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Protocol

The Study of Exposure to Isophorone and the Risk of Getting Cancer: A Systematic Review and Meta-analysis Protocol

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Background: This protocol recommends ways to conduct a systematic review and meta-analysis on the association between isophorone exposure and cancer risk.
Methods: This study will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Eligible studies will include observational research examining the association between isophorone exposure and cancer outcomes. General search terms will be used to search databases such as PubMed, Web of Science, and Scopus. Two independent reviewers will screen articles, extract data, and assess study quality and risk of bias. Data synthesis and analysis will include meta-analysis, subgroup analyses, sensitivity analyses, and assessment of publication bias.
Results: The systematic review and meta-analysis will provide a comprehensive assessment of the association between isophorone exposure and cancer risk. Data from multiple studies will be pooled to achieve an overall estimate of the association, considering sources of heterogeneity and evaluating the quality of included studies. Publication bias will also be assessed. The findings will contribute to our understanding of the potential health effects of isophorone exposure and inform future research and decision-making.
Conclusion: This protocol outlines a systematic and transparent approach to assessing the association between isophorone exposure and the risk of cancer. This study will provide insights into the potential health implications of isophorone exposure, preventive measures, and regulatory decisions. By following established guidelines and employing methodology, this study will provide an evidence-based assessment of the available literature, advancing our understanding of the association between isophorone exposure and cancer risk.

1. Introduction

Cancer is a formidable foe, with statistics revealing its far-reaching impact on society. According to the World Health Organization (WHO), cancer is one of the leading causes of death worldwide, responsible for an estimated 10.0 million deaths in 2020 alone [1].

Isophorone, a colorless liquid with a distinctive minty fragrance, has long been recognized for its remarkable properties. Notably, it possesses the unique ability to dissolve in water, a characteristic that sets it apart from other organic compounds. Its relatively rapid rate of evaporation, outpacing that of water, further contributes to its diverse range of applications. In the industrial realm, isophorone finds itself indispensable, serving as a solvent in the formulation of printing inks, paints, lacquers, and adhesives. Beyond its role as an industrial workhorse, this intriguing compound reveals a surprising twist – it occurs naturally in cranberries, connecting the realms of industry and nature in an unexpected symbiosis [2-4].

Despite its multifaceted roles, the spotlight has recently shone on isophorone due to concerns regarding its potential impact on human health, specifically its possible association with the development of cancer. This apprehension arises from the compound's widespread usage, resulting in exposure across various occupational and environmental settings. In response to these concerns, multiple studies have attempted to elucidate the connection between isophorone exposure and the risk of cancer. Yet, a comprehensive consensus remains elusive, with the existing evidence yielding a complex and inconclusive narrative [3, 5-7].

While the overarching research question of the study centers on the association between isophorone exposure and cancer risk, it is crucial to acknowledge the need for depth and granularity in our inquiry. The primary research question itself, though appropriate, could benefit from the inclusion of sub-questions. These sub-questions, designed to dissect the broader inquiry into more digestible components, can enhance the robustness of our investigation. For instance, sub-questions could focus on specific types of cancer, variations in exposure levels, potential confounding factors, and the influence of different sources of exposure. By embarking on this layered journey, we aim to gain a more nuanced understanding of the intricate interplay between isophorone exposure and cancer risk.

By adhering to rigorous methodologies and engaging with the available literature, we aim to contribute to the ongoing dialogue, enriching our comprehension of the potential link between isophorone exposure and cancer risk.

2. Research Question

The research question seeks to unravel the association between exposure to isophorone and the risk of cancer. However, acknowledging the complexity of this relationship, the inclusion of sub-questions could provide a more comprehensive exploration. These sub-questions might delve into the specific types of cancer, varying levels of exposure, potential confounding factors, and the influence of exposure sources. This broader approach would enhance the robustness of the inquiry and provide a more nuanced understanding of the intricate interplay between isophorone exposure and cancer risk. Developing a comprehensive and well-defined research question is fundamental to the integrity of our study. We acknowledge the guidance offered by the Prisma-P suggestion, which highlights the importance of constructing a research question based on key components such as the planned population, intervention, comparator, and outcome, often referred to as the PICO elements.

In alignment with this principle, our research question is meticulously designed to encompass these critical dimensions:

Population: Individuals exposed to isophorone across various contexts, including occupational and environmental settings.

Exposure: The intricate relationship between exposure to isophorone, a versatile industrial solvent, and its potential association with cancer risk.

Comparator: A comparative analysis between individuals with varying degrees of isophorone exposure, including those with minimal or no exposure, to unravel the potential risk differentials.

Outcome: A meticulous examination of cancer outcomes, both specific to certain cancer types and inclusive of broader assessments of overall cancer risk.

By grounding our research question within the framework suggested by Prisma-P, we strive to develop a question that is not only specific and well-defined but also encapsulates the complexities and nuances inherent in the investigation of isophorone exposure and its potential impact on cancer risk. This approach ensures that our study is both focused and robust, leading to meaningful insights that contribute to our understanding of the association between isophorone exposure and cancer risk.

3. Objectives

The objectives of our systematic review and meta- analysis encompass a comprehensive and methodical exploration of the association between exposure to isophorone and the risk of cancer. Our primary aim is to provide a rigorous and evidence-based evaluation of the existing literature, shedding light on the potential health implications of isophorone exposure within the context of cancer development.

4. Methods

4.1 Study Design

This study will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-Protocol) guidelines for conducting systematic reviews and meta-analyses protocols [8]. And this protocol was registered in PROSPERO (CRD42023441595).

4.2 Eligibility Criteria

Our meticulous selection process will be guided by a well-defined set of eligibility criteria that ensures both the comprehensiveness and specificity of our study's focus.

4.2.1 Inclusion Criteria:

Selection of studies for inclusion will adhere to the following criteria:

Study Design: Our inclusion criteria embrace observational studies, such as cohort studies and case- control studies, that delve into the intricate relationship between exposure to isophorone and the risk of cancer. This approach aims to capture the complexities of real- world scenarios and the consequential health outcomes.

Population: Our scrutiny will encompass studies conducted on individuals exposed to isophorone,

acknowledging the pivotal role of human subjects in unraveling the association between exposure and cancer risk.

Exposure: Eligible studies will meticulously document isophorone exposure, encompassing a spectrum of contexts, whether occupational or environmental, and embracing a multitude of sources that contribute to exposure variability.

Comparator: To facilitate nuanced insights, our criteria include studies that juxtapose individuals with substantial isophorone exposure against unexposed or less exposed counterparts. This comparative lens enhances our capacity to pinpoint potential associations.

Outcome: A vital criterion is the presentation of cancer outcomes in the selected studies. This encompasses not only examinations of specific cancer types but also broader evaluations of overall cancer risk – a comprehensive approach that caters to the multifaceted nature of our inquiry.

Language: Our review will include studies published exclusively in English, ensuring consistency in interpretation and enhancing the accessibility of our findings to a broader audience.

4.2.2 Exclusion Criteria

Exclusion of studies will be guided by the following criteria:

Studies lacking full-text availability: To maintain the rigor of our analysis, studies that lack full-text accessibility will be excluded from consideration.

Studies of an animal nature, reviews, conference abstracts, and editorial pieces: While diverse in their own right, these types of literature fall outside the scope of our investigation into human exposures and cancer outcomes. It is important to underscore that experimental studies, particularly randomized controlled trials (RCTs), will be excluded. The exclusion of experimental studies is deliberate, stemming from the recognition that such studies often involve controlled settings and interventions that differ from the real-world complexities of exposure scenarios. By excluding experimental studies, our criteria emphasize a focus on observational research, mirroring the intricate interplay between isophorone exposure and the risk of cancer within real-world contexts.

4.3 Search Strategy

A comprehensive search strategy will be developed in collaboration with a professional medical librarian. The following databases will be searched: PubMed, Web of Science, and Scopus. The search terms will encompass variations and synonyms for "isophorone," "exposure," and "cancer." The search strategy will be tailored to meet the specific requirements of each database. Additionally, the reference lists of included studies and relevant review articles will be manually searched to identify any additional studies. Once the manuscript is accepted, a literature search update will be performed using the methodology of peer-reviewed studies.

To ensure the inclusion of the most relevant and up-to-date studies, our search strategy will encompass studies published until August 2023. This time frame strikes a balance between capturing recent developments while also allowing us to account for the accumulation of evidence up to the current date.

PubMed: ("neoplasms"[MeSH Terms] OR ("cancer"[Title/Abstract] OR "carcinogenesis"[Title/Abstract] OR "neoplasms"[Title/Abstract] OR "malignancy"[Title/Abstract] OR "tumor"[Title/Abstract])) AND (("isophorone"[Title/Abstract] OR "diisophorone"[Title/Abstract]))

Scopus: (TITLE-ABS-KEY (isophorone OR diisophorone) AND TITLE-ABS-KEY (neoplasms OR neoplasm OR cancer OR carcinogenesis OR malignancy OR tumor))

Web of Sciences: isophorone OR diisophorone (Topic) AND neoplasms OR neoplasm OR cancer OR carcinogenesis OR malignancy OR tumor (Topic)

4.4 Study Selection

Two independent reviewers will screen the titles and abstracts of identified articles to assess their eligibility for full-text review. Discrepancies will be resolved through discussion or consultation with a third reviewer. Full-text articles of potentially relevant studies will be obtained and assessed for eligibility based on the inclusion criteria. The reasons for exclusion at the full-text stage will be recorded.

4.5 Data Extraction

A standardized data extraction form will be developed to collect relevant information from included studies. The following data will be extracted: • Study characteristics: author, year of publication, study design, country of origin.

• Participant characteristics: sample size, demographic information, inclusion/exclusion criteria. • Exposure assessment: methods of measuring isophorone exposure, duration and intensity of exposure, and exposure sources.

• Cancer outcomes: type of cancer, cancer incidence or prevalence, diagnostic criteria. • Effect measures: odds ratios, relative risks, hazard ratios, or any other relevant effect measures, along with their corresponding confidence intervals. • Covariates: adjustment factors considered in the analysis. • Quality assessment: risk of bias assessments.

4.6 Quality Assessment

The quality and risk of bias of included studies will be independently assessed by two reviewers using appropriate tools. The Newcastle-Ottawa Scale (NOS) will be employed for cohort studies and case-control studies. The NOS evaluates studies based on participant selection, comparability, and outcome assessment [9]. We will utilize the Newcastle-Ottawa Scale (NOS) as our quality assessment tool. The NOS offers a structured framework for evaluating the quality of both cohort and case-control studies. It consists of three main components: selection of study groups, comparability between groups, and ascertainment of exposure or outcome. To address the issue of bias, we will assess each study for its risk of bias across these components. Specifically, we will evaluate the potential biases related to participant selection, comparability of groups, and the ascertainment of exposure and outcome in each study.

This comprehensive evaluation will provide a nuanced understanding of the methodological quality of each study and the potential sources of bias that could influence their findings. By employing the NOS and thoroughly assessing potential bias, we aim to enhance the robustness and credibility of our review's findings. This meticulous approach to quality assessment contributes to the overall reliability and validity of our systematic review and meta- analysis, reinforcing the integrity of our evidence-based conclusions. Any discrepancies between reviewers will be resolved through discussion or consultation with a third reviewer.

4.7 Data Synthesis and Analysis

As we transition from data extraction to data synthesis and analysis, the choice of statistical software plays a pivotal role. For our quantitative synthesis and meta- analysis, we will employ STATA software version 17. This software, known for its robust statistical capabilities, will enable us to conduct comprehensive analyses, calculate pooled effect estimates, explore sources of heterogeneity, and assess publication bias with precision. By harnessing the capabilities of STATA software version 17, we ensure that our analytical process is not only rigorous but also transparent, contributing to the integrity of our review and the accuracy of our findings. The data synthesis and analysis stage of our study represents a critical juncture where the mosaic of evidence converges into a coherent narrative. This synthesis is guided by a rigorous approach that takes into account potential challenges, such as sparse data and non-normality.

Quantitative synthesis will be conducted using a meta-analysis approach when a sufficient number of studies exhibit homogeneity. Pooled effect estimates, such as odds ratios, relative risks, or hazard ratios, along with corresponding 95% confidence intervals, will be calculated using random-effects models. The choice of random-effects models acknowledges the possibility of heterogeneity across studies, reflecting the inherent variability within the diverse body of evidence.

However, we acknowledge that encountering sparse data could pose a challenge to the meta-analysis. In such cases, where studies are limited and data is sparse, a cautious approach will be adopted. We will interpret the findings with due consideration of the limitations and the potential impact of sparse data on the robustness of our conclusions. Sensitivity analyses will also be performed to assess the influence of studies with small sample sizes on the overall effect estimates, contributing to a comprehensive evaluation of the strength and consistency of our findings.

Moreover, the normality of data distribution represents another dimension of analysis. Given the potential non- normal distribution of effect measures in some studies, we will explore appropriate methods to address this challenge. Robust statistical techniques, such as bootstrap methods or transformations, will be considered to ensure the validity of our findings even in the presence of non- normal data distributions. These methods enable us to derive meaningful estimates while accounting for the complexities that arise from the nature of the data.

In summary, the data synthesis and analysis phase of our study encompasses a comprehensive yet cautious approach. We are mindful of potential challenges posed by sparse data and non-normal distributions, and we are committed to employing appropriate techniques to mitigate these challenges and ensure the robustness and reliability of our findings. Through these meticulous strategies, we aim to distill the collective evidence into a synthesized narrative that enriches our understanding of the association between isophorone exposure and cancer risk.

Assessment of Strength of Evidence using GRADE: The synthesis and analysis of data collected from various studies constitute a critical phase of our systematic review and meta-analysis. In response to the comment requesting information about how the strength of the body of evidence will be assessed (Prisma checklist item 17), we have expanded this section to address this important aspect.

To assess the strength of the body of evidence, we will employ the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. This well-established framework provides a systematic and transparent method for evaluating the quality of evidence across various studies [10].

The GRADE approach involves considering several factors that contribute to the overall quality and strength of the evidence:

1. Study Design: We will evaluate the study designs used in the included studies, giving higher

weight to well-designed observational studies and controlled trials. The choice of study design significantly influences the confidence we can place in the evidence.

2. Risk of Bias: We will assess the risk of bias within individual studies, analyzing elements such as selection bias, information bias, and confounding factors. Studies with a low risk of bias are more likely to yield reliable and valid results.

3. Consistency of Findings: We will examine the consistency of findings across different studies. When multiple studies consistently demonstrate similar results, the strength of evidence is bolstered.

4. Precision of Effect Estimates: The precision of effect estimates, reflected by narrow confidence intervals, contributes to the robustness of evidence. Studies with precise estimates are more informative and contribute to higher-quality evidence.

5. Potential Sources of Bias: We will consider factors that might introduce bias, such as publication bias or selective reporting of outcomes. Addressing and quantifying potential biases enhances the credibility of the evidence.

By systematically evaluating these components, the GRADE framework allows us to assign a level of confidence to the body of evidence. The levels of evidence range from "high" (indicating a high degree of confidence) to "very low" (indicating very little confidence). This comprehensive evaluation will provide insights into the robustness and reliability of the evidence we gather from the included studies.

By employing the GRADE framework, we ensure a standardized and rigorous assessment of the strength of the body of evidence. This process enhances the credibility and impact of our systematic review and meta-analysis, contributing to a nuanced understanding of the association between isophorone exposure and cancer risk.

4.8 Publication Bias

Publication bias will be assessed using funnel plots and statistical tests, such as Egger's test [11] if a sufficient number of studies are available. If publication bias is detected, appropriate adjustments, such as the trim-and-fill method, will be considered.

5. Ethics and Dissemination

Since this study is based on published data, ethical approval is not required. The findings of this systematic review and meta-analysis will be disseminated through a peer-reviewed publication and/or conference presentations. The results will contribute to the existing knowledge on the association between exposure to isophorone and cancer risk.

In conclusion, this protocol provides a detailed outline for conducting a systematic review and meta-analysis on the association between exposure to isophorone and the risk of cancer. By following this methodology, we aim to obtain an evidence-based assessment of the available literature, contributing to the understanding of the potential link between isophorone exposure and cancer.

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References

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. *International Journal of Cancer.* 2021. DOI
2. National Center for Biotechnology Information (2023) [Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Isophorone.
3. Kataoka H, Terada Y, Inoue R, Mitani K. Determination of isophorone in food samples by solid-phase microextraction coupled with gas chromatography-mass spectrometry. *Journal of Chromatography. A.* 2007; 1155(1)DOI
4. Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles. Toxicological Profile for Isophorone. *Atlanta (GA): Agency for Toxic Substances and Disease Registry (US); 2018.*
5. Rodrigues EG, Stewart J, Herrick R, Palacios H, Laden F, Clark W, Delzell E. Retrospective Exposure Assessment for Semiconductor and Storage Device Manufacturing Facilities. *Journal of Occupational and Environmental Medicine.* 2019; 61(4)DOI
6. Rodrigues EG, Herrick RF, Stewart J, Palacios H, Laden F, Clark W, Delzell E. Case-control study of brain and other central nervous system cancer among workers at semiconductor and storage device manufacturing facilities. *Occupational and Environmental Medicine.* 2020; 77(4)DOI
7. Huang Q, Pan L, Luo G, Jiang R, Ouyang G, Ye Yu, Cai J, Guo P. Exploring the release of hazardous volatile organic compounds from face masks and their potential health risk. *Environmental Pollution (Barking, Essex: 1987).* 2023; 333DOI
8. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews.* 2015; 4(1)DOI
9. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al.. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Ottawa Health Research Institute. 2013..
10. Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, Moe-Byrne T, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. *Systematic Reviews.* 2014; 3DOI
11. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed.).* 1997; 315(7109)DOI