Review
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Toxicity and Safety Analysis of Polyhexamethylene Guanidine: A Comprehensive Systematic Review

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Abstract: Polyhexamethylene guanidine (PHMG) is a commonly used disinfectant, but safety concerns have arisen due to poisoning cases. This systematic review assesses the toxicity and safety of PHMG by inhalation, oral administration, skin contact, and ocular contact to determine its potential medical applications and acceptable concentration limits. Searches in PubMed, ScienceDirect, CENTRAL, and CyberLeninka up to January 2024 identified 11 in vitro studies with human cell lines, 28 animal studies, and 10 articles involving patients and healthy volunteers. The review found that inhalation of PHMG leads to pulmonary fibrosis and malignant neoplasms, making aerosol forms unacceptable. PHMG can also affect liver function and have adverse effects on the heart, kidneys, and hematopoietic system. For dermal use, PHMG appears to be safe at concentrations up to 3%, although practical use may limit this to 1% due to potential discomfort. Still, it is important to consider possible sensitization, especially in patients with pre-existing skin conditions. In oral hygiene, 1% PHMG-P has been used safely in periodontal treatment, suggesting its potential in dentistry. For ophthalmic use, concentrations should be carefully monitored. PHMG-P solutions below 0.13% appear to be safe for human corneal epithelium, however lower concentrations still pose a risk of corneal fibrosis, as shown in animal studies. Physicians should prefer lower concentrations and consider alternatives or formulations with reduced toxicity for sensitive applications such as eye drops. Overall, although PHMG and its derivatives show promise in a variety of medical applications, their use should be reasonable, with careful consideration of the associated risks.

Introduction

The emergence and spread of resistant bacteria, combined with the shortage of new antibiotics, has escalated into a global health crisis. Nevertheless, research and development programs for new antimicrobial agents are considered unattractive investments for pharmaceutical companies. Among the potential solutions to delay the onset of the "post-antibiotic era" is the use of established antibiotics in combination with the local application of antiseptics, which is common practice, for example, in wound treatment. In ophthalmology, particularly in developing countries, it has even been suggested to use antiseptics instead of antibiotics for the treatment of conjunctivitis or keratitis due to the low availability of the latter. However, given the increasing number of pathogens resistant to antiseptics as well, there is an urgent need for antimicrobial approaches that can effectively inactivate pathogens without the risk of developing resistance. Polyhexamethylene guanidine (PHMG) may be used to reduce the spread of antibiotic resistance by inactivating extracellular DNA (eDNA), commonly found in bacterial biofilms, and by limiting the development of the biofilms themselves (1-7).

PHMG belongs to the family of polymeric guanidines and have been used for many years as antiseptics. It is often the subject of numerous studies in medicine, vaccine production, veterinary, agriculture, food industry, and water purification systems (8-16). The main representative of the class of polyguanidines is PHMG hydrochloride (PHMG-H). PHMG phosphate (PHMG-P) has stronger biocidal and flocculating properties. Despite the fact that PHMG-H and PHMG-P are the most common modifications of PHMG, there are

also other chemical modifications, for example, PHMG salt with citric acid and others. It is believed that PHMG hydrocitrate, compared with PHMG-H, has increased biocidal activity against bacteria, mold fungi, and yeast, while having lower toxicity (17). There is experience in obtaining PHMG hydrosuccinate. It was shown that PHMG hydrosuccinate has a more pronounced sporicidal effect against Aspergillus niger than PHMG-H. PHMG hydrosuccinate is also superior to PHMG-H in its disintegrating effect on formed biofilms of Pseudomonas aeruginosa. Therefore, this compound may be useful for the treatment of infectious eye diseases (18). A natural question arises: is it possible to use PHMG and its derivatives in human medicinal products, and how safe is it?

Despite the widespread use of PHMG in different fields, its safety has come under comprehensive scrutiny, and such concerns are not unfounded. Evidence of this lies in the health damage caused by PHMG in humidifier disinfectants (HD) available for sale in South Korea from 1994 to 2011. These products led to interstitial lung diseases (ILD) among the population, with average PHMG concentrations in HD brands reaching 3100.9 ppm (19, 20). It is important to note that the average molecular weights of PHMG in products HD range from 422 to 678 g/mol, indicating the oligomeric nature of PHMG, where each isomeric polymer exhibits different biocidal effects depending on the end group (21). Subsequently, most studies have focused on investigating the toxic effects and mechanisms of action of PHMG when inhaled. Another significant incident that drew serious criticism towards PHMG involved a surge in cases of poisoning from alcohol-containing household chemical products, affecting 12,500 people. The presumed concentration of PHMG in the consumed products ranged from 0.10 to 0.14 ± 0.01%. For these reasons, the European Commission prohibited the placement on the market and use of PHMG as a biocide through the directive of the European Parliament and the Council of the European Union (22-24).

The main objective of this systematic review was to comprehensively assess the toxicity and safety of PHMG not only through inhalation but also through oral ingestion, skin contact, and eye exposure. Evaluative tests included studies conducted on human cells and those involving patients, including those who succumbed to the consequences of exposure to this compound. This information will help establish the guidelines for using PHMG in medicines and medical devices.

Methodology

Inclusion and Exclusion Criteria

Articles were included based on the following criteria: (I) published work with full text; (II) coverage of various salts of PHMG, particularly PHMG-H, and PHMG-P, as they represent the most common chemical modifications used, along with their various applications in the System Organ Class: oral cavity, eyes, skin, liver, kidneys, heart, blood components, reproductive function; (III) assessment of the toxicity of these compounds *in vitro*, primarily in human cell models; (IV) evaluation of the toxicity of these compounds in animal studies, primarily in rodents, providing data on acute and subchronic toxicity, as well as reproductive toxicity, nephrotoxicity, and cardiac toxicity; (V) assessment of potential adverse events in healthy volunteers and patients, including those who died as a result of exposure to the study compounds; (VI) regardless of the year of publication; and (VII) *in vitro* and *in vivo* studies covering the maximum possible number of test models, as well as a wide range of substance concentrations.

The exclusion criteria were the following: articles (I) that do not evaluate the toxicity/safety of PHMG, for example, articles devoted to the study of compositions containing PHMG, or various modifications of PHMG, with the exception of various salts of PHMG, as well as articles studying regimens for the relief of pathological symptoms caused by exposure to PHMG, as in the study "Anti-fibrotic effect of Pycnogenol® in a polyhexamethylene guanidine-treated mouse model"; (II) without access to full text; (III) duplicate articles; (IV) articles that examined similar routes of administration or used the same test models, or that showed similar concentrations of the same component as other studies reviewed; (V) articles investigating the effect of unhealthy habits on PHMG toxicity, such as in PHMG-induced pulmonary fibrosis; (VI) articles that mention polyhexamethine biguanidine (PHMB); (VII) studies where aquatic organisms served as a test model; (VIII) studies considering environmental aspects, particularly the use of PHMG as a means of recycling biological waste; (IX) studies related to multidrug resistance developed, including as a result of exposure to PHMG; (X) studies characterizing the molecular weight characteristics of PHMG; and (XI) studies where PHMG was used as a plant treatment.

Search Strategy

A search was performed on January 20, 2024, in PubMed, ScienceDirect, CENTRAL, and CyberLeninka and updated on August 10, 2024. The search included 7 Mesh (Medical Subject Heading): (polyhexamethylene guanidine), (PHMG), (safety profile), (human), (adverse event), (side effect), and (toxicity) joined by the Boolean operators "OR" and "AND". Following the inclusion and exclusion criteria, using the bibliographic manager Zotero, the titles and abstracts of 250 articles were analyzed. When the information in the abstract was not sufficient, we proceeded to read the full text.

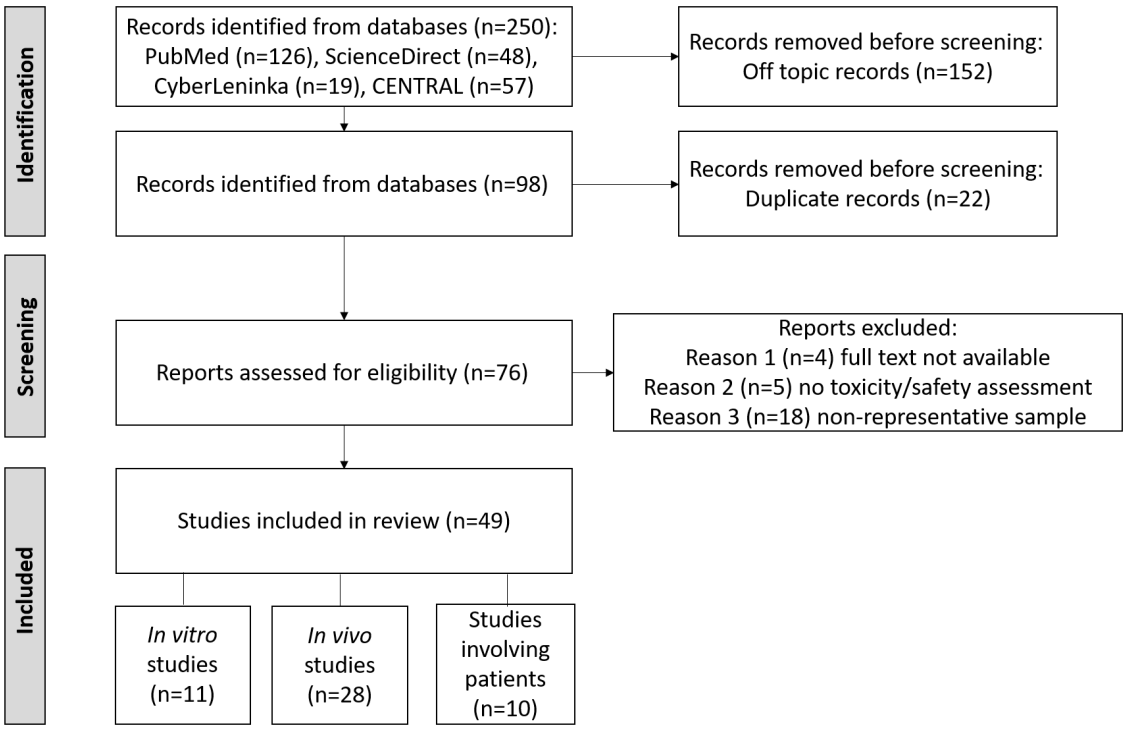


Figure 1. Systematic review flow diagram.

For data analysis, the year of publication, authors, type of study, country, and journal were recorded. For the synthesis of the methodology of the studies, a summary table was made with the following data: availability of open access literature source, the main purpose of the study, subjects used/participated in the study, their type (human cell lines and animals), number (animals, patients, and healthy volunteers).

The main purpose of this study is to provide a comprehensive overview of the toxicity of PHMG. The information presented aims to clarify in which forms PHMG is strictly prohibited for use and to identify potential areas of its application. Based on *in vitro* studies, the authors sought to determine the subcytotoxic doses of various chemical modifications of PHMG for different System Organ Classes (lungs, skin, eyes, oral cavity, liver), primarily using human cell lines. The scope of PHMG applications has been significantly expanded through the screening of animal study data, including acute and subchronic toxicity, as well as studies on cardiac toxicity, hematotoxicity, nephrotoxicity and reproductive toxicity. This provides a more complete picture of the possible side effects associated with the use of PHMG in humans. At the end of the study, data regarding the effects of PHMG on healthy volunteers and patients, including those who died as a result of exposure to the compound, are also presented.

Quality and Risk of Bias Assessments

The risk of bias in the included studies was analyzed according to the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) risk of bias tool for animal studies. According to this guide, the answer "Yes" indicates a low risk of bias, while the answer "No" indicates a high risk of bias. The answer "Unclear" indicates an unclear risk of bias. If any of the relevant signaling questions were answered "No," it indicated a high risk of bias for that particular entry (25).

Result and Discussion

Study Selection and Flow Diagram

The search produced a total of 250 articles related to the toxicity and safety profile of PHMG. One hundred twenty-six were found on PubMed, 48 from ScienceDirect, 57 in CENTRAL, and 19 in CyberLeninka. One hundred fifty-two records were irrelevant to the review topic and were subsequently discarded. With the bibliographic manager Zotero, 22 duplicated records were discarded, leaving 76 reports. On reading the title and abstract of the resulting articles, 27 were excluded, as they did not meet the inclusion criteria (see Figure 1). The remaining 49 articles were read in full text. Of these, 11 were involved *in vitro* studies, 28 involved *in vivo* studies, and the remaining 10 were involved in patient studies. These studies include 11 articles focused exclusively on *in vitro* experiments with human cell lines exposed to PHMG and 28 articles involving animal experiments. The remaining 10 articles were conducted on patients and healthy volunteers, including medical records data for cases where subjects died from PHMG exposure.

Table 1. *In vitro* toxicity data of PHMG in studies using human cell lines.

Study	Subject	Outcome parameters	Results
Pulmonary toxicity			
Wei et al (2021) (26)	A549	Determination of cytotoxicity of PHMG (0–32 μg/ml) and study of the expression of IL-8[1] and IL-6.	PHMG (≤ 2 μg/ml) had little effect on cell proliferation, cytotoxicity was observed at >4 μg/ml at 6 and 24 h, and IL-8 and IL-6 expression was also increased.
Lee et al (2022) (27)	HPAEpiC	Long-term exposure concentration of PHMG-P that is not surface reactive at 24, 48, and 72 h and determination of the carcinogenic effect of PHMG-P.	CV using 2 μg/ml PHMG-P after 72 h was ~90%. Exposure to 1 μg/ml PHMG-P for 10 days caused changes in 2 protein-coding genes and 5 non-coding genes and for 27–35 days - 24 protein-coding and 5 non-coding genes.
Choi et al (2022) (28)	BEAS-2B A549	Effect of PHMG-P (2.5 μg/ml, 1 h) on SG[2] formation under stress conditions.	PHMG-P under stress and infection conditions increased the formation of SG, induced the expression of fibrotic genes, and caused cell death due to DNA[3] damage.
Jin et al (2020) (29)	BEAS-2B	Determination of CV[4] under conditions of exposure to PHMG-P (1–16 μg/ml for 4–24 h).	Exposure to >4 μg/mL PHMG-P reduced CV by >50% at 24 h and also increased LDH[5] release by 3-fold, promoting epithelial barrier breakdown.
Jung et al (2014) (30)	A549 IMR-90 BEAS-2B	Determination of the cytotoxic effect of PHMG and its mediated changes in gene expression in A549 cells.	PHMG (5 μg/ml) reduced the viability of IMR-90 and BEAS-2B cells by more than 90% after 24 h, while the viability of A549 cells exceeded 60%.
Song et al (2019) (31)	A549 MRC-5 THP-1	Determine the toxic effects of PHMG-P by assessing cell survival rates as a function of dose (0.25–20 μg/mL) and time (24, 48, and 72 h).	Exposure of A549 and MRC-5 to PHMG-P (5 μg/ml) reduced CV by 44.7% and 64.9% at 24 h, by 19% and 25.8% at 48 h, and by 11.2% and 12.7% at 72 h, respectively, while THP-1 was 86.9% at 24 h, 73.8% at 48 h, and 69.4% at 72 h in THP-1 cells.
Hepatic toxicity			
Kim et al (2013) (32)	THP-1	Studying the hepatotoxicity of PHMG-P by assessing the number of SA-β-gal-positive cells[6].	By the 13th passage, cells treated with PHMG (0.03%) showed an 8-fold increase in the number of SA-β-gal-positive cells compared to the control, indicating the effect of acute aging of liver tissue.
Kim et al (2019) (33)	HepG2	Study of hepatotoxicity under the influence of PHMG-P for 24, 48, and 72 h based on CV.	The IC_{50}[7] values after 24, 48, and 72 h of incubation with PHMG-P in HepG2 cells were 7.612, 5.822, and 5.840 μg/mL, respectively.
Skin toxicity			
Yang et al (2021) (34)	THP-1	Skin sensitization potential of PHMG by MIT[8] assessment by h-CLAT[9].	The MIT for PHMG was 0.87 μg/mL, a strong sensitizer.
Oral toxicity			
Vitt et al (2017) (35)	HGF[10]	Cytotoxic effect of PHMG-P (0.005% and 0.00009%) by measuring the number of vital cells at a clinically relevant exposure time (1-30 min) and for 24 h. Determination of the immunomodulatory effect of PHMG-P by assessing the levels of PGE2[11], IL-6, IL-8, and MMP-1[12].	Exposure to PHMG-P (0.005%) for 1–30 min resulted in loss of CV within 5 min. Exposure to PHMG-P (0.00009%) for 24 h resulted in loss of fibroblast viability. The addition of PHMG-P together with IL-1b significantly reduced PGE2 levels ($p<0.001$) as well as the production of IL-6, IL-8, and MMP-1 by fibroblasts ($p<0.05$) at all concentrations tested.
Ocular toxicity			
Park et al (2019) (36)	RHCIE[13]	Study the ophthalmic toxicity of PHMG by tissue viability assay.	Aqueous solutions of PHMG (≤0.13%) had no irritant effect.

Note: [1]IL – interleukin; [2]SG – stress granule; [3]DNA - deoxyribonucleic acid; [4]CV – cell viability; [5]LDH - lactate dehydrogenase; [6]SA-β-gal - senescence-associated β-galactosidase; [7]IC_{50} - half maximal inhibitory concentration; [8]MIT - minimal induction threshold; [9]h-CLAT - human cell line activation test; [10]HGF - human gingival fibroblasts; [11]PGE2 - prostaglandin E2; [12]MMP-1 - matrix metalloproteinase-1; [13]RHCIE - reconstructed human cornea-like epithelium.

Table 2. *In vivo* toxicity data of PHMG.

Study	Subject	Outcome parameters	Results
Acute / Subchronic toxicity			
Kovalenko et al. (2011) (37)	M[14]	Acute toxicity study of PHMG-H (0.05-0.1%) intragastrically.	The detected LD_{50}[21] of PHMG-H was 1434 mg/kg. The substance was low toxic.
Kim, H. R. et al. (2015) (38)	ME[15] RAW264.7	To study the inflammatory effect induced by PHMG-P at concentrations from 0.14 mg/ml to 35.10 mg/ml for 6 and 24 h.	PHMG-P caused dose-dependent cytotoxicity LC_{50}[22] of 11.15-0.99 mg/ml at 6 and 24 h, respectively. PHMG-P induced pro-inflammatory cytokines including IL-1β, IL-6 and IL-8.
Asiedu-Gyekye, I. J. et al. (2014) (39)	RSD[16]	Study of the possible effects of subchronic toxicity of PHMG-H administered intragastrically.	The detected LD_{50} of PHMG-H was 600 mg/kg.
Dias, F. G. G. et al. (2021) (40)	RW[17]	Assessment of acute oral toxicity of 0.5% PHMG-H solution.	PHMG-H 5% is classified as Acute Toxicity Category 5 (LD_{50} > 2000–5000 mg/kg).
Lee, Y. H. et al. (2020) (41)	RF344[18]	Assess subacute inhalation toxicity of PHMG-H (1, 5, or 25 mg/m^3 over 6 h per day, 5 days per week for two weeks).	NOAEL[23] PHMG-H < 1 mg/m^3.
Skin toxicity			
Kovalenko et al. (2011) (37)	GP[19]	Study of the sensitizing properties of PHMG-H (1% and 3%) when applied to the skin twice a day.	The drug did not have a cumulative, sensitizing or irritating effect at the indicated concentrations.
Dias, F. G. G. et al. (2021) (40)	RW, M	Evaluation of possible side effects of cutaneous PHMG-H 0.5%.	PHMG-H reduced the area of skin lesions and increased the number of fibroblasts, with no side effects. At a concentration of 5%, PHMG-H exhibited neither genotoxicity nor cytotoxicity at doses up to 1500 mg/kg by micronucleus assay.
Oral toxicity			
Sklyanova et al. (2006) (42)	R[20]	To determine the toxicity of PHMG-P injection (0.25%) in a histomorphological study when exposed to cheek tissue.	PHMG-P (0.25%) caused aseptic inflammation at the injection site. The least irritating effect on cheek tissue and subcutaneous connective tissue was produced by 1.0 ml of injection.
Pulmonary toxicity			
Jeong S.H. et al (2024) (43)	R	To study the severity of lung injury resulting from intratracheal instillation of PHMG-P (0.2, 1.0, and 5.0 mg/kg).	The severity of lung damage, as well as the number, size and malignancy of tumors, increased as the dose of PHMG-P was increased. Bronchiolar-alveolar hyperplasia developed in all groups.
Song, J. et al. (2022) (44)	M	Study of the lung injury process of PHMG-P when administered intravenously (0.9 or 7.2 mg/kg) or intratracheally (0.9 mg/kg).	PHMG-P promoted the production of pro-inflammatory cytokines and also caused fibrotic changes in the lungs when administered intratracheally (0.9 mg/kg).
Li, X. Et al. (2021) (45)	M C57BL/6J	Study of the mechanism of PHMG-induced (0.05, 0.1, 1, and 2 mg/ml) pulmonary fibrosis based on increased surface tension mediated by pulmonary surfactant inhibition.	PHMG-H induced pulmonary fibrosis along with increased surface tension.
Lee, J. D. et al (2020) (46)	RW	Determination of pulmonary toxicity caused by intratracheal PHMG-P (single dose 1.5 mg/kg or 0.1 mg/kg, 2 times a week, for 4 weeks).	Upon single administration, PHMG-P induced alveolar macrophage aggregation and granulomatous inflammation. Pulmonary fibrosis, chronic inflammation, bronchiole-alveolar fibrosis, and squamous cell metaplasia were observed in the repeated administration group.

Lee, Y. H. et al. (2019) (47)	Males RF344	Assessment of oxidative stress in the lungs induced by inhaled exposure to PHMG-H (0.13, 0.40 or 1.20 mg/m^3 6 h per day, 5 days per week for 13 weeks).	The number of oxidative stress markers in the bronchial epithelium of rats increased in a dose-dependent manner. At 1.20 mg/m^3 an increase in respiratory rate and a decrease in body weight were observed. At 0.13 mg/m^3, no deviations in the lung structure were observed.
Lee, Y. H. et al. (2020) (41)	RF344	Subacute inhalation toxicity study of PHMG-H (1, 5, or 25 mg/m^3 for 6 h per day, 5 days per week for 2 weeks).	The severity of lung damage increased in a dose-dependent manner. Exposure to PHMG-H (5 and 25 mg/m^3) caused squamous metaplasia of the bronchial and bronchiolar epithelium, as well as alveolar emphysema and necrosis with inflammation. Lymphoid hyperplasia of broncho-associated lymphoid tissue was observed in rats exposed to 1, 5, and 25 mg/m^3. Alveolar macrophage aggregation was observed in male rats exposed to 0, 1, 5, and 25 mg/m^3 and female rats exposed to 1 and 25 mg/m^3.
Park, S. et al. (2014) (48)	RSD	Assessment of lung injury resulting from nasal inhalation of PHMG-P (1.6 mg/m^3) aerosol 6 h per day, 5 days per week, for 4 weeks.	PHMG-P (1.6 mg/m^3) caused typical bronchiolocentric destruction with inflammation and fibrosis.
Cardiac toxicity			
Choi, J. H. et al. (2024) (49)	RSD	Study of platelet procoagulant activity induced by PHMG-P (2.5 µg/ml)	PHMG-P causes procoagulant platelet activation, which may contribute to prothrombotic risk and cardiovascular disease.
Ocular toxicity			
Lee, H., et al. (2021) (50)	Rabbit cornea cells	Study of the adverse ocular effects of PHMG-H (1, 5, 10 and 25 µg/ml for 24, 48, 72 and 96 h).	PHMG-H can cause fibrosis. IC_{50}^{24} of PHMG-H at 24, 48, 72 and 96 h: 20.8 µg/ml, 13.8 µg/ml, 8.5 µg/ml and 6.2 µg/ml, respectively. PHMG-H induced cyclooxygenase-2 at 25 µg/ml and hemeoxygenase-1 at all concentrations.
Hepatic toxicity			
Choi, Y. J. et al (2022) (51)	M	Study of the effect of PHMG (0, 60 and 200 µg/kg) on the pathophysiology and metabolism of the liver when administered intratracheally 3 times a week, 12 times in total.	PHMG significantly reduced liver cholesterol levels. mRNA-seq[25] analysis revealed changes in the expression of genes associated with cholesterol biosynthesis and metabolism to bile acids.
Asiedu-Gyekye, I. J. et al. (2014) (39)	RSD	To study the possible subchronic toxicity effects of PHMG-H (0.006 mg/kg, 0.012 mg/kg, and 0.036 mg/kg) administered intragastrically.	In 10% of animals at all doses, local areas of mild pericentral degeneration of hepatocytes were observed in the liver tissue.
Kim, M. et al (2022) (52)	M C57/BL6 male	To study the pathophysiology of liver fibrosis induced by intraperitoneal administration of PHMG-P (0.03% and 0.1%) twice a week for 5 weeks.	Diffuse fibrotic lesions of the liver were revealed without affecting the lungs. PHMG-P induces liver fibrosis in the pericentral, periportal, and capsular regions.
Dias, F. G. G. et al. (2021) (40)	RW	Investigate the potential for liver injury when 0.5% PHMG-H topical solution is administered orally by gavage.	Alanine aminotransferase/aspartate aminotransferase and urea/creatinine did not differ significantly from the control group.
Hematological toxicity			
Sung HJ et al. (2022) (53)	RSD males	Study of possible disorders of hematopoietic function 20 weeks after intratracheal instillation of PHMG-P (1-5 mg/kg).	PHMG-P affects hematopoiesis involved in monocyte differentiation and platelet production.

Asiedu-Gyekye, I. J. et al. (2014) (39)	RSD (males and females)	Study of hematological parameters during intragastric administration of PHMG-H (0.006 mg/kg, 0.012 mg/kg, and 0.036 mg/kg).	PHMG-H did not have any harmful effects on the hematopoietic system of animals.
Lee, J. et al. (2021) (54)	Females RSD	Study of hematological parameters in pregnant female rats by inhalation of PHMG-P aerosol (0.14, 1.60, and 3.20 mg/m^3).	PHMG-P (3.20 mg/m^3) increased the total number of red blood cells, hematocrit, hemoglobin and neutrophils, decreased the number of reticulocytes, lymphocytes, eosinophils, basophils, decreased alanine aminotransferase, alkaline phosphatase, total bilirubin, total cholesterol, sodium, phospholipids, and chloride. PHMG-P (1.60 mg/m^3) also increased the total number of red blood cells, hematocrit, and hemoglobin, and a decrease in alkaline phosphatase and chloride was observed.
Lee, Y. H. et al. (2020) (41)	RF344 (males and females)	Study of hematological parameters as part of a study of subacute toxicity of PHMG-H in the form of an aerosol (1 mg/m^3, 5 mg/m^3, or 25 mg/m^3 for 6 h a day, 5 days a week for two weeks).	PHMG-H (1, 5, and 25 mg/m^3) increased the total number of red blood cells, hematocrit, and hemoglobin. Hemoglobin increased significantly at 25 mg/m^3. Reticulocytes were significantly reduced at 5 and 25 mg/m^3. Platelets decreased at 25 mg/m^3. Monocytes and neutrophils increased at 25 mg/m^3. Lymphocytes were reduced in males at 25 mg/m^3, and in females at 5 and 25 mg/m^3. Eosinophils were significantly reduced in females at 25 mg/m^3. Alanine aminotransferase increased in males at 25 mg/m^3, and in females at 5 and 25 mg/m^3. Aspartate aminotransferase increased significantly in all at 25 mg/m^3.
Reproductive toxicity			
Lee, J. et al. (2022) (55)	R	To study the postnatal development of offspring after exposure to PHMG-P (0, 0.14, 1.60, and 3.20 mg/m^3).	PHMG-P (1.60 and 3.20 mg/m^3) increased perinatal mortality and decreased the viability index; F1 offspring had lower birth weight. Pregnant rats had severe systemic toxicity and a prolonged gestation period.
Lee, J. et al (2019) (56)	RSD	To study the toxic effects of orally administered PHMG-P (0, 13, 40, and 120 mg/kg)	PHMG-P (120 mg/kg) exhibited toxicity including depressed behavior, thinness, decreased body weight, decreased food intake, and decreased body weight of F1 offspring. NOAEL was 40 mg/kg/day.
Nephrotoxicity			
Asiedu-Gyekye, I. J. et al. (2014) (39)	RSD	To study the possible subchronic toxicity effects of PHMG-H (0.006 mg/kg, 0.012 mg/kg, and 0.036 mg/kg) administered intragastrically.	At 0.006 mg/kg and 0.036 mg/kg, 20% of animals showed mild degrees of hydropic changes in the proximal tubules.

Note: [14]M – mice; [15]ME - Mice macrophage; [16]RSD – Rats Sprague-Dawley; [17]RW – Rats Wistar; [18]RF344 – Rats F344; [19]GP - guinea pig; [20]R – Rats; [21]LD_{50} - median lethal dose; [22]LC_{50} – median lethal concentration; [23]NOAEL - No-observed-adverse-effect level; [24]IC_{50} - half maximal inhibitory concentration; [25]mRNA-seq - messenger ribonucleic acid sequencing.

The majority of articles (67.3%) were published within the last 5 years, indicating a growing interest and research focus on the topic. The peak in publication volume occurred in 2021, with 10 studies published, followed by 2019, which saw the release of 8 studies. Geographically, South Korea emerged as the leading contributor to the literature, likely due to a mass poisoning event involving HD, which spurred significant research and analysis in the country.

Quality Evaluation

Results of Toxicity Assessment of PHMG in *In Vitro* studies using Human Cell Lines as Models

The toxicity results of PHMG from *in vitro* studies are presented exclusively using human cell models. These results are summarized in Table 1, which provides basic information about the studies conducted.

Table 3. Safety data of PHMG in trials involving people.

Study	Subject	Outcome parameters	Results
Pulmonary toxicity			
Ryu et al (2019) (57)	Patients with lung damage (n=453), control group (n=700).	Assessment of inhalation exposure to HD[26].	In 259 (57.2%) patients with ILD[27], it developed within one year of HD use, where the average level of inhaled PHMG was 145.1 μg/m^3.
Lamichhane et al (2019) (58)	Patients with IIP (n=244), control group (n=244).	Frequency distribution of characteristics associated with HD exposure.	The use of HD-containing PHMG was associated with a higher risk of lung damage compared to those who used other disinfectants.
Lee et al (2021) (59)	Patients (n=362).	Study of asthma induced by PHMG-based HD exposure using data from a panel study of South Korean children.	Asthma associated with PHMG exposure was characterized by decreased lung function, less positive bronchial hyperresponsiveness scores, and different plasma protein distribution.
Park et al (2014) (60)	Patients with lung damage (n=38).	Assessing PHMG-based HD exposure through medical record review.	Three pregnant women and six preschool-aged children died as a result of lung damage. Another six pregnant women and 22 preschool-aged children experienced non-lethal lung injury. Three adult male office workers did not suffer fatal lung damage.
Ju et al (2021) (61)	Patients with fatal injuries (n=1413)	Analysis of the distribution of causes of death among applicants according to medical records.	43.0% of the affected individuals had more than one case of ILD identified. Among the causes of mortality in the deceased, respiratory organ diseases accounted for 54.4%. Among those who died from respiratory diseases, ILD were the most common cause of death (65.5%).
Hepatic toxicity			
Kim et al (2023) (62)	Patients (n=3) who used HD.	To examine the likelihood of developing toxic hepatitis due to the inhalation of HD-containing PHMG by analyzing patients' medical records.	Patients exhibited an increase in aspartate aminotransferase and alanine aminotransferase levels up to 2000-4000 IU/L. One fatality was recorded, while two patients were discharged after treatment. Hepatotoxicity due to inhalation was not confirmed.
Makarov et al (2009) (63)	Blood serum of patients (n=40) with toxic hepatitis and healthy volunteers (n=50).	Determining the impact of consuming alcohol surrogates containing PHMG-H on the lipid profile of blood.	Patients differed from healthy volunteers by a twofold decrease in the relative content of total phospholipids, free fatty acids, cholesterol esters, and phosphatidylcholine, but had higher levels of free cholesterol and total lysophospholipids. The overall lipid levels in patients were three times higher than the norm. The development of toxic hepatitis has been confirmed.
Ostapenko et al (2011) (22)	Patients with poisoning from surrogate alcohol (n=579).	Study of the clinical presentation and outcomes of poisoning with surrogate alcohol containing PHMG-H.	Jaundice was observed in 99.7%, with detected foci of cholestasis, fibrosis progressing to cirrhosis and inflammatory infiltration. The development of cholestatic hepatitis has been confirmed.
Skin Toxicity			
Pummi et al (2012) (64)	Patient with skin sensitization (n=1) and previously observed dermatitis.	Assessing the risk of skin sensitization from a PHMG-containing antiseptic.	Sensitization developed within 1-2 months with frequent use of a non-alcoholic disinfectant containing PHMG at concentrations of 0.1-1%.
Oral Toxicity			
Vitt et al (2019) (65)	Patients with severe chronic periodontitis (n=19).	Evaluation of side effects of irrigation with antiseptic PHMG-P (1%) in periodontal treatment.	No adverse effects were observed with PHMG-P (1%) during the study.

Note: [26]HD - humidifier disinfectants; [27]ILD - interstitial lung diseases.

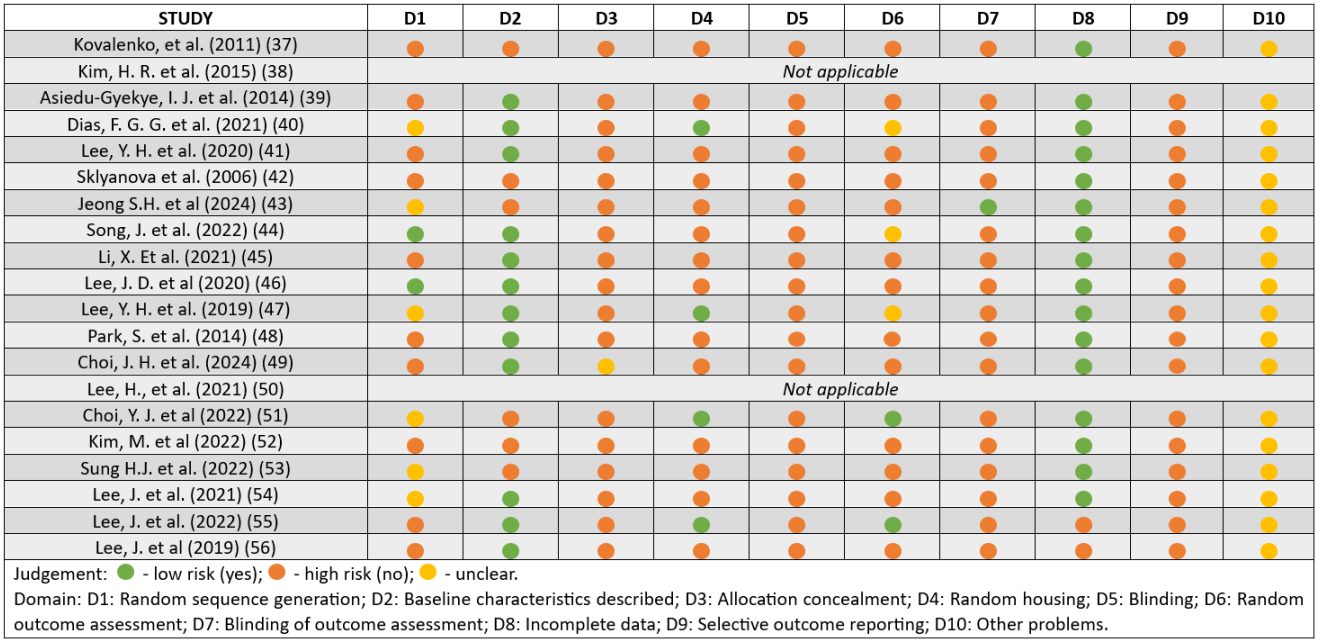


Figure 2. SYRCLE's risk of bias in the individual animal studies is included.

Results of Toxicity Assessment of PHMG in Trials Involving Animals

The toxicity results of PHMG from animal studies are summarized in Table 2, which provides basic information about the studies conducted.

Results of Toxicity Assessment of PHMG in Trials Involving Human

The results of PHMG toxicity studies in trials involving people are summarized in Table 3, which provides basic information about the studies conducted.

SYRCLE's Risk of Bias Tool

The results of the attribution of bias based on each domain of SYRCLE's tool are shown in Figure 2.

Notably, all studies failed to clearly define whether the animals were randomly housed during the experiment if proper blinding of the caregivers/investigators concerning which intervention each animal received during the experiment was performed, or if there was a random selection of the animals for outcome assessment.

Conclusion

In conclusion, the systematic review indicates that inhalation exposure to PHMG poses significant health risks, including lung fibrosis and malignant tumors, making its use in aerosol medications unacceptable. Additionally, PHMG negatively impacts liver function, heart activity (inducing procoagulant platelet activation), kidneys (causing mild hydropic changes in proximal tubules), and hematopoietic function, leading to changes in erythrocyte counts, hematocrit, and hemoglobin levels. Although one animal study showed that a 0.5% aqueous solution of PHMG-H did not significantly alter liver enzyme levels or kidney function, the overall evidence suggests caution.

The clinical implications of these findings are significant. Given the severe respiratory consequences, PHMG should not be used in any form that could lead to inhalation exposure, especially in aerosolized medications. For dermal applications, PHMG appears safe at concentrations up to 3%, though practical use might limit this to 1% due to potential discomfort. Clinicians should be aware of the possibility of sensitization, particularly in patients with pre-existing skin conditions. The use of PHMG in wound care, particularly in combination with chitosan, could offer benefits, but close monitoring for allergic reactions is advisable. In oral health, 1% PHMG-P has been used safely in periodontal treatment, suggesting its potential in dental care. For ophthalmic use, concentrations should be carefully controlled. Solutions of PHMG-P below 0.13% appear safe for human corneal epithelium, however, lower concentrations still pose a risk of corneal fibrosis, as shown in animal studies. Clinicians should prefer lower concentrations and consider alternatives or formulations with mitigated toxicity for sensitive applications like eye drops.

Overall, while PHMG and its derivatives show promise in various medical applications, their use must be reasonable, with careful consideration of the associated risks. The potential benefits in a post-antibiotic era are significant, but only with strict adherence to safety protocols can PHMG be effectively integrated into clinical practice.

Abbreviations

PHMG=polyhexamethylene guanidine; HD=humidifier disinfectants; ILD=interstitial lung diseases; ppm=parts per million; PHMG-H=polyhexamethylene guanidine hydrochloride; PHMG-P=polyhexamethylene guanidine phosphate; PHMB=polyhexamethine biguanidine; IL=interleukin; SG=stress granule; DNA=deoxyribonucleic acid; CV=cell viability; LDH=lactate dehydrogenase; SA-β-gal=senescence-associated β-galactosidase; IC_{50}=half maximal inhibitory concentration; MIT=minimal induction threshold; h-CLAT=human cell line activation test; HGF=human gingival fibroblasts; PGE2=prostaglandin E2; MMP-1=matrix metalloproteinase-1; RHCIE=reconstructed human cornea-like epithelium; M=mice; ME=mice macrophage; RSD=rats Sprague-Dawley; RW=rats Wistar; RF344=rats F344; GP=guinea pig; R=rats; LD_{50}=median lethal dose; LC_{50}=median lethal concentration; NOAEL=no-observed-adverse-effect level; IC_{50}=half maximal inhibitory concentration; mRNA-seq=messenger ribonucleic acid sequencing.

Declarations

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Conflict of Interest

The authors report there are no competing interests to declare.

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