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# An Overview on Common Organic Solvents and Their Toxicity

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***Authors' contributions***

*This work was carried out in collaboration between us. Author DRJ designed the review, performed literature review and wrote the first draft of the manuscript. Author NA managed the manuscript through updating needed information and proof checking. Both authors read and approved the final manuscript.*

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## ABSTRACT

Organic solvents are known as carbon-based solvents and their general property is primarily based on their volatility, boiling point, the molecular weight and color. Having enormous hazards associated with the organic solvents, they are used for millions of purposes which alert us to think more on its toxicity points. Almost all of the solvents are hazardous to health, if swallowed or inhaled more than the limit quantity and on contact to the skin most of them cause irritation. Some of the common solvents are acetone, ethyl acetate, hexane, heptane, dichloromethane, methanol, ethanol, tetrahydrofuran, acetonitrile, dimethylformamide, toluene, dimethylsulfoxide etc. Researchers, scientists, workers in the chemical industry and research institutes use these solvents on regular basis leading them to be affected in major aspects. But also, the nearby persons are affected by the contamination to the soil, water, air etc. If constantly exposed with solvents, it will badly affect the function of CNS and other body parts. The level of impact, sign and symptoms will depend on concentration, time, duration, frequency and nature of solvents, leading

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to common effects like headache, dizziness, tiredness, blurred vision, behavioral changes, unconsciousness, and even death. To overcome it, the green chemistry concept is growing rapidly, and the solvent selection guide is in practice in many big company and research institute. A researcher or chemical worker is the primary person who works with solvents and they need to consider throughout these things while performing their activities for their own good health and for the sake of the world. The purpose of this review is to provide needed basic knowledge about common organic solvents and their potential toxicities which will alert researchers to think twice and always think for their health as well as for the environment via safe and green practice.

*Keywords: Organic solvents; toxicity; acetone; toluene; n-hexane; green chemistry.*

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## 1. INTRODUCTION

The presence of solvents in any vegetables, fruits, meats etc. makes them easily deteriorated when stored for long at room temperature which means that the solvents make many easy things to happen i.e. occurrence of chemical reaction, which results in change in its form. The dry meat, dry fish, dry vegetables, dry grains etc. remains very stable in normal condition if the dryness maintained properly. This basic understanding teaches us how the chemical reactions are done in the liquid state. The common organic solvents are generally classified as an aliphatic hydrocarbon, aromatic hydrocarbon, cyclic hydrocarbon, halogenated hydrocarbon, amines, ketones, esters, ether, aldehyde, alcohols etc. (Table 1). It's hard to talk about organic synthesis without organic solvents. In common, the organic solvents are chemicals that are used to dissolve other chemicals but in detail, we need to understand the reactivity of respective solvents on specific reactions conditions. So, the selection of appropriate solvents for a reaction is to be noted always. The choice of solvents is usually done by previous experience with particular solvents or the following similar pattern literature review and practice it in a laboratory setting [1]. However, the scenario does not remain same nowadays because of some strict rules and regulation we need to consider like solvent power, volatility that leads to toxicity to the researcher and to our society and overall environment. This leads to search new and new best option and because of which, nowadays the solvent-free organic synthesis is rapidly growing [2,3]. Many research about the toxicity of solvents gives us the molecular mechanism and possible major body parts to be affected [4-6]. The knowledge of risk associated with organic solvents is increasing rapidly among the researcher and in a lesser amount to the public which creates a louder voice for safety, strict rules and regulation; these all decreases the potential danger and associated health effects. Now the well-equipped laboratory setup, proper ventilation to draw the solvent and reagent fumes to the highly diluted atmosphere, proper disposal system is rapidly increasing; but the scale of synthesis, the number of researchers are increasing rapidly which has resulted in larger volume of organic solvent consumption that still become risk factor and many organizations are working on it.

As the skeleton of organic solvents contain carbon and hydrogen as major with hetero atoms some time so, they show high lipophilicity and very volatile. In toxicity view, the lipophilicity influences the distribution of solvents to various body parts. The lipophilic compounds need to be converted to a water-soluble form via several osmotic conversions that enhances the excretion via the kidney. Sometime the resulting metabolite could be more toxic than the original one.

Due to the high lipophilicity character of organic solvents, they can easily enter the brain and affects severely sometimes. At high dose with respect to certain chemical can cause anesthetic effects (eg. Trichloroethylene [7]), anxiolytic effects (eg. Toluene [8]), convulsant effect (eg. Fluorothyl [9]), anticonvulsants (eg. Toluene [10]), narcotic effects (Trichloroethylene), antidepressants (benzyl chloride).

Due to the rapid growth of plastic and chemical industries, major population is affected by organic solvents. Since the organic solvents are highly volatile, it leads to the exposure of solvents to air rapidly. It is being inhaled via respiration, so lungs are the primary organ to be affected which alerts to have enough ventilation in workplace. As being a synthetic chemist, the researcher needs to work in a lab for a long time handling many kinds of toxic reagents and organic solvents repeatedly i.e. almost every day and throughout.

**Table 1. A general class of organic solvents**

| Hydrocarbons | Alcohols | Ethers | Chlorinated solvents |
|---|---|---|---|
| *n*-Pentane | Methanol | Diethyl ether | Methylene chloride |
| *n*-Hexane | Ethanol | Diisopropyl ether | Chloroform |
| *n*-Heptane | n-Propanol | Dibutyl ether | Carbon tetrachloride |
| *n*-Octane | *i*- Propanol | Methyl *tert* butyl ether | 1,2-dichloroethane |
| *n*-Nonane | *n*-Butanol | 1,4-Dioxane | 1, I,1 -Trichloroethane |
| n-Decane | *i*-Butanol | Tetrahydrofuran | Trichloroethylene |
| Benzene | 2-Butanol | Esters | Perchloroethylene |
| Toluene | n-Amyl alcohol | Methyl acetate | Monochlorobenzene |
| 2,2,4-Trimethyl pentane | *i*-Amyl alcohol | Ethyl acetate | Miscellaneous solvents |
| Cyclohexane | Cyclohexanol | Isopropyl acetate | Dimethylformamide |
| 2,2,4-Trimethylpentane | *n*-Octanol | *n*-Butyl acetate | Dimethylacetamide |
| Cyclohexane | Ethanediol | Cellosolve acetate | Dimethylsulphoxide |
| Ethylbenzene | Diethylene glycol | Glycol Ethers | Sulfolane |
| Ketones | 1,2-Propanediol | Propylene glycol methyl ether | Carbon disulphide |
| Acetone | | Ethylene glycol methyl ether | Acetic acid |
| Methyl ethyl ketone | | Ethylene glycol ethyl ether | Aniline |
| Methyl isobutyl ketone | | Ethylene glycol monobutyl ether | Nitrobenzene |
| Cyclohexanone | | | Morpholine |
| n-Methyl-2-pyrrolidone | | | Pyridine |
| Acetophenone | | | 2-Nitropropane |
| | | | Acetonitrile |
| | | | Furfuraldehyde |
| | | | Phenol |

The hydrophobic nature of the organic solvents and the polar water has a great role in organic synthesis; from the quenching practice to the extraction of organic compounds and excretion of undesired side products to the water layer. The separation action plays a crucial role in chemical and pharmaceutical industries, drug development research institute, University Research Centre and so many, where solvent accounts 40-70% of the overall research cost [11] because to get a milligram scale of the compound we need to lose liters of the organic solvents. Moreover, the organic solvent used as a raw material in chemical synthesis, cleansing purposes (e.g. Acetone to clean glassware) that have to be discarded at the end of the process or recovered (which is an expensive process) [11] (Fig. 1).

The boiling point, solubility, polarity, pka value etc. all need to be consider (Table 2). The Fig. 2 shows the chemical structure of common organic solvents, from which we can predict some concept about polarity, boiling point, physical nature of the solvents etc. Most of the organic reaction is carried out in the liquid phase to enhance its homogeneity and for an effective collision between the reactants for the smooth reaction.

On increasing concern about safety, efficacy, available alternative the solvent selection practice is increasing now. The green chemistry (GC) also known as a sustainable chemistry tool is also influencing the organic chemist to search for the possible less toxic option. They are focusing on designing the products with minimum toxicity, minimize use, and reuse option by putting the environment in center point. The big pharmaceutical company develops their own solvent selection guide [13]. Table 3 describes Pfizer company solvent selection guide [14]. The solvents subjected to the red category due to having these potencies: toxic, carcinogenic, mutagenic, low flash point, environmental risk of ozone layer depletion etc.

For this, a compiled form of the information about the common organic solvents is desired. For the beginner who is entering for organic synthesis, they need to know about the commonly used solvents and their property that will enhance their handling and decrease the risk associated with it.

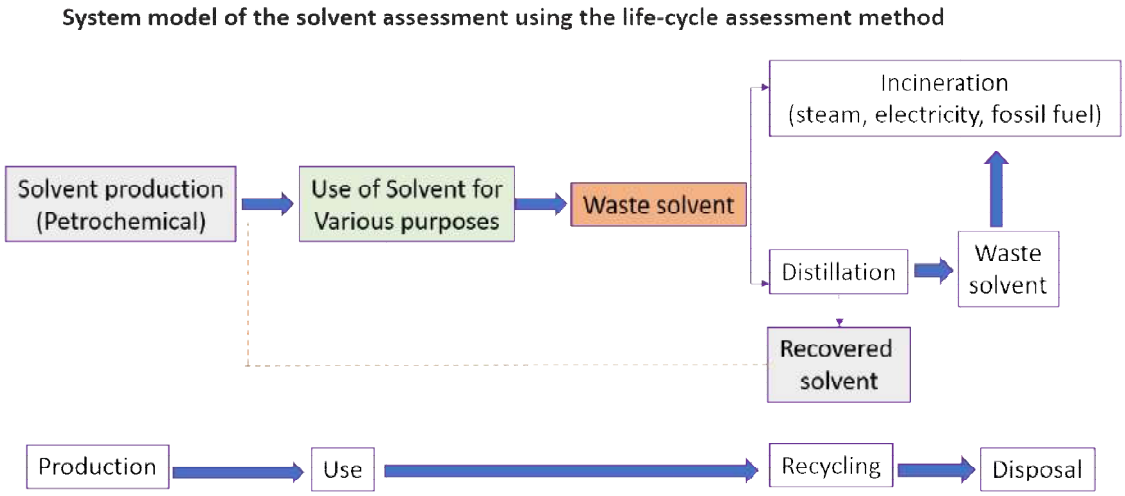


**Fig. 1. System model of the solvent assessment using the life-cycle assessment method [12]**

**Table 2. Shows the list of common organic solvents, their formula, molecular weight, boiling and melting point, density, solubility in water, dielectric constant and flash point**

| Solvent name | Formula | MW | BP (°C) | MP (°C) | Density (g/mL) | Solubility in water (g/100 g) | Dielectric Constant | FP (°C) |
|---|---|---|---|---|---|---|---|---|
| acetic acid | $C_2H_4O_2$ | 60.052 | 118 | 16.6 | 1.0446 | Miscible | 6.20 | 39 |
| acetone | $C_3H_6O$ | 58.079 | 56.05 | -94.7 | 0.7845 | Miscible | 21.01 | -20 |
| acetonitrile | $C_2H_3N$ | 41.052 | 81.65 | -43.8 | 0.7857 | Miscible | 36.64 | 6 |
| benzene | $C_6H_6$ | 78.11 | 80.1 | 5.5 | 0.8765 | 0.18 | 2.28 | -11 |
| 1-butanol | $C_4H_{10}O$ | 74.12 | 117.7 | -88.6 | 0.8095 | 6.3 | 17.8 | 37 |
| 2-butanol | $C_4H_{10}O$ | 74.12 | 99.5 | -88.5 | 0.8063 | 15 | 17.26 | 24 |
| 2-butanone | $C_4H_8O$ | 72.11 | 79.6 | -86.6 | 0.7999 | 25.6 | 18.6 | -9 |
| *t*-butyl alcohol | $C_4H_{10}O$ | 74.12 | 82.4 | 25.7 | 0.7887 | Miscible | 12.5 | 11 |
| carbon tetrachloride | $CCl_4$ | 153.82 | 76.8 | -22.6 | 1.594 | 0.08 | 2.24 | -- |
| chlorobenzene | $C_6H_5Cl$ | 112.56 | 131.7 | -45.3 | 1.1058 | 0.05 | 5.69 | 28 |
| chloroform | $CHCl_3$ | 119.38 | 61.2 | -63.4 | 1.4788 | 0.795 | 4.81 | -- |
| cyclohexane | $C_6H_{12}$ | 84.16 | 80.7 | 6.6 | 0.7739 | 0.0055 | 2.02 | -20 |
| 1,2-dichloroethane | $C_2H_4Cl_2$ | 98.96 | 83.5 | -35.7 | 1.245 | 0.861 | 10.42 | 13 |
| diethylene glycol | $C_4H_{10}O_3$ | 106.12 | 246 | -10 | 1.1197 | 10 | 31.8 | 124 |
| diethyl ether | $C_4H_{10}O$ | 74.12 | 34.5 | -116.2 | 0.713 | 7.5 | 4.267 | -45 |
| diglyme (diethylene glycol dimethyl ether) | $C_6H_{14}O_3$ | 134.17 | 162 | -68 | 0.943 | Miscible | 7.23 | 67 |
| dimethyl-formamide (DMF) | $C_3H_7NO$ | 73.09 | 153 | -60.48 | 0.9445 | Miscible | 38.25 | 58 |
| Dimethyl sulfoxide(DMSO) | $C_2H_6OS$ | 78.13 | 189 | 18.4 | 1.092 | 25.3 | 47 | 95 |
| 1,4-dioxane | $C_4H_8O_2$ | 88.11 | 101.1 | 11.8 | 1.033 | Miscible | 2.21* | 12 |
| ethanol | $C_2H_6O$ | 46.07 | 78.5 | -114.1 | 0.789 | Miscible | 24.6 | 13 |
| ethyl acetate | $C_4H_8O_2$ | 88.11 | 77 | -83.6 | 0.895 | 8.7 | 6* | -4 |
| ethylene glycol | $C_2H_6O_2$ | 62.07 | 195 | -13 | 1.115 | Miscible | 37.7 | 111 |
| glycerin | $C_3H_8O_3$ | 92.09 | 290 | 17.8 | 1.261 | Miscible | 42.5 | 160 |

| Solvent name | Formula | MW | BP (°C) | MP (°C) | Density (g/mL) | Solubility in water (g/100 g) | Dielectric Constant | FP (°C) |
|---|---|---|---|---|---|---|---|---|
| heptane | $C_7H_{16}$ | 100.20 | 98 | -90.6 | 0.684 | 0.01 | 1.92 | -4 |
| hexane | $C_6H_{14}$ | 86.18 | 69 | -95 | 0.659 | 0.0014 | 1.89 | -22 |
| methanol | $CH_4O$ | 32.04 | 64.6 | -98 | 0.791 | Miscible | 32.6* | 12 |
| methyl *t*-butyl ether (MTBE) | $C_5H_{12}O$ | 88.15 | 55.2 | -109 | 0.741 | 5.1 | ?? | -28 |
| methylene chloride | $CH_2Cl_2$ | 84.93 | 39.8 | -96.7 | 1.326 | 1.32 | 9.08 | 1.6 |
| *N*-methyl-2-pyrrolidinone (NMP) | $CH_5H_9NO$ | 99.13 | 202 | -24 | 1.033 | 10 | 32 | 91 |
| nitromethane | $CH_3NO_2$ | 61.04 | 101.2 | -29 | 1.382 | 9.50 | 35.9 | 35 |
| pentane | $C_5H_{12}$ | 72.15 | 36.1 | -129.7 | 0.626 | 0.04 | 1.84 | -49 |
| Petroleum ether (ligroine) | -- | -- | 30-60 | -40 | 0.656 | -- | -- | -30 |
| 1-propanol | $C_3H_8O$ | 60.10 | 97 | -126 | 0.803 | Miscible | 20.1* | 22 |
| 2-propanol | $C_3H_8O$ | 60.10 | 82.4 | -88.5 | 0.785 | Miscible | 18.3* | 12 |
| pyridine | $C_5H_5N$ | 79.10 | 115.2 | -41.6 | 0.982 | Miscible | 12.3* | 17 |
| tetrahydrofuran (THF) | $C_4H_8O$ | 72.106 | 65 | -108.4 | 0.8833 | 30 | 7.52 | -14 |
| toluene | $C_7H_8$ | 92.14 | 110.6 | -93 | 0.867 | 0.05 | 2.38* | 4 |
| triethyl amine | $C_6H_{15}N$ | 101.19 | 88.9 | -114.7 | 0.728 | 0.02 | 2.4 | -11 |
| water | $H_2O$ | 18.02 | 100.00 | 0.00 | 0.998 | -- | 78.54 | -- |
| water, heavy | $D_2O$ | 20.03 | 101.3 | 4 | 1.107 | Miscible | ?? | -- |
| *o*-xylene | $C_8H_{10}$ | 106.17 | 144 | -25.2 | 0.897 | Insoluble | 2.57 | 32 |
| *m*-xylene | $C_8H_{10}$ | 106.17 | 139.1 | -47.8 | 0.868 | Insoluble | 2.37 | 27 |
| *p*-xylene | $C_8H_{10}$ | 106.17 | 138.4 | 13.3 | 0.861 | Insoluble | 2.27 | 27 |

*Adapted from https://www.organicdivision.org/wp-content/uploads/2016/12/organic_solvents.pdf. T= 20 ℃, *25; Abbreviations: BP= boiling point, MP= melting point, MW= molecular weight, FP= flash point*

We can get enough information about the individual solvents by searching on internet, but this review will provide most of the needed information at once in a very convenient way as well as with summarized form.

## 2. GUIDE ON USING SOLVENTS AND CHEMICALS

Before handling any chemicals, always wear proper protective cloths, and check Material Safety Data Sheet (MSDS) to gain the proper knowledge about the individual chemicals, which will provide information about potential hazards, safety measures, and other handling procedures etc. The handling of any chemicals and solvents should always be carried out on fully functional chemical fume hood. If in case of chemical contact to eye, remove any contact lenses if used and immediately flush with running water for at least 15 minutes, by keeping the eyelid open will allow proper air supply to the eye which will enhance fast evaporation of solvents from eye surface and decrease the further more risk. Similarly if chemical contact to the skin, immediately wash with excess of water, cover the irritated skin with emollient, remove contaminated clothes and shoes, and get medical attention in all the cases if needed. If possible don't work in the laboratory alone. Always think below points when working with chemicals.

**Table 3. Pfizer solvent selection guide**

| Preferred | Usable | Undesirable |
|---|---|---|
| Acetone | Acetonitrile | Benzene |
| 1-Butanol | Acetic acid | Chloroform |
| *t*-Butanol | Cyclohexane | Carbon tetrachloride |
| Ethyl acetate | Dimethyl sulfoxide | Dichloromethane |
| Ethanol | Ethylene glycol | Diethyl ether |
| Isopropyl acetate | Heptane | Dichloroethane |
| 2-propanol | Isooctane | Di-isopropyl ether |
| 1-Propanol | Methylcyclohexane | Dimethylformamide |
| Ethyl acetate | 2-MethylTHF | Dioxane |
| Ethanol | Methyl *t*-butyl ether | Dimethyl acetate |
| Methanol | Toluene | Dimethoxyethane |
| Methyl ethyl ketone | Tetrahydrofuran | Hexane(s) |
| Water | Xylenes | *N*-Methylpyrrolidinone |
| | | Pentane |
| | | Pyridine |

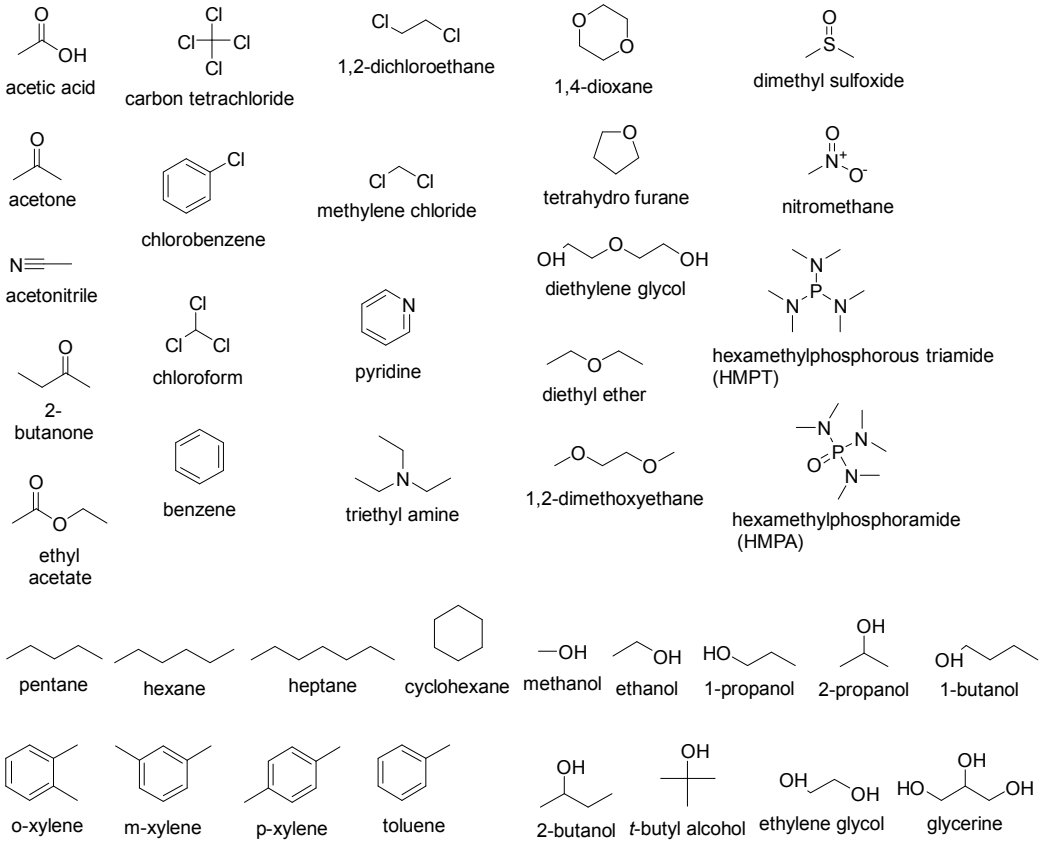


**Fig. 2. Structure of common organic solvents**

- Every time ask yourself, "What am I working with? What are the hazards?"
- Be prepared: attend all required laboratory safety training before starting research, read all procedures and related safety information prior to starting an experiment.
- Always take permission from a supervisor before carrying outing new experiments and take guidance from lab members if needed.
- Clearly understand the operation of safety equipment and their location.

- Be alert and work with caution all time, immediately notify the supervisor in any unsafe conditions.
- Know the right emergency response process for injury or accidents.
- Always perform experiments in a responsible manner, no prank, no practical jokes.
- Always wear a protective lab coat, gloves, and shoes, cover exposed skin, proper mask, and tie back long hair.
- Never drink beverages, eat foods, chew gum, apply cosmetics or handle contact lenses in the laboratory.
- Always use a chemical fume hood.
- Never put solvents near hot place or reaction under heating.
- Always maintain good personal hygiene, don't touch body parts with hands during handling chemicals, wash hands after removing gloves and before leaving the laboratory.
- Properly segregate all lab waste and dispose them as per the rules and regulation.

## 3. TOXICOKINETIC

The lipophilic nature of organic solvents promotes their absorption immediately after inhalation or the surface dermal contact or oral exposure [15,16]. Once the solvent is being absorbed, the metabolism and long-term or shorter deposition is affected by the route of exposure and the chemical-physical nature of that solvent. The metabolism and excretion can occur immediately with liver and lungs, without entering the systemic circulation. The relative toxic metabolite of solvents depends on the individual chemical nature. Some are metabolized to less toxic but some to a severely toxic metabolite. The un-metabolized solvent is distributed largely in fatty tissue which affects the human body on a long-term basis.

The CNS toxicity of the organic solvents is a major concern because of their rapid entrance capacity to cross blood-brain barrier [16]. Due to the nature of chemical synthesis, we need to expose to multiple solvents at a time which could lead to the synergistic toxic effects. Solvent like ethanol can induce the metabolic enzymes, these enzymes can involve in metabolic activation or detoxification of others. So, the activation of certain enzymes can severely lead to the potentiation of toxicity of other solvents and vice versa.

## 4. MSDS FOR ORGANIC SOLVENTS

We always need to check MSDS; which is a document that contains information on possible potential hazards like health, fire, reactivity, and environment etc. Moreover, it provides information about how to work with a chemical product. So, for a researcher or chemist it is the first point to check about the safety of chemicals. It also contains more information about use, storage, handling, and emergency procedure. Usually, MSDS is prepared by the producer or supplier of those chemicals that provides complete health and safety needed [17-20]. Below show some points that are usually included in the MSDS sheet.

- Identification (chemical product and manufacturer)
- Hazard(s) identification (potential acute and chronic health effects)
- Composition/ information on ingredients
- First-aid measures (for inhalation, ingestion, eye and skin contact etc.)
- Fire-fighting measures (flammability, flash point, auto-ignition temperature etc.)
- Accidental release measures (small spill and large spill)
- Handling and storage (precautions and storage conditions)
- Exposure control/ personal protection
- Physical and chemical properties (physical state, odor, taste, molecular weight, color, boiling and melting point, specific gravity, density, vapor pressure, volatility, solubility etc.)
- Chemical stability and reactivity data (stability, instability temperature, conditions of instability, incompatibility with various substances, corrosivity, reactivity, polymerization etc.)
- Toxicological information (route of entry, toxicity to animals, chronic effects to human, special remarks on toxicity to animals and human, special remarks on other toxicity to humans etc.)
- Ecological information (Eco-toxicity, products of biodegradation, other special remarks)
- Disposal considerations (waste disposal)
- Transport information (DOT classification, identification, special provision for transport etc.)
- Regulatory information (federal and state regulation, other regulation)

- Other information references, other special consideration, creation date, last update date etc.)

Before handling every solvent if we check the MSDS of that solvents, we will have a broader idea on the nature of chemicals, protective measures needed and many more in case of any accidents.

## 5. GREEN CHEMISTRY CONCEPT

Paul Anastas and John Warner introduced Green Chemistry (GC) concept, which means during the application of chemistry techniques and the methodology, always we need to think about the possible option to reduce or eliminate the generation of products, feedstock, byproducts, reagents, and solvents etc. which are hazardous to both humans and environments. In synthesis, the solvents are used in a large quantity and to overcome this situation, the feasible way is to reduce hazard related to them by substituting with the safer option. As in Table 3, some big companies tried more for green concept use. The Pfizer presented SSD to the medicinal chemist with including 39 solvents. Depending on their possible toxicity and the various hazard associated with them they are categorized as preferred, usable, undesired, highlighted with green, yellow and red color respectively [13,14]. For the proper solvent selection, the chemometrics and the multicriteria decision analysis is introduced by Marek *et al* for 151 solvents [13]. The green solvent concept is popular now which is described in detail by Christian et al. [12]. Always, the selection of proper solvent remains a crucial point in a wide range of chemical processes. Regarding this, but sometimes there couldn't be always a proper option to the toxic or undesired one but our best tries should be always to do with a minimum toxic solvent which will sustain our nature as well as our chemistry in a environmental friendly way. The 12 principles of GC can be condensed in below form (PRODUCTIVELY) [21].

Prevent wastes
Renewable materials
Omit derivatization step
Degradable chemical products
Use safe synthetic methods
Catalytic reagents

**Table 4. Red category solvents[14]**

| Red solvents | Reason |
|---|---|
| Benzene | low flash point (-11℃), carcinogen (CMR category 1), very low TLV (0.5 ppm), toxic to humans and environment, strongly regulated in the US (HAP) and the EU |
| Carbon tetrachloride | carcinogen (CMR category 3), toxic, ozone depleter, not available for large-scale use, strongly regulated in the US (HAP) and EU |
| Chloroform | carcinogen, classified as a HAP in the US |
| Dichloroethane | carcinogen, classified as a HAP in the US |
| Dichloromethane | large volume use, classified as HAP in the US, regulated by EU solvent directive |
| Diethyl ether | very low flash point (-24℃), good alternative ethers available |
| Diisopropyl ether | very low flash point (-12℃), very powerful peroxide former, good alternative ethers available |
| Dimethoxyethane | carcinogen (CMR category 2), toxicity |
| Dimethylacetamide | strongly regulated by EU solvent directive, toxicity |
| Dimethylformamide | toxicity, classified as a HAP in the US, strongly regulated by EU solvent directive |
| Dioxane | Carcinogen (CMR category 3), classified as HAP in the US |
| Hexane(S) | Very low flash point (-23℃), more toxic than the alternative heptane, in the US classified as a hazardous airborne pollutant (HAP) |
| N-Methyl pyrrolidinone | strongly regulated by EU solvent directive, toxicity |
| Pentane | very low flash point (-49℃) and good alternative available |
| Pyridine | carcinogenic/mutagenic/reprotoxic (CMR) category 3 carcinogen, toxicity, and very low exposure threshold limit value TLV for worker exposures |

**Table 5. Solvent replacement table (alternative to undesired one)[14]**

| Undesired solvents | Alternatives |
|---|---|
| Benzene | Toluene |
| Chloroform, carbon tetrachloride or dichloroethane | Dichloromethane |
| Dichloromethane (chromatography) | Ethyl acetate/heptane |
| Dichloromethane (extraction) | Ethyl acetate, toluene, MTBE, 2-MeTHF |
| Di-isopropyl ether or diethyl ether | 2-MeTHF or *tert*-butyl methyl ether |
| Dimethylformamide, dimethyl acetamide or *N*-methyl pyrrolidinone | Acetonitrile |
| Dioxan or dimethoxyethane | 2-MeTHF or *tert*-butyl methyl ether |
| Hexane(S) | Heptane |
| Pentane | Heptane |
| Pyridine | $Et_3N$ (if pyridine used as a base) |

Temperature, pressure ambient
In-process monitoring
Very few auxiliary substances
E-factor, maximize feed in product
Low toxicity of chemical products
Yes, it is safe

The reason of putting some solvents to red category solvents is summarized in Table 4. And the alternative to the red/ undesired/ more toxic solvents are summarized in Table 5.

## 6. HEALTH HAZARDS OF COMMON ORGANIC SOLVENTS

### 6.1 Neurotoxicity of Organic Solvents

Due to the low boiling point of most of the organic solvents, it can easily enter in our body via respiration as well as distribution in the air is rapid so the large group of mass is affected including the atmosphere. So, this becomes the most emerging issue in the field of occupational health. In recent decade major presentation, meetings, and discussion with controversial subjects are happening. The nervous system is a major part which handles all the body. To be a person fit and fine he/ she should have a good mental state. For fruitful research, a researcher should first survive with good health and mental condition. So, this is the key factor to be considered and various safety measures are recommended to follow for their life. Since once damaged to CNS or PNS is a potentially irreversible process such repeated exposure results in severe cumulative impairments [4,6]. Usually, the neurotoxic solvents on exposure show neuropathy, psychosis, dyskinesia, peripheral neuropathy, pyramidal and other types of irreversible brain dysfunction, trigeminal neuralgia, anorexia, ototoxicity, encephalopathy, transverse myelopathy, facial paralysis, and limb numbness etc. [4]. The organic solvent exposure and contrast sensitivity comparison between men and women shows, the men visual impaired is wider than that of women over wide range of spatial frequencies, the researcher conclude this is due to higher body fat mass in women that can serve as a protective factor against neurotoxic effects in comparison to men [22].

### 6.2 Normal Hexane and Other Alkanes

*n*-Hexane is a known chronic human neurotoxicant [4,23]. In animal and human, *n*-Hexane is metabolized into a gamma diketone, 2,5-hexanedione which is more potent neurotoxicant than the parent alkane [4]. The comparative study of the toxicity of n-heptane, n-hexane, and n-pentane in peripheral nerve of the rat also shows n-hexane is far more neurotoxic than the Pentane and Heptane to the peripheral nerves of the rat [5,24].

### 6.3 Aromatic Hydrocarbons

Benzene, xylenes, and toluene are aromatic hydrocarbon solvents widely used in past time and still popular but are quite limited due to their toxicity. In liver the Cytochrome P450 2E1 converts benzene to its metabolic form benzene oxide, which can further metabolize to various other intermediate like o-benzoquinone and p-benzoquinone, which are the major metabolite for benzene toxicity. Based on the exposed dose the benzene affects the bone marrow that cause anemia, leukopenia, and thrombocytopenia, if even more exposure continued for longer time it leads to aplasia and pancytopenia [15]. Due to this severe toxic effect of benzene, it is replaced with little safe xylene and toluene which has hematopoietic toxicity. The toluene is widely

used in paints, thinner, glue, cleansing agent and the widely abused as an inhalant [15].

### 6.3.1 Toluene toxicity

The aromatic hydrocarbons are highly used in organic synthesis, most commonly abused is benzene and toluene [25]. The toluene is a colorless liquid with a sweet and distinct smell. The toluene is largely found in gasoline, hair dye, nail polish, airplane glue, cleansing product, plastic cement, acrylic spray paint, and paint thinner etc. The primary target organ for acute and chronic toluene toxicity is CNS and to the pulmonary, peripheral nervous system, GI tract, CVS, hepatic, renal, hematological and dermal also. The long-term exposure shows a headache, nausea, drowsiness and a higher concentration cause cardiac arrhythmia [26-28]. The toluene is also responsible to cause an elevated anion gap metabolic toxicity [29]. The acute high amount of toluene exposure to rats decreases hippocampal neurogenesis [30].

### 6.3.2 Xylene toxicity

Xylene or dimethylbenzene is any one of the three isomers with central atom benzene containing two methyl groups. All isomers are colorless, flammable liquids having great value in research and chemical industry. The vapor of xylene is absorbed rapidly via lungs and slowly through the skin. Most of the xylene metabolized in the liver (95%) to Methyl Hippuric acid and around 80% of metabolites are excreted via urine. So, the remaining parts are the indicator for xylene presence in the body. The higher concentration of xylene exposure to the body has narcotic effects leading neuropsychological dysfunction with respiratory tract impairment. More delayed exposure cause anemia, leukopenia, and thrombocytopenia, cyanosis, dyspnea, chest pain.

### 6.3.3 Benzene toxicity

The use of benzene is very much limited nowadays, due to its severe toxicity. It can cause cancer [31,32]. Research shows that the MiR-133a is a potential biomarker for benzene toxicity via targeting Caspase-9 by inhibiting apoptosis which is induced by 1,4-Benzoquinone (benzene metabolite) [33]. In rat model benzene shows its potential toxicity in ovary [34]. Due to its severe toxicity many country throughout the world are making strict rules and regulation to control its use in a very safe manner [35].

## 6.4 Halogenated Hydrocarbons

Those containing at least one halogen atom like fluorine, chlorine, bromine, and iodine are referred to as a halogenated hydrocarbon. Some common halogenated hydrocarbon solvents are methyl chloride, chloroform, trichloroethylene, and tetrachloroethylene.

### 6.4.1 Chloroform toxicity

In 1847 chloroform was introduced as an anesthetic but due to its toxic effect no longer practiced as an anesthetic in human. Various options to chloroform are tried but due to some special character in organic synthesis it is still used in laboratory and chemical industry as solvents to put reaction, for extraction, purification etc.

The metabolic product of chloroform is toxic because it can bind to the macromolecules like protein and lipids of the endoplasmic reticulum. The primary affecting organ is liver and causing necrosis [15]. After liver, the kidney [36] is the second target of chloroform after oral or inhalation exposure causing tubular necrosis, swelling, increased weight of kidney in rats after oral administration. Other carcinogenicity and chronic toxicity are reported with inhalation of chloroform [37]. Depends on species, strain, and sex of the animals, metabolizing enzymes [38,39], chloroform shows kidney and liver tumor in a dose-dependent manner [15]. The metabolic product of chloroform to phosgene severely affect the kidney [36]. Chloroform toxicity in mice is being largely studied by many researchers [40]. Different pathway of chloroform metabolism has been studied [41], Fig. 3.

### 6.4.2 Methylene chloride toxicity

It is also known as dichloromethane (DCM), the widely used solvent in organic synthesis. It can dissolve a wide variety of chemical compounds. Its density is higher than water so during extraction processes in organic synthesis it makes convenient not to collect the water layer to a separate flask, just put more DCM then shake and collect again repeated the same process and finally trace aqueous undesired part. But it is more toxic than ethyl acetate and cause burning irritation on contact with skin because it can easily melt the latex gloves and enter inside but cannot evaporate easily due to covered with gloves so cause irritation for a long time. So, if

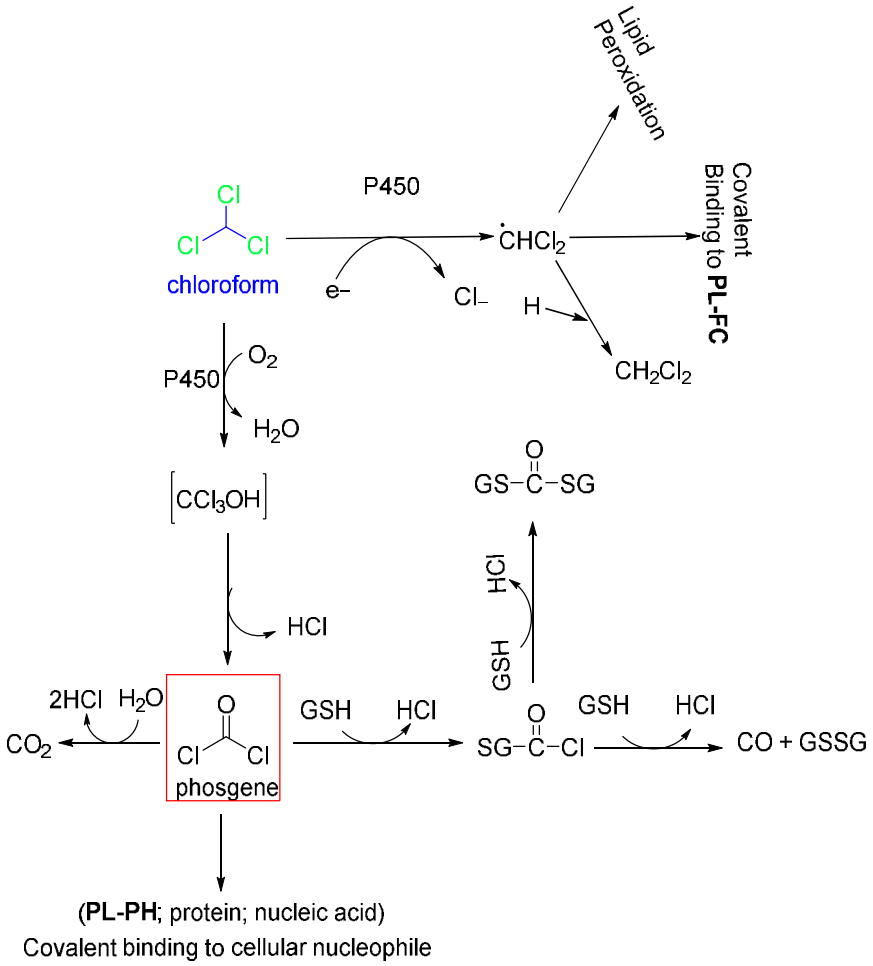


**Fig. 3. Two pathway of chloroform bio-activation [42]**

contact occurs with skin immediately remove the gloves and use a new one. In past, it was used in hairspray until 1989 and to remove caffeine from coffee. It is a potential human carcinogen which is the primary concern of it. The oral exposure to DCM can increase liver cancer [43-49].

## 6.5 Alcohols

Various kinds of alcohols are used in organic synthesis as a solvent, cleansing agents, and a reagent. Most common are methanol, ethanol, isopropanol, cyclohexanol, diethylene glycol etc. Usual pronounced term is 'toxic alcohol' which is a collective meaning representing methanol, ethylene glycol and isopropyl alcohol [50].

### 6.5.1 Methanol toxicity

Methanol can cause serious effects like acidosis and retinal damage. In liver methanol converted to formate in the presence of enzyme alcohol dehydrogenase, which is toxic [51]. Methanol can produce severe acidosis and retinal damage [52-56]. The intoxication by methanol can cause various effects like retinal edema, ocular lesions, loss of ganglion cells, demyelination of temporal retina, necrosis of cells with or without significant

hemorrhage [57]. Methanol can cause abnormal movement of the body usually due to drinking of homemade liquor contaminated with methanol [58]. In the case of methanol toxicity, the usual treatment is ethanol due to chemical competitiveness to the same receptor [51]. The metabolism of methanol is summarized in Fig. 4.

## 6.6 Ethers

The commonly used ether solvents are diethyl ether, tetrahydrofuran, 1,4-dioxan etc. The ether solvents are toxic, many experimental models showed the toxicity of ether to the HepG2 cells [59], toxicity to blood lymphocytes [60], testicular toxicity [61], carcinogenicity [62]. The tetrahydrofuran (THF) shows CNS toxicity with dizziness, headache, loss of sense of smell and fatigue etc. [63].

## 6.7 Miscellaneous Solvents

### 6.7.1 Acetonitrile toxicity

Acetonitrile is a common organic solvent used in organic synthesis and chemical industry. It is hazardous to health and even can cause death. Usually, the effect associated with it is from the inward breath of its vapors or contact of fluid to skin and eyes. Acetonitrile interferes with oxygen requirement for cell breath and leading to cytotoxic anoxia. The potential safety hazards with acetonitrile should be considered when using strong acid or strong base because acetonitrile can be hydrolyzed by it [64]. The concurrent exposure to acetonitrile and acetone increases the toxicity of acetonitrile. The metabolized form of acetonitrile is cyanide [65] which is severely toxic to animals and human [66]. The amount of formation of cyanide from acetonitrile is increased with co-administration to acetone [67]. The mechanism of acetonitrile toxicity revealed the detail pharmacokinetic distribution of acetonitrile to the different body parts, leading to a CNS major toxicity [68]. The acetonitrile toxicity in human is due to the *in vivo* formation of cyanide as a metabolite, the associated onset signs and symptoms depend on exposure route, amount, and duration of exposure. However, it is typically delayed from 2 to 13 h due to the slow conversion rate to cyanide. Various signs and symptoms are: a) respiratory: bronchial/chest tightness, respiratory insufficiency; b) Cardiovascular: bradycardia, tachycardia, hypotension, cardiac arrhythmia, cardiac arrest, and death; c) neurologic: headache, dizziness, confusion, agitation, seizures, weakness, and coma; d) gastro-intestinal: initially nausea and vomiting are common, leading to metabolic acidosis and lactic acidosis. The 1-2 g/kg of acetonitrile ingestion is lethal [69,70]. The proper understanding of acid-base chemistry with structural interactions could be helpful in finding the solvents interactions and generation of relative toxic products [71].

### 6.7.2 Dimethylformamide

In short it is written and spoken as DMF. It is a polar aprotic solvent with high boiling point. It is miscible with water and majority of the organic solvents. At an elevated temperature DMF hydrolyzed by strong acid and base. It is also used as a reagents in many cases, like a reagent in the Vilsmeier-Haack reaction where it first convert to chloroiminium ion known as Vilsmeier reagent that attacks arenes [72]. Many research has been carried out to reveal the toxicity of DMF, viz hepatotoxicity [73,74] and other many more [75-77].

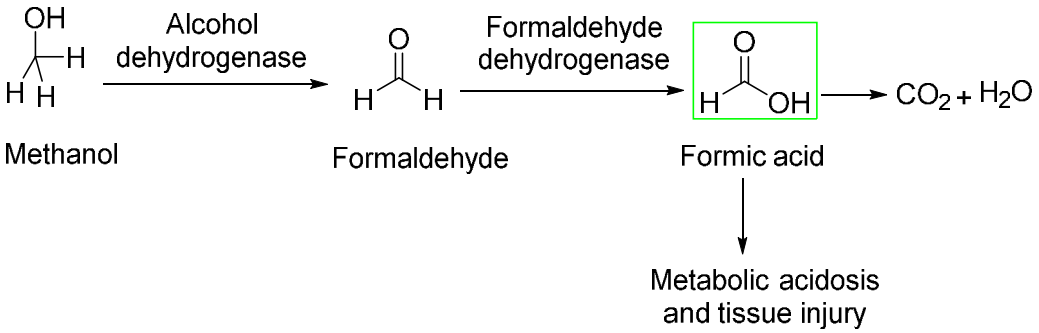


**Fig. 4. Metabolism of methanol leading to toxicity**

### 6.7.3 Acetone

Acetone is a simplest and smallest ketone, colorless, volatile and a flammable liquid, widely used in cleansing purposes in chemical industry, research institute and other generalized form. It is miscible with water that increases its use in cleansing purposes. It is largely produced for purpose of its use as solvent, cleansing agent, production of methyl methacrylate and bisphenol A [78]. Acetone is the least toxic industrial solvents [78], however the high concentration vapor exposure should be avoided, acetone can cause temporary narcosis and eye irritation. The repeated exposure to skin cause defatting and dermatitis. The common household use is in nail polish remover and as a paint thinner [78]. Although the acetone is nontoxic or least toxic in many experimental study but it potentiate the acetonitrile toxicity and trihalomethane toxicity [67,79].

### 6.7.4 Ethyl acetate

Ethyl acetate is a colorless liquid with sweet smell and used in nail polish remover, glues, decaffeinating, in cigarettes, paint (as an activator of hardener), perfume, and confections (as an artificial flavor) etc. In laboratory, the mixture of ethyl acetate with other solvents are commonly used for column chromatography and extraction. It is low toxic solvent with LD50 for rat is 5620 mg/kg [78]. The above threshold limit exposure cause irritation to nose, eyes and throat, weakness, drowsiness and even unconsciousness [80].

## 7. RESEARCH DISCUSSION ON SOLVENT TOXICITY STUDY AND SEARCH FOR SAFER OPTION

Although many research are needed to find out the micro and micro effect of each and every solvents to the human, animal, aquatic life and overall the environment where we live. Some of the potential hazards are already reported related to organic solvents which we discussed above also. Some latest key discovery related to solvents toxicity will be presented here. Much toxicity related to the n-hexane is reported. The reactive oxygen species (ROS) mediated toxicity of n-hexane to the Jurkat T-cell [81], toxicity to gonad of female mice [82], neurotoxicity in rat via modulating P450 enzyme [83], in adult female rat the gestational administration of n-hexane cause alteration in expression of gene that are mainly related to DNA methylation and ovarian hormone production [84], exposure of n-hexane to sub-TLV shows sensorimotor polyneuropathy [85] etc. The detail hydrocarbon toxicity are discussed by Tormoehlen et al. [86]. The various environmental effects of dioxin and its aryl hydrocarbon receptor biology is discussed by Mandal PK [87]. The aquatic life is also largely affected by petroleum products. The effect of petroleum hydrocarbon in Corals is elaborated by Turner et al. [88]. Hydrocarbon induced neuropathy in male rate presented by Alden CL [89]. As the benzene is severely toxic and discussed above also [90]. The toxicity of gamma benzene hexachloride discussed in detail by Solomon et al. [91]. The major effect of polycyclic aromatic and the halogenated hydrocarbon mediated by AHR (aryl hydrocarbon receptor), its toxicity and tumorigenesis are discussed by Marlowe et al. [92]. Heipieper *et al* explained the resistance developed by whole cells towards organic solvent toxicity [93]. The tolerance of bacteria towards organic solvents [94-99], and solvent toxicity to bacteria and other microorganism are also studied throughout the time [100-103]. The pharmacokinetic based study of organic solvents vapor for causing toxicity gives the idea about safe handling of solvents in fume hoods [104]. Much other literature discussed about the nature and the toxicity caused by the organic solvents [1,6,105-112]. So, the voice for better and safer option is growing and researchers, pharmaceutical industries and other concern bodies are working on it but still not enough. The concept of green solvents becomes popular now to overcome with the toxic effect of general organic solvents [12, 113-118]. Many organic synthesis are successfully done in water [119-122].

## 8. CONCLUSION

In research laboratory and chemical industry, organic solvents belong to the most important group of chemicals due to its huge amount of use annually [12]. Thus, the solvents revel a major part of human as well as environmental toxicants. In the research and chemical industry, the selection of solvents for reaction process as well as cleansing and other chemical processes and the waste solvent management all mostly depends on economic, logistic and safety considerations [123]. The environmental concerns are often of minor consideration for the decision makers also due to lack of easy availability of proper tools, which accumulates such happenings from large groups of chemicals industry, institute, researcher etc. which leads to

a big problem to the environment, human and all around us, leading to a chemical toxicity. In this review, we have presented a general overview of solvent's nature and their toxicity. The primary person who works with chemicals is the key person, so after studying these kinds of detail information we hope the researchers and all the concern bodies will make a proper solvent selection and practice accordingly to save their life as well as the environment where we live.

## CONSENT AND ETHICAL APPROVAL

It is not applicable.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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