. This finding suggests that further studies are needed—not only to classify workers as occupationally exposed but also to include details of their specific activities so that direct and/or indirect exposures can be categorized, yielding more comparable data in terms of hormone measurements.

In all selected studies, the subjects included were rural workers occupationally-exposed to pesticides, including sprayers, farmers, and others. However, it is important to note that although all individuals working in rural areas are occupationally exposed, studies indicate that pesticide applicators—who handle, mix, and apply these toxic substances directly—are most affected and more likely to develop hormonal disorderss [16, 30].

Only the study by Yucra et al. [31] selected a sample consisting of 31 pesticide sprayers (with at least two years of exposure) and 80 non-exposed men, and it observed that serum testosterone and LH levels were significantly lower in the exposed group compared to those not exposed to organophosphate (OP) pesticides. This finding suggests that further studies should be developed, not only classifying workers as occupationally exposed, but also to include details of their specific activities so that direct and/or indirect exposures can be categorized, yielding more comparable data in terms of hormone measurements.

The hormones evaluated in these studies were testosterone. FSH, LH, SHBG, and prolactin. Most studies (n= 6) suggested that exposure to pesticides alters the levels of sex hormones. However, the study by Celik-Ozenci et al. [27] did not find any significant change in hormone levels but concluded, based on other biomarkers, that exposure to the pesticide abamectin can impair male fertility, and affect semen quality.

The data from this meta-analysis reveal both excitatory and inhibitory effects of androgenic and pituitary hormones in different rural populations exposed to pesticides, as observed in previous studies [16,20]. In the forest plot comparing the groups, there is strong evidence that pesticide exposure is associated with inhibitory effects on the testosterone and prolactin production, excitatory effects on SHBG levels, and no significant associations for FSH and LH. However, the data in table 2 indicate that average hormone levels remain within the normal range, except for prolactin, which was elevated in two of the three selected studies, for both control and exposed groups.

Several studies have already suggested an inverse association between pesticide exposure and testosterone levels, which is consistent with the findings of this meta-analysis [16, 32-35]. Lower testosterone levels may indicate abnormal functioning of Leydig cells of these workers, leading to a reduced hormone production. This hypothesis is corroborated by the histopathological findings in Leydig cells of rats and mice exposed to pesticides, suggesting that tissue injury may contribute to decreased testosterone levels [36-40].

It is also suggested that this small change in testosterone level among the groups could be exacerbated by the significant increase in SHBG observed in exposed workers. An excessive increased in SHBG levels can reduce free testosterone, as more androgens (including DHT and testosterone) become bound, potentially leading to a symptomatic state of androgen deficiency, sometimes progressing to hypogonadism [41-43]. A study carried out by Cremonese [44] in the rural area of Farroupilha (RS) corroborates these findings found in this meta-analysis, as It reported that farmers with longer pesticide exposure had higher SHBG and lower testosterone levels. There are also studies with divergent results, indicating a negative association between pesticide exposure and SHBG levels [45,46].

This meta-analysis found an apparently null association between pesticide exposure with FSH and LH levels, a finding that is corroborated by other studies [27, 45,47,48]. At first glance, this might suggest that the hypothalamic-pituitary axis is not compromised. However, the lower prolactin levels observed in exposed individuals challenge this assumption, since prolactin regulation is also controlled by central nervous system factors, specifically, by dopamine produced in the hypothalamus [49,50].

Based on these findings, it can be predicted that the blood-brain barrier, which is formed by endothelial cells connected by tight junctions [51], may limit the extent of pesticides penetration into the brain, thereby reducing endocrine disruptions in the hypothalamic-pituitary complex. On the other hand, androgen receptors and glands, located in the peripheral part of the human body, would receive a higher toxicological load, leading to more pronounced changes in hormone levels, which may explain our findings.

There are conflicting interpretation of the prolactin data in this study. The forest plot shows a decrease in this hormone for the exposed group compared to the control group, corroborating the study by Khan et al. [52]. However, in the analysis of table 2, reveals that most studies [44,46] present values above the reference curve (0.9 to 17 ng/mol) for both groups, with a lower mean prolactin level in the exposed group.

Therefore, in both studies, there is evidence of increased prolactin production \ (hyperprolactinemia) that can cause negative effects on reproduction, even lead to erectile dysfunction in men.

It is important to note that, among the main known causes of elevated prolactin levels are the use of some medications and clinical conditions such as macroprolactinemia, hypothyroidism and pituitary adenoma (53). If the subjects of the aforementioned research were affected by such conditions, this could be explain the findings in both groups studied. However, these instruments applied during the research did not evaluate these aspects.

Despite the significant differences observed between the control and exposed groups, the endocrine hormone levels remain within the normal range, except for prolactin. This raises the question of whether these differences might affect the functionality of organs mediated by these hormones. In this sense, a study carried out by Bapayeva et al. (54) in southern Kazakhstan suggested that the population exposed to pesticides already showed impairments in sexual development due to hormonal changes. In the referred work, 524 female adolescents aged between 10 and 17 years (exposed, n = 253; unexposed, n = 271) were assessed via questionnaires on secondary sexual characteristics studies in parallel with the biological samples analysis. Pesticides have been linked to a numerous of health problems, especially due to their toxicity and mutagenic and carcinogenic potential. Over time, continuous exposure to these substances can result in serious clinical conditions, especially affecting the endocrine system (55).

According to Souza et al (16), it suggests that there is a possible tendency for a negative association between testosterone and LH levels and exposure to various types of pesticides. On the other hand, it is observed that there is a possible positive association with FSH. In the long term, it can be suggested that rural populations may present disorders of the reproductive system such as infertility, prostate, testicular and breast cancer, as has already been reported by Koifman and his collaborators (56).

In the present work, we compared sex hormones levels across several studies that varied in methodology, duration and intensity of exposure, types of pesticides applied, the use of personal protective equipment, and characteristics of agricultural work. These differences may limit data interpretation in this meta-analysis. A study focused solely on the hormonal impact of pesticide exposure might have a gap by not considering other important markers. Cholinesterase activity, concentration of metabolites or pesticide compounds in blood and urine and even exposure variables, these are examples of factors that would contribute to a more accurate interpretation of the results.

Although most hormone levels remained within the normal range—with the exception of prolactin—it is suggested that discreet changes in the physiological patterns of sex hormones are occurring in this population, as indicated by statistically significant differences between the exposed and non-exposed groups in each study.

The literature demonstrates a subtle pattern of hormonal changes resulting from pesticide exposure; however, further studies incorporating additional biomarkers are needed to fully understand the residual and long-term effects on this population. These observations, based on the potential risks of pesticide exposure, underscore the considerable need for public authorities to enhance healthcare measures for rural workers and the general population.

CONCLUSION

In summary, this is the first systematic review with meta-analysis aimed at investigating the effects of pesticides on the sex hormone levels of rural workers. A careful qualitative analysis of the selected studies provided strong evidence that pesticide exposure can affect the production of several sex hormones. Inhibitory effects were observed for testosterone and prolactin, while excitatory effects were noted for SHBG levels in individuals exposed to pesticides compared to the non-exposed group. Although most hormone levels remained within the normal range, with the exception of prolactin, it is suggested that discreet changes in the physiological patterns of sex hormones are occurring in this population, as indicated by statistically significant differences between the exposed and non-exposed groups in each study.

The literature demonstrates a subtle pattern of hormonal changes resulting from pesticide exposure; however, further studies incorporating additional biomarkers are needed to fully understand the residual and long-term effects on this population. These

observations, based on the potential risks of pesticide exposure, underscore the considerable need for public authorities to enhance healthcare measures for rural workers and the general population.

REFERENCES

[1]. FAO – Food and Agriculture Organization of the United Nations. Pesticides Use Indicators. Rome: FAO, 2021. Disponível em: https://openknowledge.fao.org. Access at: 18 fev. 2023.

[2]. Ibama. Comercialização de agrotóxicos e afins. Série histórica 2000-2019, 2020 [Internet]. Available in : <https://www.gov.br/ibama/pt-br>. Access at: 7 set. 2022.

[3]. Food and Agriculture Organization of the United Nations (FAO). Pesticides Indicators. FAOSTAT, 23 de dezembro de 2022. Available in: https://www.fao.org/faostat/en/#data/EPA. Access at: 23 dez. 2022.

[4]. Silva YRA.Pesticide poisonings registered in the notification system and Brazilian toxicological information centers: an integrative review [Course Completion Work - Graduation - Health Sciences]. ITACOATIARA – AM; 2023.

[5]. Fucic A, Duca RC, Galea Ks, Maric T, Garcia K, Bloom MS, Andersen HR, Vena JE. Reproductive Health Risks Associated with Occupational and Environmental Exposure to Pesticides. Int J Environ Res Public Health. 2021 Jun 18;18(12):6576. doi: 10.3390/ijerph18126576. PMID: 34207279; PMCID: PMC8296378.

[6]. Paula IB, de Paula LB, de Paula LB. Exposição de gestantes aos agrotóxicos e suas consequências: uma revisão sistemática. Cuadernos de Educación y Desarrollo. 2024;16(2 Edição Especial). DOI: 10.55905/cuadv16n2-ed.esp.040. Available in: https://ojs.europubpublications.com/ojs/index.php/ced/article/view/2651. Access at: 8 abr. 2024.

[7]. Santos Barros SE, Moreira MB. Characterization of pesticides used in irrigated fruit growing agricultural areas in the São Francisco Valley. Irrigated Fruit Farming: vulnerabilities and prospects for sustainable production. Year 2023; Volume 1. Digital Scientific Editor.

[8]. Andersen RH, Vinggaard AM, Rasmussen TH, Gjermandsen IM, Bonefeld-Jorgensen EC. Effects of pesticides currently used in in vitro estrogenicity, androgenicity and aromatase activity assays. Toxicol Appl Pharmacol. 2002;179(1).

[9]. Kojima H, Katsura E, Takeuchi S, Niiyama K, Kobayashi K. Screening for estrogen and androgen receptor activities in 200 pesticides by reporter gene in vitro assays using Chinese hamster ovary cells. Environ Health Perspect. 2004;112(5):524-531.

[10]. Orton F, Rosivatz E, Scholze M, Kortenkamp A. Widely used pesticides with previously unknown endocrine activity revealed to be antiandrogens in vitro. Environ Health Perspect. 2011;119(6):794-800.

[11]. Saillenfait AM, Ndiaye D, Sabate JP. The estrogenic and androgenic potential of pyrethroids in vitro. Rev Toxicol In Vitro. 2016;34:321-332.

[12]. Ye X, Liu J. Efeitos de inseticidas piretróides no eixo hipotálamo-hipófise-gonadal: Uma perspectiva de saúde reprodutiva. Environ Pollut. 2019. doi:10.1016/j.envpol.2018.11.031

[13]. Otero MMMP, Rodrigues ERM, Yokoya ABA, Miyata GN, Gedolin BP, Pinto RS. Influência do Glifosato em distúrbios do sistema endócrino: um estudo de revisão narrativa. Brazilian J Health Rev. 2024;7(3):183. doi:10.34119/bjhrv7n3-183.

[14]. Mnif W, Hassine AI, Bouaziz A, Bartegi A, Thomas O, Roig B. Effect of endocrine disrupting pesticides: a review. Int J Environ Res Public Health. 2011;8(6):2265-2303.

[15]. Oliveira SM, López ML. Epidemiological overview of congenital malformations in Brazil (2013-2017). Rev Saúde Multidiscipl (Online). 2020;8(2):1-5.

[16]. Souza JP, Porto MJ, Credidio GC, Faria HA, Nepomuceno AFSF, Santos LO, Teles ALB. Changes in sex hormone levels caused by exposure to pesticides. RevIPI. 2022;11(2):VOL. 12.

[17]. Cavalier H, Trasande L, Porta M. Pesticide Exposures and Cancer Risk: Assessment of Recent Epidemiological Evidence in Humans and Ways Forward. Int J Cancer. 2023;152(5):879-912.

[18]. Pantaleon LP. Influence of exposure to atrazine during puberty on the sexual sphere of adult rats [Master's Dissertation in Experimental and Comparative Pathology]. São Paulo: University of São Paulo; 2021. doi:10.11606/D.10.2021.tde-14032022-145914. Access at: 8 abr. 2024.

[19]. Rawlings et al., 1998; Rocha VA. Effects of the Western diet and exposure to 2,4-dichlorophenoxyacetic acid (2,4-D) on the prostate of mice. Botucatu, 2023.

[20]. Freire C, Koifman RJ, Sarcinelli PN, Rosa ACS, Clapauch R, Koifman S. Association between serum levels of organochlorine pesticides and sex hormones in adults living in a heavily contaminated area in Brazil. Int J Hyg Environ Health. 2014;217:370–378.

[21]. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. A declaração PRISMA 2020: diretriz atualizada para relatar revisões sistemáticas e meta-análises de estudos que avaliam intervenções em saúde. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.

[22]. Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7). https://doi.org/10.1371/journal.pmed.1000097.

[23]. Fuchs SC, Paim BS. A Guide for Systematic Reviews of Observational Studies. Texto Contexto Enferm. 2024;33:e0221. doi:10.1590/1980-265X-TCE-2023-0221en.

[24]. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.

[25]. UnitsLab. Available in: https://unitslab.com/taxonomy/term/8. Accessed on: July 20, 2021. Scholten RJ, Clarke M, Hetherington J. The Cochrane Collaboration. Eur J Clin Nutr. 2005 Aug;59 Suppl 1:S147-9; discussion S195-6. doi: 10.1038/sj.ejcn.1602188. PMID: 16052183.

[26]. Scholten RJ, Clarke M, Hetherington J. The Cochrane Collaboration. Eur J Clin Nutr. 2005 Aug;59 Suppl 1:S147-9; discussion S195-6. doi: 10.1038/sj.ejcn.1602188. PMID: 16052183.

[27]. Celik-Ozenci C, Tasatargil A, Tekcan M, Sati L, Gungor E, Isbir M, Erler F. Effect of abamectin exposure on semen parameters indicative of reduced sperm maturity: a study with rural workers in Antalya (Turkey). Andrologia. 2012;44(6):388–395. doi: 10.1111/j.1439-0272.2012.01297.x.

[28]. Cunha TS, Moura MJCS, Reis LO. Níveis séricos de testosterona e globulina ligadora de hormônios sexuais em homens saudáveis: influência da idade e do índice de massa corporal. Revista Brasileira de Medicina do Esporte. 2022;26(4):314-318. doi:10.1590/1517-869220202604223202.

[29]. Nunes GS. Immunochemical methods for analyzing environmental contaminants: concepts, state of the art and perspectives. Quím Nova. 2005;28(3). https://doi.org/10.1590/S0100-40422005000300018.

[30]. Abbassy MA, et al. Adverse biochemical effects of various pesticides on cotton field sprayers in El-Behira Governorate, Egypt. Biomed Aging Pathol. 2014. http://dx.doi.org/10.1016/j.biomag.2014.04.004.

[31]. Yucra S, et al. Dialkyl phosphate metabolites of organophosphorus in applicators of agricultural pesticides in Majes - Arequipa (Peru). J Occup Med Toxicol. 2006;12(4):355-361.

[32]. Straube E, Straube W, Krüger E, Bradatsch M, Jacob-Meisel M, Rose HJ. Disruption of male sex hormones with regard to pesticides: pathophysiological and regulatory aspects. Toxicol Lett. 1999;107:225–231.

[33]. Czarnywojtek A,et al. The effect of endocrine disruptors on the reproductive system-current knowledge. European Review for Medical & Pharmacological Sciences, 2021; 25:15.

[34]. Freire C, Koifman RJ, Sarcinelli PN, Rosa ACS, Clapauch R, Koifman S. Association between serum levels of organochlorine pesticides and sex hormones in adults living in a heavily contaminated area in Brazil. Int J Hyg Environ Health. 2014;217:370–378.

[35]. Santos R, Piccoli C, Cremonese C, Freire C. Thyroid and reproductive hormones in relation to pesticide use in an agricultural population in Southern Brazil. Pesquisa Ambiental. 2019;173:221–23.

[36]. Krause W, Homola S. Alterations of the seminiferous epithelium and the Leydig cells of the rat testis after the application of dichlorvos (DDVP). Bull Environ Contam Toxicol. 1974 May;11(5):429-433. Springer Science and Business Media LLC. http://dx.doi.org/10.1007/bf01685299.

[37]. Fattahi, Parivar, Jorsaraei, Moghadamnia. The effects of diazinon on testosterone, FSH and LH levels and testicular tissue in mice. Int J Reprod Biomed. 2009 Nov;7(2):59-64.

[38]. Erthal RP, Siervo GEML, Frigoli GF, Zaninelli TH, Verri WA, Fernandes GSA.Exposure to malathion during the juvenile and peripubertal periods decreases the regulation of the androgen receptor and the expression of the testicular 17-ß-HSD gene and compromises sperm quality in rats. J Dev Orig Health Dis. 2023 Apr;14(2):286-293. DOI: 10.1017/S2040174422000599. EPub 2022 Nov 7. PMID: 36336997.

[39]. Erthal RP, Siervo GEML, Staurengo-Ferrari L, Fattori V, Pescim RR, Verri WA, Fernandes GSA. Impairment of postnatal epididymal development and immune microenvironment following administration of low doses of malathion during juvenile and peripubertal periods of rats. Hum Exp Toxicol. 2020 Jun 4;39(11):1487-1496. SAGE Publications. http://dx.doi.org/10.1177/0960327120930076.

[40]. Liu C, Qu J, Wu M, Huang X, Li L. Cypermethrin triggers YY1-mediated testosterone biosynthesis suppression. Ecotoxicol Environ Saf. 2021 Dec 1;225:112792. doi: 10.1016/j.ecoenv.2021.112792. Epub 2021 Sep 17. Erratum in: Ecotoxicol Environ Saf. 2022 Jul 8;242:113871. PMID: 34544022.

[41]. Vieira S. SHBG, obesity, diabetes and PCOS: more free and bound hormones. 2017. Available at: https://drasuzanavieira.med.br/2017/02/01/shbg-obesidade-diabetese-sop/. Accessed on: February 24, 2021.

[42]. Gineco Academy.2023 Principais condições que aumentam ou diminuem os níveis séricos de SHBG. Disponível em: https://app.ginecoacademy.com/principais-condicoes-que-aumentam-ou-diminuem-os-niveis-sericos-de-shbg/?utm_source=chatgpt.com. Acesso em: 21 fev. 2025.

[43]. MORAIS, Irani da Silva. Avaliação da puberdade e indução de neomachos de tambaqui Colossoma macropomum através da administração de esteroides sexuais na ração. 2023.

[44]. Cremonese C. Exposure to pesticides and reproductive disorders: study in rural workers, their families and young people in the municipality of FarroupilhaRS. 2014.

[45]. Ubaid ur Rahman, H., Asghar, W., Nazir, W., Sandhu, M. A., Ahmed, A., & Khalid, N. (2020). A comprehensive review on chlorpyrifos toxicity with special reference to endocrine disruption: Evidence of mechanisms, exposures and mitigation strategies. Science of The Total Environment, 142649. doi:10.1016/j.scitotenv.2020.1426.

[46]. Cremonese C, Piccoli C, Pasqualotto F, Clapauch R, Koifman RJ, Koifman S, Freire C. Occupational exposure to pesticides, reproductive hormone levels and sperm quality in young Brazilians. Reprod Toxicol. 2017;67:174-185. doi: 10.1016/j.reprotox.2017.01.001.

[47]. Kamijima M, Hibi H, Gotoh M, Taki K, Saito I, Wang H, Itohara S, Yamada T, Ichihara G, Shibata E, Nakajima T, Takeuchi Y. A Survey of Semen Indices in Insecticide Sprayers. J Occup Health. 2004;46:109–118.

[48]. Manfo FPT, Moundipa PF, Déchaud H, Tchana AN, Nantia EA, Zabot M-T, Pugeat M. Effect of agropesticide use on male reproductive function: A study in farmers in Djutitsa (Cameroon). Environ Toxicol. 2010;27(7):423-432. doi: 10.1002/tox.20656.

[49]. Bole-Feysot C, et al. Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. Endocr Rev. 1998;19(3):225-268.

[50]. Guelho D, et al. Prolactin and metabolism – a different perspective on a multifunctional hormone. Port J Endocrinol Diabetes Metab. 2016;11(2):268-276.

[51]. Petronilho, F; Giustina, A D; Danielski, L G. Chapter 4 - The role and function of specialized blood–neuronal barriers: Blood–CSF, blood–retinal, blood–spinal cord, blood–labyrinth, blood–nerve barriers, and blood–brain barrier (BBB).Neurobiology of Infectious Diseases. Neurobiology of Disease. 2025, Pages 49-69.

[52]. Snyder PJ. Causes of hyperprolactinemia [Internet]. Waltham (MA): UpToDate; 2017. Available from: https://www.uptodate.com/contents/causes-of-hyperprolactinemia. Accessed on: March 12, 2022.

[53]. SANTANA, Lidiana Bandeira de. Características clínicas e laboratoriais de mulheres com diagnóstico de artrite reumatóide e sua associação com as concentrações séricas de prolactina. 2021. 161 f., il. Dissertação (Mestrado em Ciências da Saúde) — Universidade de Brasília, Brasília, 2021.

[54]. Bapayeva G, Poddighe D, Terzic S, Zhumadilova A, Kulbayeva S, Terzic M. Exposure to organochlorine pesticides in adolescent females: potential impact on sex hormones and interleukin-1 levels. Pesquisa Immunológica. 2018. doi: 10.1007/s12026-018-9049-9.

[55]. Teresa U, et al. Dietary intake of potentially toxic elements and children's chemical exposure. Curr Opin Environ Sci Health. 2022;30:100393. doi:10.1016/j.coesh.2022.100393.

[56]. Koifman S, Hatagima A. Exposure to pesticides and environmental cancer. Available in: Accessed on: April 29, 2012.

[57]. Hernández, IB, Carrillo, RV, García, IC. (2009). Alteraciones en la fertilidad masculina por exposición a pesticidas.Rev Int Androl. , 7(2), 98–105. doi:10.1016/s1698-031x(09)71614-0

Submitted: August 14, 2024

Accepted: February 21, 2025

Published: July 7, 2025

Author Contributions	
Jaciara Pinheiro de Souza:	Lead author, responsible for the study's conception and design, as well as data interpretation. She drafted the introduction, methods, and results sections, and also handled the submission on the Prospero platform. She made significant contributions to the critical review of intellectual content and approved the final version for publication. She is committed to ensuring the integrity and accuracy of all aspects of the work.
Cristiani Isabel Banderó Walker:	Substantially contributed to data analysis and actively participated in drafting the results. They critically reviewed the manuscript content to ensure its scientific relevance. They approved the final version for publication and took responsibility for the accuracy and integrity of the work.
Murilo de Jesus Porto:	Responsible for data acquisition and detailed review of the methods, contributing to the study's robustness. They participated in the critical review of intellectual content and in drafting the discussion. They approved

	the final version of the manuscript and ensured that all issues related to data integrity were resolved.
Jeferson de Menezes Souza:	Participated in the study's conception and data interpretation, contributing to the drafting of conclusions. They conducted the final manuscript review and approved the version for publication. They are committed to investigating and resolving any issues related to the integrity of the work.
Liz Oliveira dos Santos:	Substantially contributed to the study's design and data collection, ensuring that the methods were rigorously applied. They participated in drafting the introduction and critically reviewing the results to ensure scientific relevance. They approved the final version for publication and took responsibility for the accuracy and integrity of the entire work.
Maria de Fátima Santana de Souza Guerra:	Substantially contributed to the study's design and data collection, ensuring that the methods were rigorously applied. They participated in drafting the introduction and critically reviewing the results to ensure scientific relevance. They approved the final version for publication and took responsibility for the accuracy and integrity of the entire work.
André Lacerda Braga Teles:	Responsible for statistical analysis of the data and interpretation of the results, directly contributing to the study's scientific validity. They assisted in drafting the results and discussion sections, and critically reviewed the content to ensure intellectual quality. They approved the final version of the manuscript and are committed to maintaining the integrity and accuracy of all aspects of the work.
All authors contributed the final version of the text.	

Financing:	No financing.
Conflict of interest:	The authors declare no conflict of interest.

Corresponding author:	Jaciara Pinheiro de Souza Universidade Federal de Sergipe (UFS) São Cristovão/SE, Brasil jacipinheirosouza@hotmail.com