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Towards a Better Knowledge of the Neurotoxic Effects of Occupational Exposure to Organic Solvents on Human Health: A Review Study

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A B S T R A C T

This review examines existing studies on the effects of exposure to the organic solvent (OS) on human health, whereby the focus is on its associations with dementia, Alzheimer's and chronic-solvent-induced encephalopathy (CSE). OSs also known as volatile organic compounds (VOCs), are widely used in industries such as pharmaceuticals, construction, and manufacturing due to their ability to dissolve non-aqueous substances. Despite their utility, many OSs, including benzene, toluene, and hexane, are highly toxic and pose significant health risks, particularly to workers in high-exposure occupations. Prolonged exposure to these solvents has been linked to severe neurotoxic effects, including CSE, cognitive impairments, and neurodegenerative diseases such as dementia and Alzheimer’s disease. The lipophilic nature of OSs allows them to accumulate in lipid-rich tissues, including the brain, disrupting neurological functions and contributing to long-term cognitive decline.

This research reviews the mechanisms of OS-induced neurotoxicity, emphasizing the role of volatility, lipophilicity, and metabolic pathways in determining bioavailability and health impacts. It highlights the disproportionate burden of exposure on vulnerable populations, such as migrant workers and those in low-resource settings, and discusses the economic and social implications of solvent-related cognitive disorders. Conflicting evidence and research gaps are addressed, underscoring the need for large-scale, longitudinal studies to establish definitive causal relationships between solvent exposure and cognitive decline.

To mitigate these risks, it recommends stricter regulatory measures, improved workplace safety protocols, enhanced worker education, and ongoing health monitoring. By prioritizing proactive interventions, industries can reduce occupational solvent-related health risks, protect vulnerable workers, and promote safer work environments. This review underscores the importance of balancing industrial productivity with public health, advocating for a precautionary approach to solvent exposure management.

1 Introduction

Organic solvents (OS), also known as volatile organic compounds (VOCs), are a diverse group of over 200 chemical compounds capable of dissolving non-aqueous substances like fats, oils, resins, and plastics. Their versatility makes them essential in industries such as construction (e.g., paints, thinners, adhesives),

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pharmaceuticals, printing, cosmetics, and dry-cleaning (Sainio, 2015; Pandey & Yadav, 2018).

Solvents such as acetonitrile, benzene, toluene, and acetone are classified as toxic chemicals (Table 1), with well-documented links to health risks (Stacey & Winder, 2004; Li et al., 2021). Their widespread use in industries like pharmaceuticals necessitates strict management and monitoring to ensure safety and regulatory compliance (Lippmann & Leukauf, 2020). Moreover, the choice of materials (Figure 1) in pharmaceutical synthesis is crucial for optimizing both yield and purity of active pharmaceutical ingredients (APIs).

Table 1: highly lipophilicity OSs and some of their applications

Organic Solvent	Boiling point	Everyday application
Acetonitrile	81.6	Acetonitrile is a polar aprotic solvent extensively utilized in chemical extractions, especially in pharmaceutical synthesis. It is also employed in the formulation of certain pesticides, where it enhances the effective delivery of active ingredients (Zarzycki et al., 2010).
Chloroform	61.7	Chloroform is a dense, colorless liquid primarily used in chemical extractions due to its ability to dissolve a wide range of organic compounds. It is also known for its adhesive properties with plastic materials, making it advantageous in various manufacturing processes (McCulloch, 2003).
Carbon tetrachloride	76.7	Carbon tetrachloride is a clear, sweet-smelling liquid historically used as a dry-cleaning agent. It is highly effective at dissolving oils and fats, making it valuable for cleaning applications such as removing paint, rubber residues, and varnishes. However, its use has significantly declined in recent years due to serious health and environmental concerns (Tyagi, 2024).
Hexane	69.0	Hexane is a hydrocarbon that is often used as a gasoline additive to improve combustion efficiency. It is also a key component in elasticity, adhesive formulations, varnishes and print in prints that contribute to the flexible and durable properties of these products (Bayindirli & Celik, 2019).
Ethyl acetate	77.0	Ethyl acetate is a colorless liquid with a fruity odor, commonly found in nail polish removers and used as a solvent in various cosmetic formulations. It also serves as a gasoline additive and, owing to its ability to dissolve a wide range of substances, is frequently employed in the production of inks and dyes (Sen, 2015).
Benzene	80.1	Benzene is an aromatic hydrocarbon commonly used as a gasoline additive to enhance octane ratings. It is also utilized in the formulation of products designed to remove rubber and grease stains. However, its use is strictly regulated due to the significant health risks associated with exposure (Bao, 2022).
Toluene	110.6	Toluene is a clear liquid that serves as a gasoline additive and solvents for acrylic paints and offers excellent thinning capabilities. It is often contained in diluted paint and other industrial solvents because it dissolves a variety of substances (Bauer & Buettner, 2023).
Isopropanol	82.6	Isopropanol, which is often referred to as alcohol, is a versatile chemical that is used in various disinfectants with a strong ability to kill bacteria and viruses. It is often found in cosmetics, hand disinfectants and inks, which makes it an essential component for personal care products (Xiao et al., 2022).

Workers in industries like painting, printing, and manufacturing often migrant workers or those from low socio-economic backgrounds—are disproportionately affected by OS exposure due to limited access to healthcare, inadequate training, and insufficient protective equipment (Ladou, 2010). Addressing these disparities is crucial to mitigating health risks in vulnerable populations.

While some argue that the risks associated with OS exposure are overstated, the precautionary principle dictates that it is better to err on the side of caution. The devastating consequences of VOC exposure, initially downplayed by industry interest groups, underscore the importance of proactive measures to protect workers' health (Castleman, 2005).

It is essential to learn from past mistakes and prioritize the health and well-being of employees over industry interests. Implementing safety measures—such as replacing hazardous solvents, providing PPE, and enforcing ventilation standards—can significantly reduce VOC exposure risks (Crawford et al., 2017; Nielsen, 2018). Additionally, developing biomarkers to detect early signs of solvent-induced neurotoxicity would enable timely interventions and prevent long-term damage (Brown & Sen, 2017).

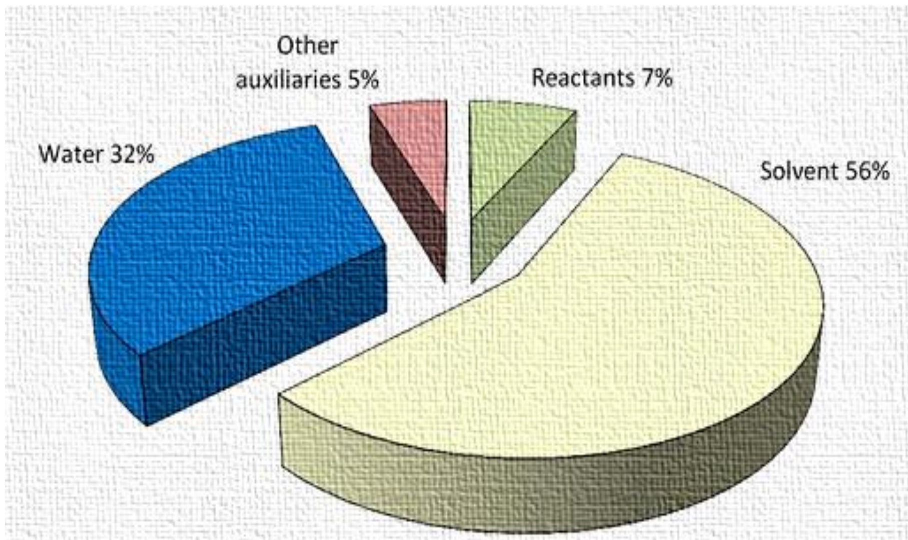

Figure 1. The relative contributions of materials typical in the production of an APIs (Sainio, 2015).

The bioavailability of OSs is fundamentally determined by their physical properties. Specifically, volatility is a significant predictor of inhalation exposure, while the lipid-water partition coefficient serves as a critical indicator of transcutaneous absorption. The kinetics of these pathways help predict the health effects associated with OS exposure (Firestone et al., 2009).

Lipophilicity plays a crucial role in the distribution of solvents within the body, particularly in lipid-rich organs such as the brain and adrenal glands (Bruckner et al., 2023). Lipophilic compounds are typically eliminated through the kidneys after undergoing metabolic conversions that increase their water solubility (Das et al., 2014). However, it is important to note that the metabolites generated during this process can sometimes be more toxic than the original compounds (Bolla et al., 2009).

VOCs are inherently lipophilic and exhibit significant volatility. As a result, exposure to these compounds primarily occurs through inhalation, increasing the risk of toxicity, especially in poorly ventilated environments. Additionally, dermal absorption is possible, particularly with solvents that exhibit both lipid and water solubility alongside moderate volatility (Aminoff, 2014).

The highest levels of exposure are typically observed in industries such as chemical cleaning, screen printing, glass production, and painting. In contrast, lower exposure levels are found among petrol pump attendants, carpenters, chemical process operators, lab technicians, and cleaners. While inhalation is the most common route of exposure, dermal contact can also occur due to the lipophilic nature of solvents (Lucchini & Hashim, 2015).

1. Neurotoxic Effects Associated with Occupational Exposures of OSs:

Exposure to VOCs, such as benzene and toluene, is linked to neurological disorders like chronic solvent-induced encephalopathy (CSE), dementia, and Alzheimer's disease. These lipophilic solvents accumulate in brain tissue, disrupting neurological functions and leading to cognitive deficits, including memory loss and impaired executive function (Costa, 2017; Kukull et al., 1995; Van & Boyes, 2022). Occupations with frequent solvent exposure, such as spray painting and industrial work, show higher rates of neuropsychological dysfunction, with risk increasing with exposure duration and concentration (Sainio, 2015). Neurobiological mechanisms underlying these effects include:

- **Oxidative stress**,
- **Neuroinflammation**, and
- Disruptions in **neurotransmitter activity**,

all of which may contribute to cognitive decline (Dick, 2012; White & Proctor, 1997). However, conflicting studies indicate that factors such as genetics, overall health, and co-exposure to other environmental toxins may also influence cognitive health, making it challenging to establish definitive causal relationships (Tanner et al., 2014; Van Valen et al., 2018).

2. Dementia, Alzheimer's disease:

Alzheimer's disease (AD) is the most common form of dementia in older adults, accounting for **60–70%** of cases (Chin-Chan et al., 2015). AD is characterized by the presence of amyloid plaques and neurofibrillary tangles (Chin-Chan et al., 2015). OSs can harm the nervous system by disrupting neuronal processes at multiple levels, including:

- Alterations in ion channel receptors,
- Changes in cellular and tissue responses,
- Modifications in brain regions, and
- Ultimately, impacts on cognitive functions and behavior (Tanner et al., 2014).

Occupational exposure to OSs has been linked to memory loss, reduced executive function, and the onset of degenerative diseases such as dementia (Rauf et al., 2022; Van Valen et al., 2018). This raises significant concerns about the long-term effects on workers in industries where solvents are widely used.

2.1 Key Recommendations:

i. **Enhanced training programs** on safe solvent handling.

ii. **Regular health screenings** for at-risk workers (Lorántfy et al., 2020).

iii. Implementation of **effective ventilation systems** to reduce solvent concentrations in the air.

Extended occupational exposure to low levels of OSs has also been associated with neurobehavioral effects in male printing workers (Song et al., 2013). Certain solvents, such as n-hexane and methyl n-butyl ketone, or industrial solvent mixtures, are known to be toxic to peripheral nerves (Hume & Ho, 2019).

Additionally, the economic burden of dementia is substantial and continues to rise. According to the Alzheimer’s Disease International (ADI) 2020 Report, the global cost of dementia was estimated at $818 billion in 2015 and is projected to exceed $1 trillion by 2030, driven by increasing life expectancy and aging populations (Alzheimer's Disease International, 2020). These costs include direct medical expenses, social care, and informal caregiving burdens, making dementia one of the most financially demanding neurodegenerative conditions worldwide (Dickey, 2020; Chen et al., 2024).

In addition to the emotional toll on families and caregivers, healthcare systems are overwhelmed by the rising number of cases. Implementing robust safety measures in workplaces to prevent organic solvent exposure would not only protect workers' health but also alleviate the economic burden of these diseases.

3. Behavioral effects of long-term exposure to a mixture of Oss:

A study of 100 car painters exposed to OSs revealed significant impairments in memory, learning, and personality compared to a control group, even at exposure levels below Finnish thresholds (Hänninen et al., 1976). The solvent-exposed group showed deficits in visual skills and learning, with 50% experiencing mood disorders that further impacted performance. Higher exposure levels correlated with poorer outcomes, consistent with prior findings (Morrow et al., 2001).

One of the most significant cognitive effects of long-term OS exposure is impaired memory and learning. Studies indicate that exposure to these compounds can alter brain structure and function, leading to deficits in short-term and long-term memory (Abou-Donia, 2003). This can result in difficulties in learning new information, recalling past events, and performing daily tasks. Additionally, OSs can disrupt the development and maintenance of neuronal connections, leading to declines in cognitive flexibility and problem-solving abilities (Slotkin, 2014). As a result, individuals exposed to OSs may struggle to adapt to new situations, making everyday tasks challenging and overwhelming.

Long-term OS exposure has also been linked to emotional and mental health disorders. Studies associate OS exposure with increased anxiety, depression, and irritability (Ross et al., 2013). This can lead to mood swings, emotional instability, and a higher risk of developing mental illnesses. Furthermore, OSs can disrupt the regulation of stress hormones, increasing stress responses and the risk of anxiety disorders (Von Euler, 2015). Consequently, individuals exposed to OSs may experience persistent discomfort, making it difficult to maintain healthy relationships and perform daily activities.

4. **Social Functioning and Relationships**:

Long-term OS exposure can significantly impair social functioning and relationships. Exposed individuals may experience communication difficulties, leading to misunderstandings and conflicts (Slotkin, 2014). OSs have also been shown to influence social behavior, increasing aggression, hostility, and impulsiveness (Rohlman et al., 2015). As a result, individuals exposed to OSs may struggle to build and maintain healthy relationships, leading to social isolation and loneliness.

Sleep and Appetite Changes:

Long-term OS exposure can also disrupt sleep patterns and appetite regulation. Studies show that Oss can interfere with sleep-wake cycles, causing insomnia, daytime fatigue, and other sleep disorders (Abou-Donia, 2003). Additionally, OSs can affect appetite regulation, leading to changes in eating habits and weight (Slotkin, 2014). These disruptions can result in fatigue, lethargy, and weight-related issues, further compromising overall well-being.

Long-term OS exposure can have particularly harmful effects on children and adolescents. Prenatal exposure to OSs can impair fetal brain development, leading to cognitive and behavioral disorders later in life (Eskenazi et al., 2007). Childhood exposure has been linked to an increased risk of attention deficit hyperactivity disorder (ADHD), autism spectrum disorder, and other developmental disorders (Bouchard et al., 2010). As a result, children and adolescents exposed to OSs may face challenges in learning, socializing, and developing healthy relationships

In summary, long-term exposure to OSs can have devastating effects on human behavior, leading to cognitive, emotional, and social impairments. Cognitive effects include impaired memory and learning, while emotional effects encompass anxiety, depression, and irritability. Socially, OS exposure can impair social functioning and relationships, and disruptions in sleep patterns and appetite can further exacerbate overall well-being. The effects on children and adolescents are particularly concerning, underscoring the need for increased awareness and regulation of these compounds.

2 Discussions:

Exposure to OSs can lead to a variety of health problems, with neurotoxic effects being particularly significant. The primary mechanism behind this toxicity lies in the lipophilic properties of many organic solvents, such as benzene and toluene. These solvents have an inherent affinity for fats, allowing them to dissolve easily and accumulate in fatty tissues throughout the body, including the brain, which is largely composed of lipids.

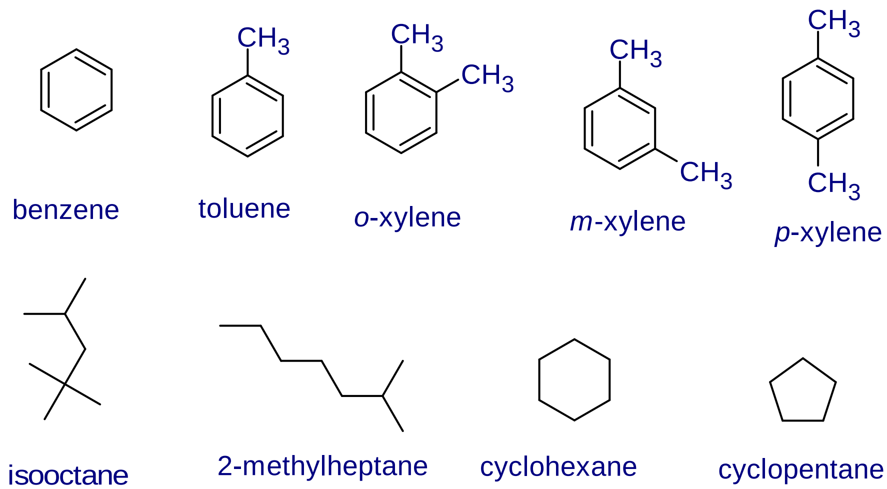

Figure 2. The non-polar structure of some OSs.

Due to their non-polar nature, organic solvents (OSs) can penetrate cellular membranes and integrate into lipid-rich environments. This accumulation in brain tissue can disrupt normal neurological functions and lead to significant damage. Figure 2 illustrates how the non-polar properties of these solvents enable them to target lipid structures in tissues, amplifying their potential for harm. Over time, exposure to these solvents can contribute to neurological disorders, cognitive impairments, and other serious health complications.

Figure 3 provides an analysis of the roles of specific brain regions involved in the pathogenesis of benzene poisoning (Hu et al., 2021). This visualization highlights the complex interactions and functions of these regions in mediating the neurotoxic effects of benzene exposure, emphasizing the need for further research into their contributions to overall cognitive and neurological health.

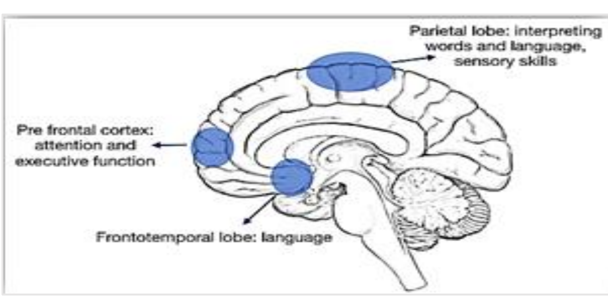

Figure 3. Illustration of the functions of brain regions associated with the pathogenesis of benzene poisoning (Hu et al., 2021).

Certain stakeholders may view the proposed measures as excessive and unjustified, arguing that existing safety protocols already provide adequate protection for employees against the potential risks of OSs exposure. Critics often highlight the lack of conclusive evidence directly linking OSs exposure to cognitive impairments or dementia. While numerous studies have identified correlations, they argue that correlation does not imply causation. Other factors, such as genetics, lifestyle choices, and socio-economic conditions, could also contribute to the development of cognitive deficits and neurodegenerative diseases.

Additionally, opponents of increased regulation argue that the financial burden associated with implementing enhanced safety protocols could negatively impact industries, particularly small businesses, potentially leading to job losses and economic strain. They advocate for a more balanced approach, which includes:

Educating workers on the safe use of solvents, and

Promoting personal responsibility,

rather than imposing strict regulations that may not effectively address the underlying causes of cognitive decline in the workplace.

2.1 Conflicting Evidence and Research Gaps

While many studies link OS exposure to cognitive impairment, conflicting evidence and the multifactorial nature of neurodegenerative diseases, such as genetics, lifestyle, and co-exposure to other toxins, complicate causal inferences.

For example, while epidemiological studies indicate that prolonged solvent exposure correlates with an increased risk of cognitive dysfunction (Kukull et al., 1995; Costa, 2017), other studies argue that this association may be confounded by other occupational hazards, comorbid health conditions, or socio-economic factors (Tanner et al., 2014). Some meta-analyses have reported only weak or inconsistent evidence linking solvent exposure to long-term neurodegenerative effects, suggesting that other risk factors might play a more dominant role (Van Valen et al., 2018).

Additionally, there are challenges in accurately measuring lifetime solvent exposure, as workers may be exposed to varying solvent mixtures at different concentrations over time. Self-reported exposure data, often used in retrospective studies, can be prone to recall bias, further complicating causal inferences (Hume & Ho, 2019).

While in-vitro and animal studies have demonstrated the neurotoxic potential of organic solvents, translating these findings to human populations remains complex. Differences in metabolism, exposure routes, and individual susceptibility make it difficult to generalize results across diverse populations. Furthermore, some longitudinal studies have failed to find a statistically significant link between solvent exposure and dementia when controlling for other occupational and lifestyle variables (Ross et al., 2013).

2.2 Balanced Interpretation of Findings

Given these inconsistencies, it is crucial to interpret the existing body of literature with caution. While there is strong evidence supporting the neurotoxic effects of certain solvents, particularly at high exposure levels, more controlled studies are needed to establish definitive dose-response relationships and to distinguish solvent-related cognitive decline from other contributing factors.

Future research should focus on:

Conducting large-scale, longitudinal cohort studies with standardized exposure assessments.

Investigating genetic and epigenetic factors that may influence individual susceptibility to solvent-induced neurotoxicity.

Utilizing advanced neuroimaging and biomarker-based approaches to detect early signs of solvent-induced cognitive dysfunction.

3 Conclusions

Occupational OS exposure poses significant cognitive health risks, including potential links to dementia and Alzheimer's. While evidence supports neurotoxic effects, inconsistencies and confounding factors—such as exposure duration and co-exposure to other toxins—highlight the need for further research and a precautionary approach.

To mitigate these risks, industries must:

- Implement **stricter safety regulations**,
- Improve **workplace ventilation**,
- Enforce the use of **personal protective equipment (PPE)**, and
- Prioritize **worker education**.

Additionally, ongoing **medical surveillance** and **large-scale epidemiological studies** are essential to better understand long-term solvent-related health impacts.

Protecting workers from harmful solvent exposure is not only a **regulatory necessity** but also a **public health priority**. By taking proactive measures, industries and policymakers can reduce the incidence of **solvent-induced cognitive impairment**, ensuring a safer and healthier workforce for future generations.

4 Recommendations

To mitigate solvent exposure risks, the following measures are recommended:

1. Regulatory Measures:

- Establish stricter occupational exposure limits based on updated neurotoxicology research.
- Ensure compliance with workplace safety regulations through routine inspections and enforcement.

2. Workplace Safety Enhancements:

- Improve ventilation systems to reduce airborne solvent concentrations.
- Require the use of personal protective equipment (PPE), such as respirators and gloves.

3. Worker Education & Monitoring:

- Implement mandatory training programs on solvent hazards and safe handling procedures.
- Conduct regular health screenings and neurocognitive assessments for workers in high-exposure occupations.

4. Further Research & Policy Development:

- Support long-term cohort studies to establish definitive links between solvent exposure and cognitive impairment.
- Encourage collaboration between policymakers, scientists, and industry leaders to refine safety standards.

By prioritizing these measures, industries can significantly reduce occupational solvent-related health risks and promote safer work environments.

Conflict of interest:

The authors declare that there are no conflicts of interest.

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