REVIEW
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Paracetamol: scoping review on the safe dose and maximum permitted daily exposure limit

Paracetamol: revisão de escopo sobre a dose segura e o limite máximo de exposição diária permitida

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ABSTRACT

Introduction: Paracetamol, also known as N-acetyl-p-aminophenol (APAP), has long been a widely used medication for pain management. The inadvertent toxicity associated with APAP poses a global concern. **Objective:** To investigate and critically evaluate the safety of the currently established dose of 4 g/day for paracetamol. To calculate the Permitted Daily Exposure (PDE) values for paracetamol. **Method:** A scoping review was performed according to the Joanna Briggs Institute (JBI), and the report was based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. The calculation of PDE values for paracetamol was carried out in accordance with the guidelines provided by the European Medicines Agency (EMA) and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). **Results:** The PDE value calculated for paracetamol was 51.1 mg/day. Characteristics such as female sex, fasting or malnutrition, alcohol abuse, age over 40 years, comorbidity, and drug interactions with phenytoin, isoniazid, and protease inhibitors such as ritonavir and zidovudine are factors that may contribute to APAP toxicity. **Conclusions:** Drugs containing paracetamol are safe when used within the dosage and posology recommended of at most 4 g/day. Based on the data presented in this study, the following were identified as relevant risk factors for paracetamol toxicity: sex, diet, age, alcohol use, and drug interactions. The calculated PDE value for APAP is 51.1 mg/day. This implies that if an individual is consistently exposed to this daily dose throughout their lifetime, it is unlikely that any adverse effects will be observed.

KEYWORDS: Paracetamol; Scoping Review; Permitted Daily Exposure; Safety Dose

RESUMO

Introdução: O paracetamol, também conhecido como N-acetil-p-aminofenol (APAP), tem sido amplamente utilizado como medicamento para o manejo da dor. A toxicidade inadvertida associada ao APAP representa uma preocupação global. **Objetivo:** Investigar e avaliar a segurança da dose atualmente estabelecida de 4 g/dia para o paracetamol. Calcular os valores de exposição diária permitida (PDE) para o paracetamol. **Método:** Foi realizada uma revisão de escopo de acordo com as diretrizes do *Joanna Briggs Institute* (JBI), e o relato seguiu o *checklist Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews* (PRISMA-ScR). O cálculo do valor de PDE para o paracetamol foi realizado conforme as diretrizes fornecidas pela Agência Europeia de Medicamentos (EMA) e pelo Conselho Internacional para Harmonização de Requisitos Técnicos para Produtos Farmacêuticos de Uso Humano (ICH). **Resultados:** O valor de PDE calculado para o paracetamol foi de 51,1 mg/dia. Ser do sexo feminino; com idade superior a 40 anos; histórico de abuso de álcool, desnutrição ou jejum; e uso concomitante de medicamentos contendo fenitoína, isoniazida, inibidores de protease como o ritonavir e a zidovudina foram fatores relatados como potencializadores da toxicidade do APAP. **Conclusões:** Medicamentos contendo paracetamol são seguros quando utilizados nas

doses e posologias recomendadas, limitadas a, no máximo, 4,0 g ao dia. Conforme dados deste estudo, identificaram-se como fatores de risco relevantes para a toxicidade do paracetamol: sexo, alimentação, idade, uso de álcool e interações medicamentosas. O valor de PDE calculado para o APAP, de 51,1 mg/dia, indica que caso um indivíduo seja exposto continuamente a essa dose diária ao longo da vida, é improvável que efeitos adversos sejam observados.

PALAVRAS-CHAVE: Paracetamol; Revisão de Escopo; Exposição Diária Permitida; Dose de Segurança

INTRODUCTION

Although it is the most widely used over the counter (OTC) medication worldwide, the safety profile and mechanism of action of paracetamol are not yet fully understood, even after many years of widespread use[1].

Paracetamol, also known as acetaminophen or acetyl-p-aminophenol (APAP), was synthesized in 1878 by Morse and introduced into medicine as an antipyretic and analgesic by Von Mering in 1893. Initially, paracetamol was used as a substitute for phenacetin, and after it was confirmed that it is its main metabolite and has lower nephrotoxic potential, it began to widely replace it starting in the 1950s, establishing itself as a medication used worldwide[1,2].

According to McCrae et al.[3], the therapeutic use of paracetamol has long been associated with markers of liver injury. Indeed, over the past few decades, several case reports and small studies have suggested a link between the ingestion of therapeutic doses of paracetamol and liver injury[3].

In case reports of liver injury in patients using therapeutic doses, additional factors, such as alcohol abuse, nutritional deficiency, or concomitant febrile illness, are often present. Regarding renal effects, acute kidney injury is reported to occur in 1–2% of patients with paracetamol overdose. Renal biopsy, although not frequently performed, shows evidence of acute tubular necrosis, particularly of the proximal tubular segment[4].

One of the tools for the toxicological evaluation of pharmaceutical active ingredients is the establishment of the permitted daily exposure (PDE). The values expressed by the PDE represent a dose that is unlikely to cause an adverse effect if an individual is exposed to that dose, or a lower one, by any route of administration, daily throughout their lifetime[5].

The objective of determining a maximum exposure limit based on health considerations is to ensure human safety. Consequently, high-quality clinical data from human studies are considered highly relevant. To determine the PDE, it is necessary to identify the most critical effect(s) of that specific pharmaceutical ingredient. If the most critical effect identified is based on pharmacological and/or toxicological effects observed in humans (rather than in animal models), a careful evaluation of the clinical data may be necessary for the calculation of the PDE[6].

In animal experiments, studies are typically conducted on single-dose (acute) toxicity, repeated-dose toxicity, reproductive toxicity, genotoxicity, and local tolerance. These assessments allow for the establishment of the dose level at which no adverse effects are observed, known as the no observed adverse effect level (NOAEL), as well as the lowest dose at which adverse effects begin to be observed, referred to as the lowest observed adverse effect level (LOAEL)[7].

However, it is recognized that acceptable differences may occur in PDE calculations, which may be related to data availability, the specific scientific policies of each laboratory, as well as the decisions and judgment of the experts involved. These discrepancies can lead to variations of up to three times for lower or higher values. Thus, the unnecessary application of high safety factors can result in an excessively conservative PDE value[8].

One of the main concerns of regulatory agencies relates to the robustness and reliability of PDE reports, since these depend on the level and depth of the assessment conducted by the toxicologist. PDE reports that do not follow rigorous risk assessment criteria or that lack relevant studies may result in the determination of imprecise and unreliable threshold values.

High-quality PDE determination, involving the comprehensive use of all available data, including pharmacological, toxicological, preclinical, and clinical studies and information, is essential for establishing a reliable PDE value[9].

In this context, the objective of this study was to investigate and critically evaluate the safety of the currently established dose of 4 g/day for paracetamol, using a scoping review. Additionally, PDE values for oral paracetamol were calculated based on toxicological data available in literature and international guidelines, to provide technical and scientific support for the revision of standards and the promotion of the drug's safe use in therapeutic contexts.

METHOD

This study was conducted in two methodological stages.

In the first stage, a scoping review of the literature was conducted, following the methodology proposed by the Joanna Briggs Institute (JBI), with the report guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist, which provides guidelines for the writing and transparency of scoping reviews[10,11].

In the second stage, based on the data obtained from the scoping review, calculations were performed to determine the PDE values for oral paracetamol, in accordance with the guidelines of the European Medicines Agency (EMA) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[12,13].

Literature review on the safe dose of paracetamol

The literature review conducted in the first stage of this study consisted of a scoping review, as recommended by the JBI. To conduct the scoping review, the methodological steps recommended by the JBI were followed: definition of the research question, establishment of inclusion and exclusion criteria, development of the search strategy, selection of studies/sources of evidence, data extraction, and analysis and presentation of results[10].

Identification of the guiding research question

According to the JBI, the formulation of the research question should follow the PCC (population, concept, and context) strategy[11]. In this study, "population" was defined as acetaminophen; "concept" as toxicity; and "context" as the maximum safe daily dose. Thus, the guiding question was: Is the established maximum daily dose for paracetamol truly safe? This question guides the PDE analysis based on more precise toxicological data.

Eligibility criteria

The eligibility criteria were defined based on the main question and guided by the PCC strategy. The following were included: preclinical studies (*in vitro* and *in vivo*) on the toxicity of acetaminophen; scientific articles, monographs, theses, dissertations, technical reports, guidelines, and official compendia; clinical studies published in English, Portuguese, Spanish, French, or German, with no date restriction. The following were excluded: studies not focused on the *in vivo* or *in vitro* toxicity of paracetamol; incomplete publications; theoretical reviews; and works that did not meet the inclusion criteria.

Search Strategy

Following the JBI approach, a broad search was conducted in the MedLine/PubMed, Science Direct, and BVS/Lilacs databases. The following descriptors were used: paracetamol, acetaminophen, toxicity, dose, safety, non-clinical, preclinical, and dosage, based on the MeSH (PubMed) and DeCS (BVS) vocabularies.

The strategies included Boolean operators (AND, OR, NOT), quotation marks for compound terms, parentheses for groupings, and truncation (* and $). The results were organized in Mendeley®, which eliminated duplicates and assisted in screening for eligibility.

Study Selection

The selection was conducted by two reviewers, independently and in a blind manner, in two stages. In the first stage, eligibility criteria were applied to titles and abstracts. In the second stage, the full texts of the preselected studies were read. Disagreements were resolved by consensus. Exclusions were recorded with justification.

Data extraction

Two researchers independently extracted data using a standardized form that had been previously tested and adjusted. The form was divided into three sections, according to the type of information available in the studies. The collected data were organized and included in the final synthesis of the review.

Qualitative synthesis

The studies were described and compared using alphanumeric coding (A1, A2, A3...), with data organized in a summary table. The synthesis highlighted key aspects and gaps and allowed for a critical analysis of the findings in relation to the study objectives, with implications for practice, public policy, and future research.

Pharmacovigilance data collection

Data were collected from the VigiMed system of the Brazilian National Health Surveillance Agency (Anvisa), filtered by the active ingredient "paracetamol." Variables included type of report, reporter profile, severity of events, annual frequency, and classification according to MedDRA. The analysis focused on the profile of reporters, severity, and temporal evolution of adverse events.

Calculation of PDE and adjustment factors

In the second stage of this study, to calculate and define the PDE, it was necessary to interpret the data found in the toxicological studies obtained through the literature review. The toxicological assessment consisted of the following phases: hazard identification, identification of critical effects, determination of POD (Point of Departure) values, such as the NOAEL, definition of safety or uncertainty factors, and calculation of the PDE.

To establish the PDE, adjustment factors—also known as safety factors, uncertainty factors, or modifiers—were applied in accordance with EMA and ICH Q3C guidelines[12,13]. The PDE values were calculated using the following equation:

PDE = POD * Standard Weight/F1*F2*F3*F4*F5[14], where:

POD: Point of Departure (NOAEL);

Standard Weight: Standard weight of an adult human = 50.0 kg[12];

F: Adjustment factors – in accordance with EMA and ICH Q3C guidelines[12,13];

F1: A factor ranging from 2 to 12 to account for interspecies extrapolation[12];

F2: A factor of 10 to account for inter-individual variability[12];

F3: A factor ranging from 1 to 10 based on the duration of exposure[12];

F4: A factor ranging from 1 to 10 for cases of severe toxicity[12];

F5: A variable factor to be applied when the NOAEL has not been established. It should be used only when the LOAEL is available. A factor of 5 or 10 will be used, depending on the severity of the toxicity[13];

The value assigned to the POD is the same as that determined for the NOAEL. The standard weight established for an adult male is 50.0 kg[12].

RESULTS AND DISCUSSION

Study Selection

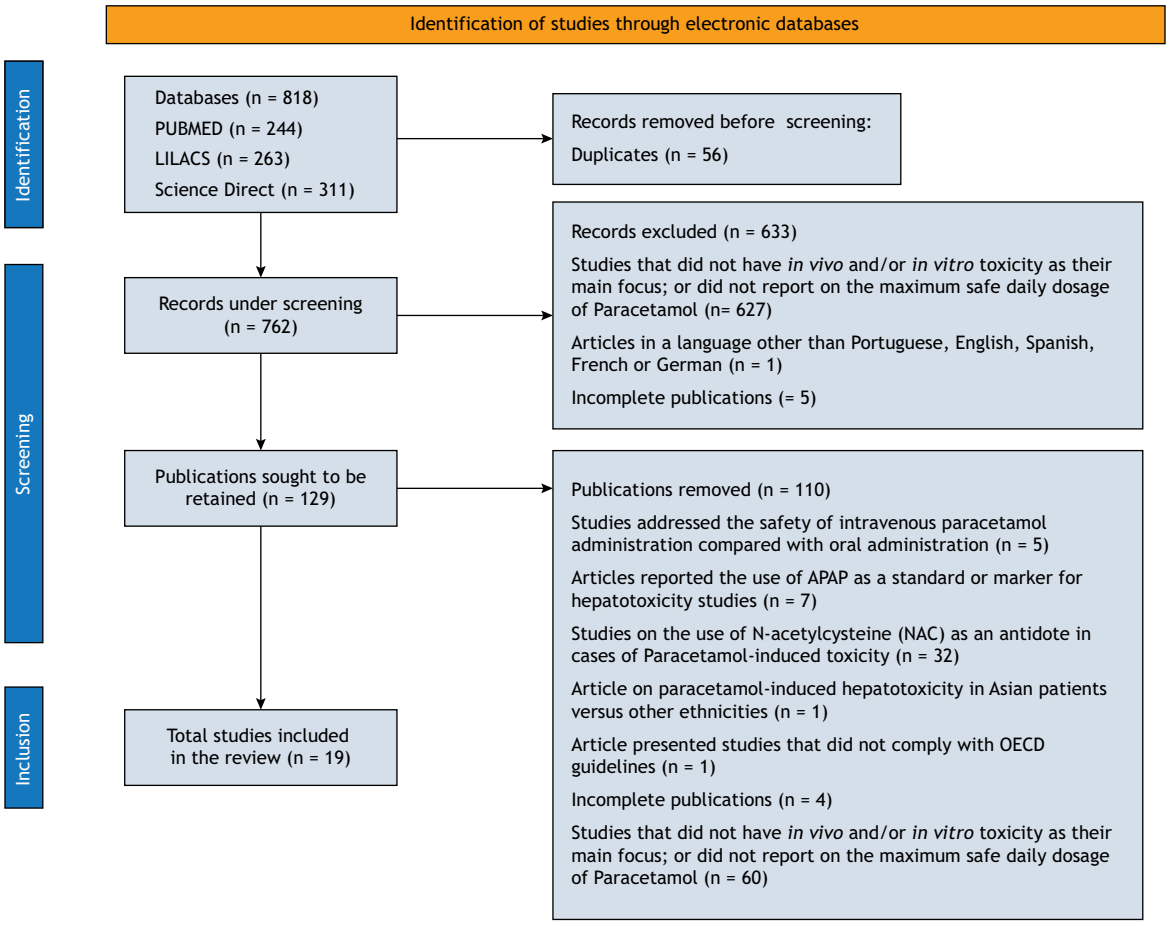
A total of 818 references were identified in the selected databases. After the automatic exclusion of 56 duplicates by the Mendeley® manager, 762 studies proceeded to screening by title and abstract, resulting in the exclusion of 633 articles for failing to meet eligibility criteria, such as inappropriate focus, incompatible language, or incomplete publications.

In the second phase, 129 articles were read in full, of which 110 were excluded for various reasons, such as a focus on intravenous administration, the use of acetaminophen as a marker, studies on antidotes such as N-acetylcysteine, methodological inadequacy, or the absence of data on toxicity or safe dose. In the end, 19 studies comprised the final sample of the scoping review.

The PRISMA-ScR flowchart (Figure) highlights the selection stages of the full-text documents analyzed in this review, as well as the exclusion of publications that did not meet the eligibility criteria.

Extraction of information from the studies selected in the scoping review related to paracetamol safety

The Table presents a summary of the main data collected from each of the studies.



Source: Prepared by the authors, 2023.

Figure. PRISMA-ScR flowchart.

Table. Summary of the main data collected in the eligible studies.

Article	Author (Year)	Study Scope	Parameters and/or assumptions and/or outcomes included	Relevant Result(s)
A1	Hantson et al. (1996)	Genotoxicity of APAP.	There was no difference in the percentage of abnormal cells (lymphocytes) before and after APAP administration in volunteers.	APAP does not exhibit mutagenic properties in humans.
A2	Shayiq et al. (1999)	Hepatotoxicity of APAP.	Study designed to simulate tolerance to lethal doses of APAP.	Rats developed mild hepatotoxicity after administration of a dose four times the lethal dose 50 (LD50).
A3	Matsunaga et al. (2004)	Relationship between APAP-induced hepatotoxicity and dose administration according to time of day and feeding.	The hepatotoxicity generated after administration of APAP at 9:00 PM was significantly more severe than that following administration of APAP at 9:00 AM.	Adjusting feeding times and selecting the most appropriate time for of APAP may help minimize hepatic hepatotoxicity.
A4	Dart et al. (2005)	Safety evaluation of APAP in extended-release formulations.	Searches conducted from 1980 to June 2003 in EMBASE and MEDLINE for extended-release paracetamol formulations.	Safety is comparable to that of immediate-release tablets.
A5	Kozer et al (2006)	Reports of liver problems associated with exposure to repeated doses of APAP above the established limit	Literature review on chronic supratherapeutic exposure to APAP in children and the different dosing guidelines.	The study suggests that liver injury secondary to repeated doses of acetaminophen should be considered when a child has received more than 75 mg/kg/day for at least two days.
A6	Krenzelok (2009)	Joint meeting of three Advisory Committees convened by the FDA. APAP is one of the leading causes of health problems following overdose worldwide, but particularly in more developed countries.	Strategies, proposals, and recommendations for the problem at hand were discussed.	The FDA proposed a reduction in the maximum daily dose from 4,000 to 3,250 mg, reducing the maximum single dose from 1,000 to 650 mg, and suggesting that 500 mg tablets be made prescription-only. The three Commissions voted in favor of each of these initiatives.
A7	Hornsby et al. (2010)	Assessment of patient knowledge regarding dosage, toxicity, and recognition of medications containing APAP	Descriptive, non-experimental, cross-sectional study.	Two-thirds of the 284 patients who completed the survey reported recent use of medication for pain, colds, or allergies. Of these, 25% reported knowing the active ingredient. Among the patients, 46% knew that acetaminophen was synonymous with Tylenol. Several patients (12%) believed that ingesting a harmful amount of APAP was difficult or impossible. One-third of the patients correctly identified the maximum daily dose, 10% reported a dose greater than 4 g, 25% were unsure of the dose, and 7% were unsure if there was a maximum dose.
A8	Guggenheimer et al. (2011)	In April 2010, the FDA conducted a review of the warning label for over the counter (OTC) acetaminophen-. The authors reviewed the potential for liver toxicity.	Literature review containing data on APAP- -associated liver toxicity.	The following factors increase the risk of APAP toxicity: being female, fasting or being malnourished, alcohol abuse, being over 40 years of age, and concomitant use of medications such as phenytoin, isoniazid, protease inhibitors (such as ritonavir), and zidovudine.
A9	Klotz (2012)	Report on the safe dose of acetaminophen.	Evaluation of the maximum daily dose of acetaminophen, widely prescribed for the treatment of acute and chronic pain, with a focus on liver safety.	It was concluded that the maximum daily dose is 4 g/day to avoid adverse effects on the liver.
A10	Thiele et al. (2013)	Review of the effects of APAP on pregnant women and fetal development.	APAP appears to cross the placenta freely; therapeutic and certainly toxic doses could affect not only the mother but also fetal hepatocytes.	It is concluded that future studies are needed to reassess the safety and dosage of APAP during pregnancy—based on advances in the field of reproduction as well as in APAP metabolism.
A11	Heard (2014)	Evaluates repeated-dose toxicity in children through a systematic review.	Examines reports of liver toxicity or death in children over 6 years of age who were administered repeated doses of APAP.	A study suggesting that doses of less than 75 mg/kg/day of acetaminophen are safe for children over 6 years of age.
A12	Venkatesan et al. (2014)	Study on subacute toxicity	Evaluation of the subacute toxicity of APAP in rats, considering administration of 250 to 1,000 mg/kg.	The NOAEL for acetaminophen in rats is 500 mg/kg.

Continue

Continuation

A13	Yiang et al. (2015)	Evaluation of whether APAP causes cytotoxic effects in human stem cells.	*In vitro* test—cell culture in rats.	High doses of paracetamol induce a greater cytotoxic effect in human mesenchymal stem cells than in renal tubular cells.
A14	Jaeschke, Hartmut (2015)	Hepatotoxicity caused by acetaminophen.	Despite the efficacy of NAC in patients presenting shortly after an APAP over, there is a need to develop intervention strategies for patients with delayed onset of toxicity.	A challenge related to acetaminophen toxicity is to better understand the mechanism of cell death to limit hepatic injury and prevent acute liver failure.
A15	Kane et al. (2016)	Paracetamol hepatotoxicity.	Assessment of the risks and mechanisms of hepatotoxicity caused by acute, subchronic, or chronic doses in elderly or frail rats.	No more severe hepatotoxicity occurs in aged rats or in frail rats.
A16	Toyoda et al. (2018)	Assessment of subchronic toxicity in rats.	Impact of hepatotoxicity in rats and a study of subchronic toxicity in obese and normal-weight rats.	Obese rats are less susceptible to APAP-induced toxicity than lean rats.
A17	Van der Leede (2020)	Information on mutagenicity for APAP.	Tests in rats and evaluation of APAP mutagenicity.	APAP was used as a reference standard because it does not exhibit mutagenic properties.
A18	Freo et al. (2021)	Scope review providing recommendations on guidelines for correct dosing and safe use of APAP, as it is the most widely used medication for pain management.	Scope review aimed at providing an overview of current guidelines for the use of paracetamol in the treatment of common pain.	APAP has a favorable safety profile across all age groups, especially among the elderly. Despite concerns about hepatic toxicity, this is considered unlikely at doses up to 4 g/day. Even amid questions regarding efficacy and safety, the drug remains recommended for acute and chronic pain, being preferred due to its better tolerability compared to NSAIDs and opioids.
A19	Sirois (2021)	Assessment of APAP carcinogenicity.	Reviews evaluating various data sources, including results on preclinical carcinogenicity and genotoxicity.	APAP is not carcinogenic when administered at recommended doses.

APAP: Acetaminophen; OTC: over-the-counter product; FDA: Food and Drug Administration.
Source: Author's own work, 2023.

Liver-related safety information

Paracetamol (acetaminophen or APAP) is widely recognized for its safe therapeutic profile, provided it is used at recommended doses. However, analysis of the articles included in this review reveals that the liver is the primary target organ of paracetamol toxicity, especially in contexts of overdose, prolonged use, specific nutritional states, and in vulnerable populations.

Of the 19 studies selected from the databases according to the eligibility criteria, eight provided data on paracetamol-induced liver toxicity: A2, A3, A4, A8, A10, A14, A15, and A18 (Table).

According to article A18, paracetamol is one of the most prescribed and widely used analgesics and antipyretics worldwide and is considered a first-line medication in various clinical guidelines. The standard dose for adults ranges from 500 mg to 1,000 mg per administration, with a maximum recommended daily dose of 3 to 4 g per day. The author of this study states that despite concerns about hepatic toxicity, this is considered unlikely at doses of up to 4 g/day[15]. Article A8 reinforces this information by reporting that ingestion of doses exceeding 4 g over a 24-hour period constitutes potentially toxic exposure, which may be associated with cases of acute liver failure[16], while Article A9 reiterates that the use of up to 4 g/day of APAP is associated with a low risk of adverse hepatic effects, reinforcing its role as a first-line drug in pain management, provided that dosage guidelines are followed[17].

As described in the same article (A8), acetaminophen overdose is the leading cause of acute liver failure in the United States. Between 2000 and 2004, approximately 1,600 cases were reported annually, of which up to 86% were related to accidental or intentional overdoses. The percentage of cases attributed to acetaminophen increased from 28% in 1998 to 51% in 2003[16]. Article A14 corroborates these findings by highlighting that, although acetaminophen is safe at therapeutic doses, it is responsible for more cases of acute liver failure than all other causes combined[18].

Article A4 investigated liver toxicity associated with extended-release formulations, concluding that, although there are no substantial differences compared to immediate-release formulations, hepatotoxicity remains the main adverse event reported[19].

The mechanism of hepatotoxicity is detailed in Articles A2 and A18. At therapeutic doses, paracetamol is predominantly metabolized by conjugation with glucuronic acid and sulfate. A smaller fraction, less than 10.0%, is oxidized by the CYP2E1 enzyme, forming the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). In cases of overdose, NAPQI accumulates, binds to mitochondrial proteins, and causes hepatocellular necrosis due to mitochondrial dysfunction and oxidative stress[15,20].

The risk of hepatotoxicity is amplified by several predisposing factors, as reported in articles A2, A3, and A8. Among these factors, the following stand out: prolonged fasting, malnutrition, chronic alcoholism, age over 40 years, and the concomitant use of hepatotoxic drugs or enzyme inducers (such as phenytoin, isoniazid, ritonavir, and zidovudine)[16,20,21]. Article A3 experimentally demonstrated that the administration of paracetamol on an overnight fast resulted in significantly more severe hepatotoxicity compared to morning administration with a meal[21].

Additional concerns regarding hepatic toxicity in pregnant women are reported in Article A10, which notes that acetaminophen appears to cross the placenta and may affect fetal hepatocytes in cases of overdose[22].

Article A6 reports that, despite its history of safe use, acetaminophen overdose remains a significant concern. In this regard, the Food and Drug Administration (FDA), in response to the growing number of cases, has implemented changes to the labeling of medications containing APAP (A8 and A6) and has convened advisory committees to discuss risk-reduction strategies[16,23].

According to Article A15, a study aimed to evaluate changes in the risk and mechanisms of hepatotoxicity associated with acute, chronic, and subacute exposure to acetaminophen in mice to assess aspects such as “aging” and “frailty.” Young and aged male C57BL/6 mice were exposed to acute (300 mg/kg via oral gavage), chronic (100 mg/kg/day in the diet for six weeks), or subacute (250 mg/kg/day for three days) paracetamol administration, with saline used for the control group. Following administration, serum and liver tissue were collected for toxicity assessment. There were no differences related to advanced age or frailty in the degree of hepatotoxicity induced by acute, chronic, or subacute exposure to acetaminophen after evaluation of serum liver enzymes and histology results. In conclusion, there was no increase in the incidence of hepatotoxicity in aged or frail mice[24]. Unlike most of the studies found, this article presents a different conclusion on the topic. Therefore, it is important that new similar studies be conducted to confirm, refute, or expand this discussion.

Based on these data, it is observed that acetaminophen is safe when used rationally. However, its widespread availability, combination with other medications, and low risk perception among users require robust educational and regulatory actions. The role of pharmacists, in conjunction with that of physicians and other healthcare professionals, is fundamental to promoting the safe use of APAP, especially in at-risk populations. The inclusion of clear warnings on labels, as well as health education, is an essential measure to mitigate cases of hepatotoxicity related to the inappropriate use of this widely consumed drug.

Safety information related to diet, alcohol use, age, drug interactions, and gender

The widespread use of acetaminophen (APAP) worldwide for the treatment of pain and fever raises ongoing debates about the safety of its administration in different population groups. Several studies discuss the characteristics of acetaminophen regarding its toxicity, therapeutic margin, drug interactions, and factors that increase the risk of adverse reactions, such as concomitant alcohol use, prolonged fasting, advanced age, use in children, and comorbidities. In this scoping review, of the 19 studies selected according to the eligibility criteria, only seven provided data on paracetamol safety considering the characteristics mentioned above, namely: A3, A5, A8, A9, A10, A11, and A18 (Table).

According to study A3, hepatotoxicity caused by a paracetamol overdose at 9:00 PM, on an empty stomach and before bedtime, was significantly more severe than hepatotoxicity resulting from an overdose at 9:00 AM, accompanied by breakfast. In other words, administering APAP after eating minimizes the risk of hepatotoxicity[21].

Patients with psychiatric disorders also present an increased risk, as reported in Article A18. Data from the Liver Failure Study Group (2007–2013) showed that cases of acute liver failure due to unintentional APAP overdose were frequently associated with psychiatric comorbidities, including depression, suggesting the need for pharmacotherapeutic monitoring in these patients[15].

Overall, studies A3, A8, A9, A10, and A18 constitute a body of evidence that reinforces the importance of the rational use of acetaminophen. The safety of acetaminophen, although well established at therapeutic doses, requires continuous monitoring by regulatory agencies, healthcare professionals, and users to prevent inappropriate exposure and potentially serious adverse events.

Studies A5 and A11 report on toxicity in children. Study A5 notes that the true incidence of paracetamol poisoning from repeated doses in children is not well known. Many parents express concern when their children have a fever; however, only 30.0% of them are able to administer the correct medication. Thus, the true prevalence of overdose may be higher than reported, even though this occurrence is rare[25].

The assessment of toxicity induced by repeated doses in pediatric patients (A11) suggests that doses of less than 75 mg/kg per day of APAP are safe for children under 6 years of age[26].

The discussion regarding the safety of acetaminophen use in relation to diet, alcohol consumption, age, drug interactions, and gender highlights the complexity of clinical management to minimize hepatic risks. Food intake can influence drug metabolism, affecting bioavailability and therapeutic response; in some cases, prolonged fasting increases vulnerability to hepatic toxicity due to reduced glutathione reserves. Alcohol consumption, especially chronic use, induces the CYP2E1 enzyme, increasing the formation of the hepatotoxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), which heightens the risk of acute liver injury even at therapeutic doses. Age is also a critical factor, as older adults are at higher risk due to pharmacokinetic changes[27].

Safety information related to patients' knowledge regarding paracetamol use

Users' inadequate perception of the risks of paracetamol, as demonstrated in Article A7, provides insights into patients' knowledge regarding the use of paracetamol. This article presents a descriptive, non-experimental cross-sectional study, reporting that only 11.0% of patients were able to correctly identify the alternative names for paracetamol (Tylenol®), and 58% of those using products containing APAP were unaware that they were using the active ingredient[28]. This lack of awareness increases the risk of unintentional overdose, especially with combination products that include both over the counter and prescription medications.

Paracetamol is a safe therapeutic necessity when administered at the recommended dose, and the wealth of published data reinforces that appropriate therapeutic use is associated with minimal risk, while overdose is strongly linked to liver damage. The author further notes that changing the legacy of decades of paracetamol use by the lay public will be a challenge, since the drug has been promoted as a safe and effective product. One solution would be to improve patient information through a collaborative effort between physicians and pharmacists. A warning on the outer packaging could also contribute to patient safety. The pharmaceutical industry should develop comprehensive and measurable educational programs aimed at reducing drug-related toxicity[28].

The discussion regarding patient knowledge about the safe use of acetaminophen reveals that, despite its widespread use, significant gaps persist in the correct understanding of dosages and associated risks. A study of health professionals showed that most recognize the risks to the liver resulting from excessive use, yet a significant proportion is unaware of the correct dosage. This lack of knowledge can lead to inappropriate use and high risks to liver health. Health education and targeted educational interventions are fundamental to promoting the rational and safe use of acetaminophen, reinforcing the need to advise patients on dosage, dosing intervals, and signs of toxicity. Promoting adequate knowledge also contributes to a culture of patient safety, helping to prevent adverse events related to the use of this very common medication. Thus, patient-directed educational practices represent an essential pillar for the safe use of paracetamol and the reduction of risks to public health[29].

Cytotoxicity

According to Article A13, studies have indicated that APAP can induce cytotoxicity in liver, kidney, and tumor cells. Most studies investigating cytotoxic mechanisms have focused on kidney and liver diseases and tumor cells. The present study was the first to demonstrate that APAP also induces cytotoxicity in human mesenchymal stem cells (hMSCs), suggesting that APAP not only triggers clinical hepatotoxicity and nephrotoxicity but is also harmful to stem cells. This study demonstrated that APAP exerts a more pronounced cytotoxic effect on hMSCs than on renal tubular cells. Stem cells are important in e fetal development, and stem cell dysfunction can be detrimental to fetal growth[30].

A matter of concern, from the perspective of embryofetal toxicity, relates to APAP's ability to cross the placental barrier[30]. This aspect may be of particular concern due to the hepatotoxicity associated with APAP and the liver's role as a hematopoietic organ during the prenatal period. Therefore, it is essential to conduct further similar studies to confirm, refute, or expand this discussion.

Paracetamol toxicological data extracted from the studies selected in the scoping review that will be used to calculate the PDE

Acute (or single-dose) and subacute oral systemic toxicity

According to Article A12, a study was conducted to evaluate the subacute oral toxicity of paracetamol in *Sprague Dawley* (SD) rats, with oral administrations of 250, 500, and 1,000 mg/kg body weight daily for 28 days. No statistically significant adverse effects were observed in hematological parameters. Biochemical parameters related to the liver and kidneys showed a significant difference at the 1,000 mg/kg body weight dose level in females, when compared to the control group. No adverse effects were observed in urinalysis parameters, nor were any macroscopic pathological changes noted. Histopathological changes in the livers of females were observed at the 1,000 mg/kg body weight dose level[31].

Genotoxicity

Study A17 provides information that APAP is a non-mutagenic compound, as previously known from data derived from tests on bacteria, *in vitro* mammalian cells, and *in vivo* transgenic rats. Furthermore, it demonstrated a good profile as a non-mutagenic reference compound for use in the international multi-laboratory validation of the *Pig-assay*[32].

These findings are consistent with several studies conducted in other non-clinical models, which have already demonstrated that APAP has no mutagenic potential[32].

Article A1 adds that short-term tests conducted with paracetamol demonstrated that this drug is incapable of producing genetic mutations in microorganisms or eukaryotic cells[33]. Thus, it can be stated that, from the perspective of genotoxicity, there is substantial evidence supporting the safety of paracetamol.

Carcinogenicity

Based on animal studies and epidemiological studies, the International Agency for Research on Cancer (IARC) reported that APAP does not pose a cancer risk to humans[34].

According to the study in Article A19, no increase in tumor incidence was observed in any organ system. This includes the results of bioassays to assess the occurrence of cancer in rats and mice, conducted over two years by the National Toxicology

Program (NTP), which found no evidence of carcinogenic activity in mice (male and female) and in male rats[35].

Therefore, from a carcinogenicity standpoint, robust evidence supports the safety of acetaminophen.

Reproductive and developmental toxicity

According to the European Chemicals Agency (ECHA), APAP does not pose a risk of reproductive and developmental toxicity[36].

Identified hazards

When establishing the PDE value for a substance, it is necessary to survey the identified hazards, which correspond to serious effects. According to the ICH, the following are considered serious effects: non-genotoxic carcinogenicity, neurotoxicity, reproductive toxicity, and teratogenicity[13].

APAP has not been associated with hazards related to genotoxicity, reproductive toxicity, or carcinogenicity[32,33,34,35,36].

Application of adjustment factors and calculation of the PDE value

According to ECHA, the NOAEL value is 357.5 mg/kg/day[36]. Considering this NOAEL value, along with the information extracted from the articles selected in the scope review, the value assigned to F1 was "7," considering that the species extrapolation was from rat to human[31]. The value for F2 was "10," which accounts for inter-individual variability and is already a pre-established value in the literature. F3 was assigned a value of "5," based on the study involving subchronic to chronic exposure lasting three months in rodents, extracted from article A16 selected in the scoping review[37]. Regarding F4, since no cases of severe toxicity were observed, the value assigned was "1"[32,33,34,35,36]. For F5, since the NOAEL value is used in the calculation, the value assigned was also "1"[36].

Regarding the POD value, the NOAEL value mentioned above was adopted[36].

As for the standard weight for an adult human, the EMA establishes the value of 50.0 kg[12].

In this context, the calculation for the PDE value was:

$$PDE = 357.5*50/\ 7*10*5*1*1 = 51.1\ mg/day.$$

The calculated value for the maximum PDE of paracetamol is 51.1 mg/day. Therefore, this value represents a dose that will not cause an adverse effect if administered to an individual every day throughout their entire life, in accordance with the current regulatory recommendation from Anvisa.

When comparing this PDE value with the maximum daily dose allowed for paracetamol (4 g/day), it is observed that the PDE value is 80 times lower than the established maximum daily dose. It is important to understand that the PDE and the maximum daily dose apply to different scenarios. The maximum daily dose is the reference for treating acute or chronic pain, with defined durations and intervals.

CONCLUSIONS

The studies selected for this scoping review indicate that paracetamol is safe when administered at the recommended dose. It is important to adhere to the maximum dose of 4 g per day to avoid the risk of toxicity from single and repeated doses. This recommendation minimizes the occurrence of acute liver injury associated with APAP use. There is robust evidence that acetaminophen is safe regarding carcinogenicity, genotoxicity, and reproductive toxicity. Characteristics such as gender, fasting or malnutrition, alcohol abuse, age over 40 years, comorbidities, and drug interactions with phenytoin, isoniazid, and protease inhibitors such as ritonavir and zidovudine are factors that may contribute to APAP toxicity.

No inconsistencies were observed in the selected studies. The calculated PDE value for APAP was 51.1 mg/day. This means that if an individual is exposed to this dose daily throughout their lifetime, adverse effects are unlikely to occur. This PDE value is 80 times lower than the established maximum daily dose of 4 g/day, which should be prescribed in cases of pain.

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Authors' Contributions

Nunes SSAS, Morais LO, Delgado IF - Conception, planning (study design), data collection, analysis, interpretation, and writing of the manuscript. All authors approved the final version of the manuscript.

Conflict of Interest

The authors declare that there is no potential conflict of interest with peers, institutions, politicians, or financial entities related to this study.

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