# Tetrakis(hydroxymethyl)phosphonium Salts – Their Properties, Hazards and Toxicities

Dmitry V. Moiseev,*[a] Brian R. James[b]

[a] Akzo Nobel, EMEA, Balashikha, Moscow Region, Russia, 143900
[b] Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Z1
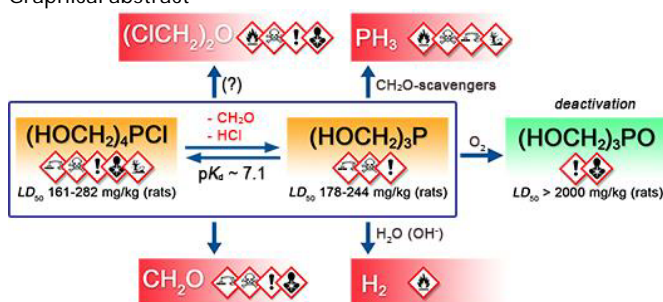
*Corresponding author.
E-mail: Dmitriy.Moiseev@akzonobel.com
ORCID: 0000-0003-0152-5880
Telephone: +7 (495) 795 01 60
Postal address: 143900 Russia, Moscow Region, Balashikha, Severnaya Promzona, Pokrovsky proezd, 9

Graphical abstract

Abstract:

Tetrakis(hydroxymethyl)phosphonium chloride (THPC) and sulfate (THPS) are of importance in the textile industry as flame retardants, in the oil industry as scale-removers, as biocides for water systems, in the leather industry as tanning agents, in nanochemistry as reductants and stabilizers of nanoparticles, and as oxygen-scavengers in medical uses. In the majority of cases, THPC and THPS themselves are not chemically active and solely play a role of reservoirs for the more reactive species tris(hydroxymethyl)phosphine (THP) and/or formaldehyde. The contents of THPC/THPS solutions greatly depend on pH, which is now recognized as a key factor, e.g., in metal hydrosol preparations, biocidal activity, and ecotoxicity. This review is intended to reveal and explain the complex behavior of THP and $(HOCH_2)_4P^+$ salts in aqueous solutions, conditions that might lead to potential hazardous compounds such as formaldehyde, hydrogen gas, phosphine $PH_3$, and bis(chloromethyl)ether. Literature data on their toxicities are reviewed.

Keywords: water-soluble phosphorus compounds; phosphine; formaldehyde; bis(chloromethyl)ether; oxidation; toxicity

Abbreviations
THP – tris(hydroxymethyl)phosphine
THP-h – monohemiacetal of tris(hydroxymethyl)phosphine
THPC – tetrakis(hydroxymethyl)phosphonium chloride
THPS – bis[tetrakis(hydroxymethyl)phosphonium] sulfate
THPO – tris(hydroxymethyl)phosphine oxide
'THPOH' – a 1:1 mixture of THP and formaldehyde
MHP – mono(hydroxymethyl)phosphine
BHP – bis(hydroxymethyl)phosphine
BHPO – bis(hydroxymethyl)phosphine oxide
BHMPA – bis(hydroxymethyl)phosphinic acid
HMPA – hydroxymethylphosphonic acid
BCME – bis(chloromethyl)ether

$LD_{50}$ – median lethal dose
$IC_{50}$ – the half maximal inhibitory concentration

Contents
1. Introduction
2. Properties of $(HOCH_2)_4P^+$ salts and THP
3. Probable hazards derived from $(HOCH_2)_4P^+$ salts and THP
4. Toxicity of THPC, THPS and THP
5. Conclusions
References

## 1. Introduction

2021 will be the 100-year anniversary of hydroxymethyl phosphonium salts. Reaction of $PH_3$ with formaldehyde ($CH_2O$) in the presence of HCl was first studied in 1921, and resulted in the isolation of a new compound, tetrakis(hydroxymethyl)phosphonium chloride, $(HOCH_2)_4PCl$ (THPC).[1] There are more than 2700 scientific papers, reports and patents, in which $(HOCH_2)_4P^+$ phosphonium salts, mostly the chloride (THPC) and sulfate (THPS), and/or the tertiary phosphine $(HOCH_2)_3P$ (THP) (Fig. 1) are the reported and discussed reactants or products. Interest in THP and $(HOCH_2)_4P^+$ salts began in the 50's from the need to impart fire retardance to cotton materials; untreated cotton can be ignited accidentally by matches, cigarette lighters, cigarettes, and gas burners leading to fire injuries and deaths.[2-6] In the 80's, THPS was reported to effectively control microorganisms in aqueous systems.[7-11] THPC and THPS are also of importance in the leather industry as tanning agents,[12-15] for the oil industry as scale-removals,[16-18] for the wool industry as effective reductants of the -S-S- bonds in keratin,[19-22] and for medical uses as oxygen-scavengers in the preparation of normoxic gels applied in polymer gel dosimetry.[23-27] THPC reduces $Au^{3+}$ to stable $Au^0$ nanoparticles.[28-30] The phosphine THP is an effective ligand in making water-soluble metal complexes[31-35] that can be used to remove metals from an organic phase after syntheses,[36-38] and is recognized as an effective crosslinking agent in biochemistry.[39-42] Our interest in THP and $(HOCH_2)_4P^+$ salts arose from an accidental finding that these water-soluble compounds were effective pulp-bleaching agents.[43-49] This discovery led us to interest in the fascinating and complex chemistry of these compounds compared to that of other water-soluble phosphines.[46,50-55]
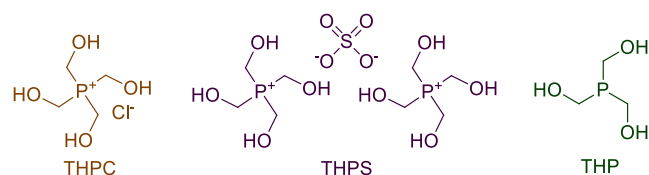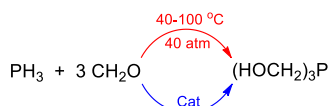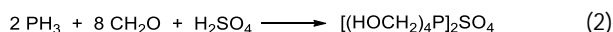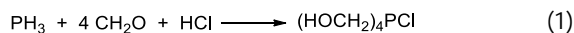


Figure 1. Chemical structures of tetrakis(hydroxymethyl)phosphonium salts and tris(hydroxymethyl)phosphine.

The highly water-soluble and air-stable THPC and THPS are among the most accessible organophosphorus compounds that are readily made in quantitative yield from PH₃ and CH₂O in the presence of the corresponding acid (Eqs. 1 and 2).[1,56-61] THP is a unique, small tertiary phosphine (regarded as relatively air-stable[34,62-64]), which can be obtained directly from PH₃ and CH₂O in high yields either under pressure[65-71] or in the presence of a metal catalyst[34,72-74] (Scheme 1). THP is the only water-soluble and relatively stable tris($\alpha$-hydroxyalkyl)phosphine. Synthesis of tris($\alpha$-hydroxyethyl)phosphine, $[CH_3CH(OH)]_3P$, was reported,[75,76] but in aqueous solutions it readily decomposes into a secondary phosphine and acetaldehyde.[77]

$$PH_3 + 4\ CH_2O + HCl \longrightarrow (HOCH_2)_4PCl \qquad (1)$$

$$2\ PH_3 + 8\ CH_2O + H_2SO_4 \longrightarrow [(HOCH_2)_4P]_2SO_4 \qquad (2)$$

$$PH_3 + 3\ CH_2O \xrightarrow[\text{Cat}]{\substack{\text{40-100 °C} \\ \text{40 atm}}} (HOCH_2)_3P$$

Scheme 1. Synthesis of THP from PH₃ and CH₂O; Cat = a metal salt or complex.

There are several reviews on THP and related chemistry, the most comprehensive and authoritative being published in 1982,[78-81] There are also smaller reviews that focus on different aspects of THP/(HOCH₂)₄P⁺ applications, for example, as a biocide,[11,82,83] an antioxidant,[27] and a flame retardant.[84-86] No other hydroxyalkyl phosphines or phosphonium salts have received so much attention, with interest in them growing exponentially since 1990. Inspired by the complex chemistry of THP and (HOCH₂)₄P⁺ salts, and the fast-growing interest in these species, we decided to assess the almost 100-year literature on THP and (HOCH₂)₄P⁺ salts and to write a review that summarizes and discusses the literature data on properties, hazards and toxicity of THPC, THPS, and THP in the light of their behavior in aqueous media.
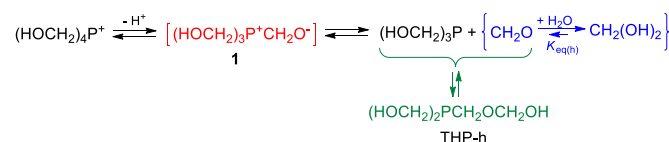
# 2. Properties of (HOCH₂)₄P⁺ salts and THP

## 2.1. Solid state properties

THPC is a hygroscopic, crystalline compound with reported melting points of 151 °C[57,58] or 153 °C,[87] and is highly water-soluble (8.7 g in 1 mL at 20 °C[4]). THPS is described as a semisolid oil;[88] however, needle crystals of THPS can be obtained by recrystallization from a 36% acetic acid.[89] During isolation, THP is often obtained in the form of an oily residue, which solidifies to form a wax-like substance[72] or colorless, hygroscopic needles;[65,90] melting points reported are 54–55 °C[90-92] and 58 °C.[34,72] THP is highly water-soluble; a 68% aqueous solution[93] and a 3 M stock solution of THP[94] are mentioned, but the exact solubility is not reported.

In solid state, THPC is stable to oxygen, while, in the literature, THP is regarded as relatively air-stable[34,62-64] compared to other small trialkylphosphines such as Me₃P and Et₃P, which are pyrophoric.[95] The IR spectrum of THP showed no noticeable increase in P=O absorption after 4 h of exposure to dry air in a desiccator or to humid air on the refractometer plates, but its refractive index dropped from 1.5564 to 1.5491 in 5 min, and to 1.5353 in 4 h.[96] Unlike other trialkylphosphines, THP is a weak base because of the electron-withdrawing effect of OH groups. Further, donor-acceptor interaction between a lone pair of the phosphorus atom of THP with protons of the CH₂OH groups, noted for other $\alpha$-hydroxyalkyl phosphines,[97] could obstruct interaction with oxygen.

## 2.2. Properties of aqueous solutions

Aqueous solutions of (HOCH₂)₄P⁺ salts are acidic: the pH of 80–85% commercial samples of THPC is < 2,[4,98-101] while the pH of 70–75% commercial samples of THPS is ~ 3–4.[7,102] Neutralization of THPC with NaOH produces an equivalent point reported at pH 8.3,[103] 8.5,[104] ~ 8.8,[96,105] or ~ 9.[106] Neutralization of THPS requires two moles of NaOH and provides the equivalence point at pH 8.9.[79,107] These equivalent points are associated with the deprotonation of (HOCH₂)₄P⁺ to the zwitterion (HOCH₂)₃P⁺CH₂O⁻ (1) (Scheme 2), and have been characterized with apparent pKₐ values of 4.41–5.07[96,108] or 5.5.[79,109,110] For THPS, a pKₐ value of 5.18 is reported.[111] Formation of 1 precedes the overall dissociation of (HOCH₂)₄P⁺ to THP and CH₂O (Scheme 2), with pK_d values of 7.06[79,96,108,110] and 7.13[112] obtained by titration with NaOH. ³¹P{¹H} NMR analysis of diluted, buffered THPC solutions gave pK_d values of 7.07 and 7.09,[50] where K_d for diluted aqueous solutions of THPC is represented by Equation 3. In aqueous solutions, CH₂O is mostly present as methanediol CH₂(OH)₂ with an equilibrium constant $K_{eq(h)}$ of ~2 × 10³.[113] CH₂O also reacts with THP to form the THP-hemiacetal (THP-h) (Scheme 2), but this reaction becomes apparent only in concentrated solutions (see below). Dissociation of the (HOCH₂)₄P⁺ cation is most likely independent of the acid counterion.[55]

$$(HOCH_2)_4P^+ \xrightleftharpoons{-H^+} [(HOCH_2)_3P^+CH_2O^-] \rightleftharpoons (HOCH_2)_3P + \left\{ CH_2O \xrightleftharpoons[K_{eq(h)}]{+H_2O} CH_2(OH)_2 \right\}$$
$$\downarrow\uparrow$$
$$(HOCH_2)_2PCH_2OCH_2OH$$
$$\text{THP-h}$$

Scheme 2. Dissociation of the (HOCH₂)₄P⁺ cation to THP.

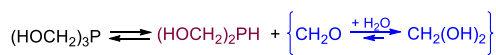$$K_d = \frac{[(HOCH_2)_3P][CH_2(OH)_2][H^+]}{[(HOCH_2)_4P^+]} \approx 8 \times 10^{-8}\ M^2 \qquad (3)$$

Analysis of the infrared spectra of 80% and 66.7% aq. THPC solutions revealed two distinct types of associated water molecules.[114] The 80% composition shows a strong IR band at 3197 cm⁻¹, with a weak shoulder at 3464 cm⁻¹, in a ~5:1 ratio, corresponding respectively to bound water, with a smaller amount of less tightly bound water – neither band are identical to that of "free" water. The 66.7% solution shows shifted bands at 3195 cm⁻¹ and 3412 cm⁻¹, in a ~1:1 ratio, implying that the water present in the solution is not "free", and is strongly hydrogen-bonded to the ions present (either the anion and/or the cation); the 80% solution of THPC was described as an ionic liquid.[114]

The variation of the (HOCH₂)₄P⁺/THP content of aqueous 0.001, 0.01, 0.1, and 1.0 M THPC solutions with pH, based on K_d = 8 × 10⁻⁸ M², is shown in Figure 2. The experimental data for diluted solutions are generally in agreement with the calculated ones: e.g., in a 5% gelatin solution (pH 4–5), 2–20 mM THPC is completely dissociated to THP and HCl, because the same concentration of THPC and HCl leads to the same pH change.[115] In a 0.0125 M solution of pure THPC, (HOCH₂)₄P⁺ is not observed at pH ≥ 6.5 in the ³¹P{¹H} spectrum, while at pH of 4.8, the ³¹P{¹H} resonances of THPC and THP are almost of equal intensity, i.e. (HOCH₂)₄P⁺/THP = 1.10, as predicted (Fig. 2).[50] THPC at millimolar concentrations is an effective oxygen-scavenger because THP, as an active species, is present even under acidic conditions, whereas concentrated THPC and THPS solutions are air-stable (see below). A commercial 80% THPC solution (~ 5.6 M) at pH 5 has only a trace amount of THP.[116] In a 40% THPC solution (~ 2.4 M) at pH 4.2, THPC and THP were found in 95.3 and 2.5%, respectively [59]. In the ³¹P spectrum of a mixture of (HOCH₂)₄P⁺ phosphate-acetate (1.84 M) and 25% excess of CH₂O in 1 M acetate buffer at pH 5.0, only the (HOCH₂)₄P⁺ cation is observed.[117] In agreement with the calculations (Fig. 2), in a 1 M THPC solution at pH 3.0, THP is not detected, while adjusting the pH to 6.0 with 6 M NaOH generates THP and its hemiacetals;[118] the

ratio between THPC and tertiary phosphines was not given, but the $^{31}P\{^{1}H\}$ spectrum indicates that the relative concentration of THPC in the mixture (40%) is below the calculated 75% (Fig. 2). Because of the parallel reaction between $CH_2O$ and THP that leads to THP-h (Scheme 2), Equation 3 is unlikely to work for concentrated THPC solutions. The content of commercial samples of THPC versus pH is studied in several reports but results are not clearly presented.[119,120] THPC and THPS at concentrations of 0.01–1 moles in 9 N $H_2SO_4$ can liberate THP, which can then reduce $NaClO_3$ to $ClO_2$.[121]

Acidity values reported for aqueous solutions of THP are somewhat variable: pH ~ 6.5[65,72,74] for crude THP, pH of 6.4[96] and 6.5[34] for 0.5 and 0.01 M THP, respectively, pH of ~5.5 for 0.008 M aq. THP,[50] and pH of 5.6–6.0 for a 1% solution of commercial THP.[122] Reported $pK_a$ values for THP are < 3,[96,108] and one of 5.5 with no experimental details.[123] Based on the acidity of tertiary phosphines in nitromethane, using the Taft substituent constants ($pK_a = 7.85 - 2.67\ \Sigma\sigma^*$),[124] a $pK_a$ of 3.40[96,125] for 2 (Scheme 4) was calculated using $\sigma^* = +0.555$ for the $CH_2OH$ group.[126] Reported $pK_a$ values for $CH_3P(CH_2OH)_2$ and $(CH_3)_2PCH_2OH$ in water-alcohol solutions are 7.18 and 7.95,[90] while $(CH_3)_3P$ in methanol-water has a $pK_a$ of 8.67.[127] Based on general linearity of the dependence of $pK_a$ values of phosphines $(CH_3)_nPR_{3-n}$ (n = 0–3; R = $CH_2CH_2CN$, Ph, H) on the Taft substituent constants (Fig. 3),[124,128] a $pK_a$ value for THP in water-alcohol solutions can be estimated as ~6.4. Of note, the $pK_a$ of tris(3-hydroxypropyl)phosphine, $(HOCH_2CH_2CH_2)_3P$, in water is ~7.2.[50,129]

In water, THP establishes an equilibrium with $CH_2O$ and the secondary phosphine $(HOCH_2)_2PH$ (BHP) (Scheme 3).[50] At pH 7–8, this equilibrium is on the side of THP, and no BHP resonance is detected by $^{31}P\{^{1}H\}$ NMR. Acids facilitate decomposition of THP because $CH_2O$ preferably reacts with this tertiary phosphine to form $(HOCH_2)_4P^+$, rather than reacts with the secondary phosphine, BHP (Scheme 4). There is no evidence for the existence of the tris(hydroxymethyl)phosphonium cation $(HOCH_2)_3PH^+$ (2) that possibly decomposes rapidly into $^+CH_2OH$ and BHP (Scheme 4). In 0.10 M HCl, THP disproportionates rapidly and completely to $(HOCH_2)_4P^+$ and BHP.[50] Similar to this, BHP disproportionates slowly to THP and the primary phosphine, $HOCH_2PH_2$ (MHP) (Eq. 4).[55] Extreme cases are reported, where THP in the presence of HCl disproportionates to THPC and $PH_3$; formation of the latter was confirmed by IR spectroscopy[103] and reaction with $AgNO_3$.[130] $CH_2O$-scavengers such as $NaHSO_3$, $Na_2S_2O_4$,[55] or $NH_3$[131,132] can cause deformylation of THP and generation of $PH_3$.

$$(HOCH_2)_3P \rightleftharpoons (HOCH_2)_2PH + \left\{ CH_2O \xrightarrow{+\ H_2O} CH_2(OH)_2 \right\}$$
BHP

Scheme 3. Dissociation of THP to BHP.

$$(HOCH_2)_3P \xrightarrow{+\ H^+} [(HOCH_2)_3P^+H] \rightleftharpoons (HOCH_2)_2PH + \left\{ {}^+CH_2OH \xrightarrow{+\ THP} (HOCH_2)_4P^+ \right\}$$
2

Scheme 4. Disproportionation of THP under acidic conditions.

$$2\ (HOCH_2)_2PH \rightleftharpoons (HOCH_2)_3P + HOCH_2PH_2 \qquad (4)$$
MHP
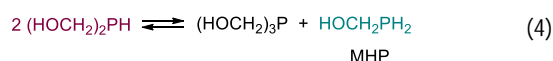
Under acidic conditions, $(HOCH_2)_4P^+$ salts are air-stable. Aqueous THPC and THPS solutions are stable over a 4 h reflux.[79,125,133] An 80% aq. THPC solution is reported to be stable at 100 °C over 24 h;[114] 75% THPC and 72% THPS are stable for 2 weeks at temperatures up to 60 °C.[99,111,134] The pH of THPC and THPS solutions affects their stability under ambient conditions, because with increasing pH, the amount of the reactive species THP increases: observed half-lives of THPS in sterile aqueous/buffered medium are: 131 days at pH 5, 72 days at pH 7, and 7 days at pH 9.[83,99,102] Neutralization of 35% aqueous THPS with NaOH accelerates gradually the rate of oxidation (Fig. 4),[107] whereas under an inert atmosphere, neutralized THPC solutions are stable for several months.[135] An aqueous solution with 3750 ppm THPS,

neutralized with $NaHCO_3$ up to pH 7.3, showed no changes after being stirred for 24 h in air.[136]
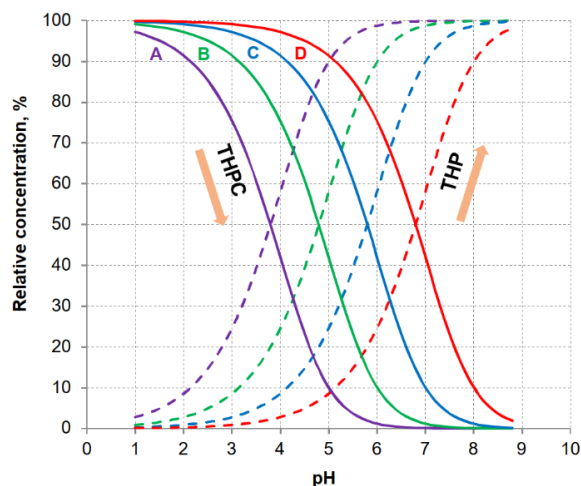


Figure 2. Calculated relative concentration of THPC and THP in aqueous solutions vs. pH, with initial THPC concentration: (A) 0.001 M, (B) 0.01 M, (C) 0.1 M, and (D) 1.0 M.
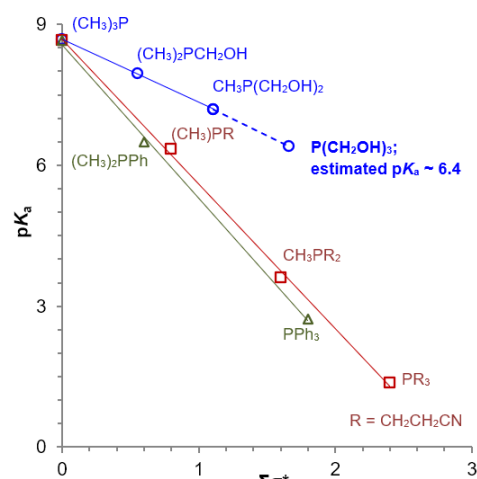


Figure 3. The dependence of $pK_a$ values of tertiary phosphines on the Taft substituent constants; estimation of a $pK_a$ value for THP in water-alcohol mixture.
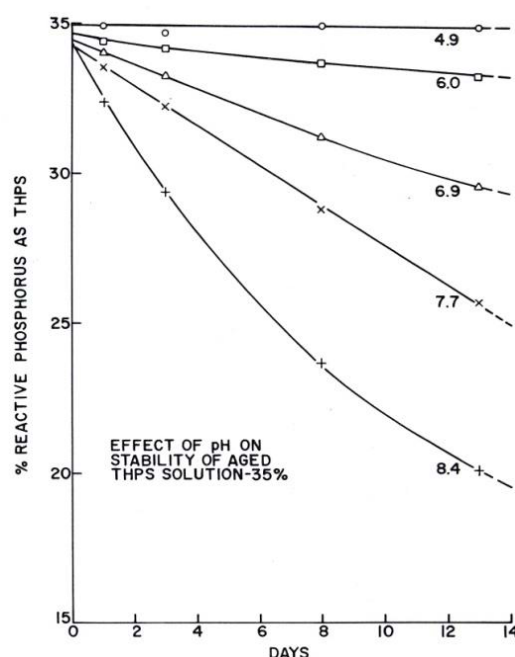


Figure 4. Effect of pH on stability of aged 35% THPS solution. Reproduced with permission from Ref. [107] via Copyright SAGE Publications Ltd.

In aqueous and alcoholic solutions, THP can be easily oxidized to THPO in air,[137-139] but in aqueous media, the conversion rate and oxidation mechanism depend greatly on pH. In buffered solutions at pH 7–8, $CH_2O$-free THP at millimolar concentrations is air-stable for a long period (Fig. 5); e.g., after one week at pH 7.5, 7% THPO is detected by NMR.[50] Under acidic conditions, THP is oxidized by atmospheric oxygen, while under basic conditions, anaerobic oxidation by water with an evolution of $H_2$ takes place (Scheme 5). Air-oxidation of THP solutions accelerates with increasing acidity of solutions, and is accompanied by disproportionation to $(HOCH_2)_4P^+$ and BHP (Scheme 4, Figs. 5 and 6), the latter being oxidized to $(HOCH_2)_2P(O)H$ [bis(hydroxymethyl)phosphine oxide, BHPO].[50] The air-stability of THP and 'THPOH' solutions clearly differs: acidifying the 'THPOH' solutions would lead exclusively to air-stable $(HOCH_2)_4P^+$, while at pH 6–8, the $CH_2O$ in 'THPOH' solutions would bind with THP to form THP-h (Scheme 2), which is a more basic phosphine than THP, and could react faster with $O_2$ and/or via a different mechanism than does THP. Use of $Na_2SO_3$ as a base, which reacts with $CH_2O$, improves air-stability;[140] e.g., a 32% THPC solution, neutralized with a mixture of $Na_2SO_3$ and $Na_2S_2O_5$ (10:1 w/w), was stable for several months.[141]
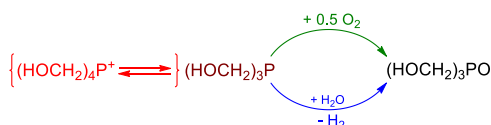


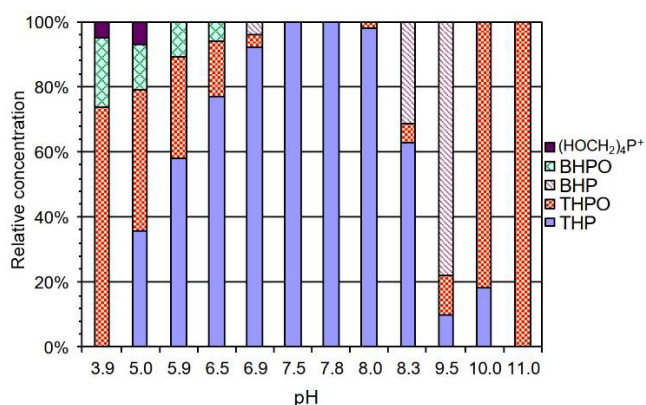Scheme 5. Aerobic and anaerobic oxidation of THP to THPO.



Figure 5. Phosphorus-containing components of buffered solutions of THP and their relative concentration vs. pH after 24 h at room temperature (r.t. ~ 20 °C) in air. Reproduced with permission from Ref. [50] via Copyright 2011 Elsevier B.V.
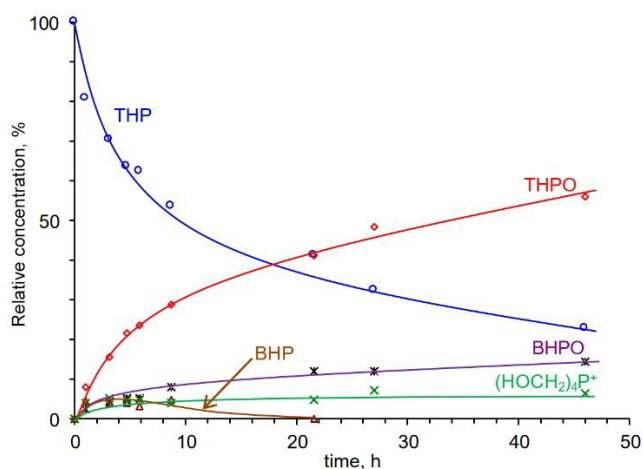


Figure 6. Relative concentration of P-containing compounds vs. time in a buffered solution of THP at pH 5.0. Reproduced with permission from Ref. [50] via Copyright 2011 Elsevier B.V.

## 3. Probable hazards derived from $(HOCH_2)_4P^+$ salts and THP

Use of THPC and THPS as fire-retardants for children's sleepwear initiated investigation of the hazard of these salts, because solutions such as sweat, urine, and saliva might extract some free THPC, and thus some children could be subjected to long-term, low-level exposure of this chloride.[98] Although THPC and THPS themselves could be dangerous to health and the environment, the contents of their solutions depend on pH. In the majority of cases, THPC and THPS are chemically inactive and solely play a role of reservoirs for the reactive species THP and/or $CH_2O$ that can be released into the media upon addition of a base. Thus, hazards of THPC and THPS can be attributed to their degradation products such as THP, $CH_2O$, HCl or $H_2SO_4$. Further, $CH_2O$ and HCl might form bis(chloromethyl)ether (BCME), a known carcinogen,[142-144] while THP under certain conditions can generate highly flammable $H_2$ or toxic $PH_3$ (Fig. 7). Aqueous solutions of $(HOCH_2)_4P^+$ salts are acidic, and thus handling them requires rubber gloves and goggles.[4]
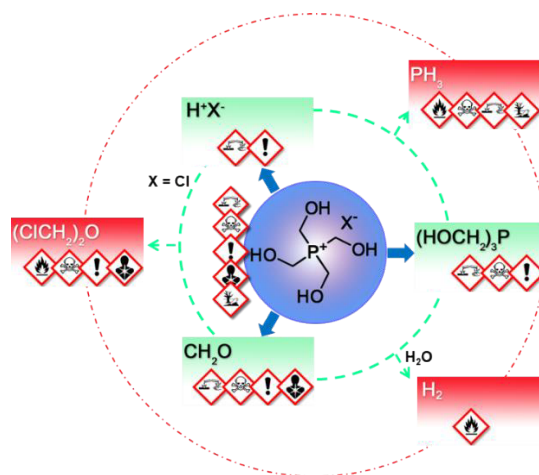


Figure 7. Potential hazards derived from $(HOCH_2)_4P^+$ salts, illustrated by GHS pictograms (https://pubchem.ncbi.nlm.nih.gov/).

Heating THP without a solvent may lead to an explosion that results from an exothermic oxidative isomerization reaction.[145,146] The nitrate $(HOCH_2)_4P(NO_3)$ can explode on drying at ~ 110 °C,[147] and tris(hydroxymethyl)phosphine oxide trinitrate, a product of reaction of THPC with fuming nitric acid, should be handled in an explosive's facility.[148,149]

### 3.1. Anaerobic oxidation of THP with evolution of $H_2$

Known since the discovery of THPC is that, in the presence of excess base at r.t. or with gentle heating, one mole of THPC evolves one mole of $H_2$, the reaction stopping with the formation of THPO.[1,109,150] An uncontrolled stoichiometry of the reaction between THPC or THPS with a base, such as NaOH, may lead to a rapid liberation of $H_2$. Fully neutralized $(HOCH_2)_4P^+$ solutions release some $H_2$ during preparation and storage, and this can be hazardous if the gas is not removed.[140] A storage container of unpurified 40–44% aq. THP with a pH of 6–7 is stated to have a slight swelling because of release of $H_2$, measurements ruling out $PH_3$.[151]

The pH threshold for visible $H_2$ evolution generally lies above 9.5 and depends on concentration, the base used, and the presence of $CH_2O$. For example, neutralization of a THPC solution with trialkylamines produces $H_2$ at pH 9.7–9.9, whereas with $Na_3PO_4$ or NaOH, pH values of 10 or 10.5, respectively, are needed.[106] During potentiometric titration of THPC with NaOH, $H_2$ formation has been observed at a pH just above 11;[109] however, formation of $H_2$ can also occur at pH < 9.5, particularly during preparation and storage of 'THPOH' solutions, and is evidenced by pressure increase in a container.[107,140,152] Evolution of $H_2$ is reported for mixtures of THP and $CH_2O$ at pH 8.5.[153,154] Heating aqueous THP in an autoclave

at 130–140 °C, in the presence of catalytic amounts of $CH_2O$, leads to pressure increase by generation of $H_2$ in ~ 90% yield.[155] Hydrogen is observed on boiling aqueous mixtures of THPC and $BaCO_3$,[58,87,150,156,157] and also in a reaction of THPC with excess of a strongly basic anion exchange resin.[103,104,158] Boil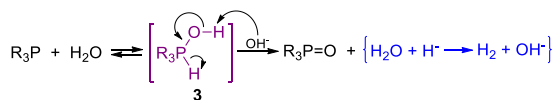ing an aqueous solution of the oxide THPO with NaOH or $Na_2CO_3$ leads to formation of bis(hydroxymethyl)phosphinic acid (BHMPA) and $H_2$ (Scheme 6),[1,58,150] whereas there is no reaction at r.t.[109]

$$(HOCH_2)_3PO + H_2O \xrightarrow[\text{reflux}]{OH^-} (HOCH_2)_2P\overset{O}{\underset{OH}{}} + CH_2O + H_2$$
BHMPA
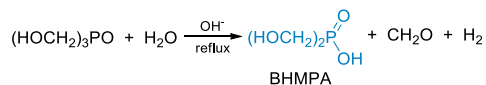
Scheme 6. Base-catalyzed oxidation of THPO to BHMPA by water.

Patents have reported that at pH > 10, THP and 'THPOH' are oxidized rapidly and completely to THPO;[159-162] pH > 12 is called critical for conversion of THPC into THPO.[163,164] In buffered THP solutions (8–9 mM), THPO is ~80% formed at pH 10.0 after 24 h; at pH 11.0, the oxidation is complete within 5 h, and in 0.1 M NaOH within 10 min (Fig. 5).[50] There are several potential applications of THP or $(HOCH_2)_4P^+$ salts requiring a pH of 9–10.[93,165-167] Surprisingly, in reactions of THPC or THP with sodium salts of amino acids performed at pH ~ 11–12, no $H_2$ evolution, or oxidation of the starting compounds, is mentioned.[163,164] Anaerobic oxidation of THP to THPO under alkaline conditions is important for formation of stable metal nanoparticles; unfortunately, pH numbers are often not mentioned, and $H_2$-generation is rarely reported.[168,169]

Base-catalyzed, anaerobic oxidation appears to be a feature of all water-soluble phosphines.[50,159,170-173] The proposed mechanism is similar to that proposed for cleavage of phosphonium hydroxides in the presence of NaOH, and includes formation of a pentacovalent phosphorus intermediate containing a P–H bond (3) (Scheme 7).[170]

$$R_3P + H_2O \rightleftharpoons \left[ R_3P\overset{O-H}{\underset{H}{}} \right] \xrightarrow{OH^-} R_3P=O + \{H_2O + H^- \longrightarrow H_2 + OH^-\}$$
3

Scheme 7. Base-catalyzed oxidation of water-soluble tertiary phosphines.

## 3.2. Phosphine-like odor issue in reactions of $(HOCH_2)_4P^+$ salts and THP

In some applications of THP, or $(HOCH_2)_4P^+$ salts, generation of a garlic-like odor associated with $PH_3$ has been reported.[55,103,130,174] A strong, phosphine-like smell has prevented application of a mixture of THPS and $Na_2S_2O_4$ for a pulp bleaching process.[175] Formation of $PH_3$ is confirmed (as an orange precipitate with $HgCl_2$) in reactions of THPS with ammonia,[131,132] and in reaction of THP with HCl.[103,130] An odor is also reported for aqueous solutions of THPS.[136] THP itself has an unpleasant smell,[34,64,176] and $PH_3$ is released during exothermic decomposition above 130 °C.[34,177] Heating other $\alpha$-hydroxyalkyl phosphines also generates $PH_3$[178] and, due to reversibility of THP formation, generation of $PH_3$ in the presence of $CH_2O$-scavengers is also possible.[55] A garlic-like odor of THP and $(HOCH_2)_4P^+$ salts has also been attributed to trace amounts of long chain phosphinates and phosphonates, such as compound 4 that is formed during the synthesis of $(HOCH_2)_4P^+$ salts in the presence of excess $CH_2O$.[59] Pyrovatex 3762, an oligomer of THPC formed by self-esterification, was withdrawn from the market because of an odor.[179] A related odor case is reported for a pad bath prepared from 75% THPS and urea at pH ~ 7.5.[180] The fresh pad smells strongly and, if the mix tank is not covered and the pad area is not well ventilated, odors will be prevalent; after 2–4 h aging, the pad odors disappear for ~ 2 days, after which they begin to reappear. The type of the odors was not specified, but the use of urea was thought to 'tie up' $CH_2O$ to produce an odorless pad bath. An unspecified, unpleasant odor is also reported for products of reaction between THPS and imidazolidine-2,4-dione derivatives.[181]


4
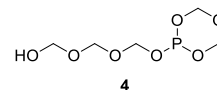
Phosphine, a precursor in the synthesis of THP and $(HOCH_2)_4P^+$ salts (Scheme 1, Eqs, 1 and 2), is a colorless, flammable, toxic gas. Pure $PH_3$ is odorless at concentrations up to 282 mg/m$^3$ (200 ppm),[182,183] but may contain $P_2H_4$ with the odor threshold in the range 0.14–7.0 mg/m$^3$.[182] Threshold for lethality by inhalation, tested on animals, occurs at ~ 7 mg/m$^3$,[184] and exposure to a concentration of 1000 ppm in air for 5 minutes can be fatal to humans.[185]

To reduce the odor, partial conversion of $PCH_2OH$ groups into the less hydrolysable $PCH_2N$ has been suggested,[174] and a significant reduction in solution odor was noted upon addition of activated carbon.[136] THPC-urea condensation products or THPC self-condensation products show an unpleasant odor that can be eliminated by an oxidative after-treatment of the condensation products, e.g., by passing air/$O_2$ into the reaction mixture, or by adding oxidants such as $H_2O_2$ or $K_2S_2O_8$.[186-188]

## 3.3. Formaldehyde release

$CH_2O$ is used in synthesis of THP and $(HOCH_2)_4P^+$ salts (Scheme 1, Eqs, 1 and 2). Commercial THPC and THPS solutions are typically marketed with < 1% of $CH_2O$ content;[99,111,189] but some reports state < 0.1%.[190] The high solids content of fire retardant compositions, based on THPC or THPS, causes some $CH_2O$ to be released during padding and drying;[140,191] such release is also observed in THPC- and THPS-based leather tanning processes.[120,192,193] In all cases, the amount released increases at higher pH (Scheme 2),[98,120,193] whereas heat and/or ammonia curing significantly reduce the amount. Reaction of THPC with $Na_2SO_3$ is a method of preparation for $CH_2O$-free THP (Eq. 5)[194] or 'THPOH' solutions with low $CH_2O$ release.[140] Several techniques are used to reduce the residual level of $CH_2O$ (< 50 ppm) in leather tanned with $(HOCH_2)_4P^+$ salts: precondensation with amino acids,[195] the use of Laponite nanoclay,[193] the essential oil of Origanum onites,[192] and glucose.[196] Also of interest, the release of $CH_2O$ during the application of THPS as a biocide is thought to be responsible for the reduction of $H_2S$ concentrations in oil-production systems.[197,198]

$$(HOCH_2)_4PCl + Na_2SO_3 \longrightarrow (HOCH_2)_3P + HOCH_2SO_3Na + NaCl \qquad (5)$$
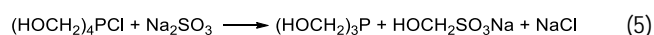
The toxicity of $CH_2O$ is acute: e.g., the oral $LD_{50}$ for rats and guinea pigs are 800 and 260 mg/kg, respectively;[199-201] two dermal $LD_{50}$ values for rabbits – 270 mg/kg[199] and > 2000 mg/kg[200] – are reported; inhalative $LC_{50}$ (exposure 4 h) for rats is 1070 mg/m$^3$.[200] Human exposure to $CH_2O$ occurs most commonly by dermal and respiratory routes, with > 90% of inhaled $CH_2O$ being absorbed in the upper respiratory tract.[202] The aldehyde, which can cause nasopharyngeal cancer in humans, is an irritant via all routes of exposure, effecting the eyes, nose, and throat in healthy humans at concentrations as low as 0.2 ppm, and there is limited epidemiological evidence that $CH_2O$ causes sinonasal cancer in humans. The level of $CH_2O$ in air within houses is typically 0.02–0.06 mg/m$^3$,[202] and there is significant evidence for a causal association between leukemia and occupational exposure to $CH_2O$; this aldehyde is also genotoxic, and causes mutation and chromosomal aberrations in a wide variety of bacteria, yeasts, fungi, and insects, as well as in some human cell systems with and without metabolic activation. Mutations or DNA damage caused by $CH_2O$ may be related to its ability to cause crosslinks in nucleic acids.[199,202]

## 3.4. Possible formation of bis(chloromethyl)ether during the synthesis of THPC

Bis(chloromethyl)ether (BCME), classified as a human carcinogen (Group 1),[142-144] could be formed during the manufacture of THPC from $CH_2O$ and HCl (Eq. 6) and could thus be a potential hazard in the synthesis, industrial use, and end-product use of THPC and THPC-treated fabrics.[98,99] This possibility of BCME formation was the reason for replacement of THPC by THPS as an industrial flame retardant.[6,203,204]

$$2\ CH_2O\ +\ 2\ HCl \longrightarrow ClCH_2OCH_2Cl\ +\ H_2O \qquad (6)$$
$$BCME$$
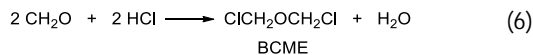
BCME undergoes rapid hydrolysis in aqueous media at ambient temperature to yield $CH_2O$ and HCl.[144,205] In humid air, the highest hydrolysis rate of BCME is $< 0.00047$ min$^{-1}$ (or $t_{1/2} > 25$ hours),[206] but data regarding BCME formation from low levels of formaldehyde and HCl are inconsistent.[207] BCME is formed at $< 0.5$ ppb from 20 ppm of both gaseous $CH_2O$ and HCl in moist air under a variety of conditions of humidity, temperature, and UV radiation.[208] At 100 ppm of each reactant, [BCME] ranges from $< 0.4$ to 8.3 ppb up to 24 h; with 300 ppm of each reactant, the data range from 5–59 ppb. However, another research group, using the 100 ppm levels, did not detect any BCME, although at high concentrations (500–3000 ppm), low ppm levels were recorded;[207,209] in contrast, another study at concentrations up to 2000 ppm resulted in no detectable BCME in either the aqueous phase, or the gas phase above the solution.[207,210] A more recent computational investigation of the thermodynamics and kinetics in a vapor-phase mixture of $CH_2O$, HCl, and $H_2O$ implies that formation of BCME is unlikely.[211]

The ether was not detected in concentrations $> 0.1$ ppm in commercial 80% THPC solutions at pH 0.4 containing 16.1% Cl.[98,99] Use of a gas chromatographic method for analysis of BCME in air, with detection limit of 0.5 ppb, reported that BCME was not detected in end fabrics treated with THPC, or in the processing of the fabrics.[203] BCME, however, was found in the reactors where THPC was produced, and in the aqueous effluent stream from the evaporators; occasionally BCME has been detected occasionally at very low levels in the head space in drums of product, but data from repeat samples were not reproducible.

## 4. Toxicity of THPC, THPS and THP

### 4.1. Oral toxicity and metabolism

Reports on acute oral toxicities of hydroxymethyl and other alkyl phosphorus compounds are listed in Table 1. The toxicities of THP, which is thought to be responsible for chemical and biochemical activity of the phosphonium salts, and of 'THPOH' (a mixture of THP and $CH_2O$), are identical to those of THPC; this might indicate that THP is responsible for toxicity of all the Table 1 hydroxymethyl compounds. All these are moderately hazardous (Class II according to WHO) or moderately toxic (Class 3 according to the Hodge and Sterner scale). Based on the $LD_{50}$ values for rats, THPC is seemingly more toxic than THPS. Of note is that the dose mixtures of THPC and THPS (mg/mL) used for the studies were prepared by dilution of weighed commercial aqueous THPC and THPS solutions;[134] 1 g of pure THPC contains ~7% more THP than 1 g of THPS and thus, since THP is an active ingredient, THPC should be the more toxic, as found. Further, the diluted solutions (stored up to 14 days) were considered as stable, on the basis that the starting concentrated solutions were stable. No pH data of the diluted solutions were presented; THPC solutions are generally more acidic than those of THPS, and are thus expected to be more air-stable (Section 2). The few reports on the toxicity of other phosphonium salts and tertiary phosphines show they are less toxic than THP and $(HOCH_2)_4P^+$ salts

(Table 1). According to their safety data sheets, the water-soluble tris(3-hydroxypropyl)phosphine and tris(2-carboxyethyl)phosphine, often used in biochemistry, are 14 times less toxic than THP, possibly because of the ability of THP to react with amino compounds.[212,213]

Table 1. Acute oral toxicity of hydroxymethyl and some alkyl phosphorus compounds.

| Compound | Acute oral $LD_{50}$, mg/kg | References |
|---|---|---|
| THPC | 161–282 (rats) | [99,134,214] |
|  | 280–600 (mice) | [99,134,215] |
| THPS | 248–622 (rats) | [99,111,134,215,216] |
|  | 200–493 (mice) | [134,217] |
| THP | 178–243.7 (rats) | [151,218,219] |
|  | 316.8 (mice) | [218,219] |
| 'THPOH' | 232 (rats) | [220] |
| THPO | > 2000 (rats) | [111] |
| [n-Bu$_4$P]Cl | 830–1002 (rats) | [221] |
| [n-Bu$_3$P(CH$_2$)$_{13}$CH$_3$]Cl | 611 (rats) | [222] |
| (HO$_2$CCH$_2$CH$_2$)$_3$P · HCl | 3500 | MSDS |
| (HOCH$_2$CH$_2$CH$_2$)$_3$P | 3500 (rats) | MSDS |
| n-Bu$_3$P | 750 (rats) | [223] |

In a 90-day oral study with Fischer rats, body weight decrements were observed at THPS doses as low as 5 mg/kg a day, whereas in chronic studies conducted with mice and the rats, no effects on body weight were seen at doses up to 10 mg/kg a day.[111] In similar 14-day studies, tremors and loss of hindlimb movement were noted at high doses ($\geq100$ mg/kg day).[111] With the oral treatment using THPS (50 mg/kg a day), 9 of 12 mice died after the fifth treatment.[224] Gavage of THP at 10% of $LD_{50}$ (~25 mg/kg) for 1.5 months caused no deaths in rats.[218,219]

The liver appears to be the critical/primary target organ in distribution of $(HOCH_2)_4P^+$ salts.[99,111,216] The absorption, metabolism and excretion of THPS was investigated in Sprague-Dawley rats using labeled $^{14}C$-THPS, administered by gavage at single doses of ~ 1 or 50 mg/kg.[99,111] Absorption was relatively rapid (0.5–2 h), while elimination from blood and plasma was much slower ($T_{1/2}$ = 126–195 h and 59–74 h, respectively). Some pharmacokinetic parameters were also affected by dose. Primary excretion routes over 24 h included urine (12–31%) and faeces (4–37%). Expiration in air reached 13% over 2 days, but was postulated to account for 30% when unaccounted mass balance was considered. No parent compound was detected in either urine or faeces, whereas 9 metabolites were detected in urine, 7 of which were also detected in faeces; the major metabolite was THPO in both urine and faeces (~ 10% and 14–24%, respectively, of the administered dose). Two other metabolites were postulated to be BHMPA and a formaldehyde adduct of THPO.[111]

The oxide THPO is of low toxicity via the oral route (Table 1). The reactivity of the $CH_2OH$ groups in THPO is reduced significantly compared to that in THP; THPO is less reactive than THP in Mannich-type condensation reactions with amines.[122,225-227] Chemically, tertiary phosphines $R_nP(CH_2OH)_{3-n}$ (n = 0, 1, 2) behave as $R_nPH_{3-n}$, while oxides or sulfides act as alcohols.[228-230] In vivo studies in normal CF1 mice have demonstrated that THPO is stable, and is excreted exclusively in urine without undergoing any metabolism;[231] the peak concentrations in the liver and kidneys were reached within 15 and 60 min, respectively, and THPO was completely cleared from the blood within 2 h. These results imply that BHMPA, if one of the 9 metabolites of THPS, is probably formed via oxidation of the secondary phosphine BHP (Scheme 8), a decomposition product of THP (Scheme 3). To the best of our knowledge, toxicities of BHMPA, BHP and BHPO have not been reported.

$$(HOCH_2)_2PH \xrightarrow{[O]} (HOCH_2)_2P\overset{O}{\underset{H}{P}} \xrightarrow{[O]} (HOCH_2)_2P\overset{O}{\underset{OH}{P}}$$
$$BHPO$$
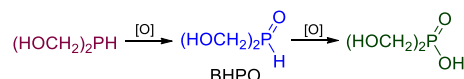
Scheme 8. Oxidation of BHP to BHMPA via BHPO.

## 4.2. Dermal and inhalation toxicities

Dermal toxicity of THPC and THPS is classed as low.[99,111] For example, the dermal $LD_{50}$ of THPC in albino rabbits after a 24 h exposure is > 4084 mg/kg, and there were no deaths of rats treated with THPS at 2000 mg/kg body weight.[99,214] THPS is relatively toxic when applied to the skin of Swiss ICR mice (male),[224] with a marked reduction in body weight and subsequent death of the animals treated at 700 and 1000 mg/kg doses. Daily dermal exposures to a 30% THPC solution were fatal to rats 9 days after the first dose.[232,233] THP is readily absorbed through skin causing death in mice and rats after one week (dosage was not reported).[218]

Studies with Sprague-Dawley rats revealed that THPS (75%) was of slight toxicity via the inhalation route with $LC_{50}$ values of 0.628 and 0.551 mg/L for male and female rats, respectively.[111] An $LC_{50}$, 4 h dose of 5.5 mg/L reported for THPS in rats,[99] was considered unacceptable because of problems with achieved particle size.[111] Intoxication and death in rats or mice by inhalation of THP were not observed because effective concentrations in vapor were not reached.[218]

## 4.3. Skin and eye irritation

Administered as a single dose (0.5 mL of 75% aq. solution), THPS caused no skin irritation with New Zealand white rabbits over a 4 h period[99], whereas in a 28-day dermal study with THPS on Sprague-Dawley rats, slight to severe irritation was observed at all doses; similar irritation data were seen using guinea pigs.[99,111,234] Related, THPC (15–30% aq. solution) caused intensive skin reactions in male, white rats,[233] but was not a sensitizer for albino guinea pigs, tested using the Buehler method with patches containing 0.5 mL of a 1% v/v dilution of the commercial THPC.[216] THP is also a skin irritant that can cause sensitization and burns.[151,218,219,235] In a 28-day dermal study with THPO, signs of irritation, increasing in incidence and/or severity with increasing dose, were noted at the lowest dose (300 mg/kg a day).[111]

THPS is a severe eye irritant in New Zealand rabbits.[99,111] When 0.1 mL of 75% THPS was introduced to an eye, opacity was observed 24 h after application, and lasted at least for another 24 h; a red coloration of the conjunctiva, accompanied by considerable swelling, was also observed.[99] Similar symptoms in rabbits were reported for THP.[218,219]

## 4.4. Carcinogenicity and other toxicities

The carcinogenicity of $(HOCH_2)_4P^+$ salts to humans (Group 3) is not classified,[232,236] and no evidence for carcinogenicity was found in female ICR/Ha Swiss mice, treated topically with 2 mg THPC dissolved in 0.2 mL acetone/water 3 times/week for 496 d,[216,237] but the same system did have moderate tumor-promoting activity in a mouse skin carcinoma assay.[98,214] After 2-year gavage studies on experimental animals, no evidence of carcinogenicity of THPS (5 or 10 mg/kg) or THPC (3.75–30 mg/kg) in either sex of rats or mice was found.[134,238]

One case of squamous cell carcinoma of the palm is reported in an elderly man who had chronic dermal exposure to THPC-containing flame retardants; over a 2-year period, the man, had regularly used bare hands to wring out fabrics soaked in THPC.[239]

THPS is a potential endocrine disruptor.[240] Both THPC and THPS have mutagenic potential in vitro, but the latter is not mutagenic in vivo.[99,111] Both salts were not active in a Salmonella typhimurim reverse mutation test, with and without S9 liver homogenate activation.[111,134,180,214,216,241-243] No evidence of mutagenic potential of THPS was seen in an unscheduled DNA synthesis assay with rat hepatocytes[111] and, in a chromosomal analysis test, there were no statistically significant increases in the frequency of structural aberrations.[99,214,243] THPC and THPS both show genotoxic activity in mammalian cells, and both induce forward mutations in mouse lymphoma L5178Y cells without metabolic activation.[111,134,243-245]

Both salts increased the frequency of sister-chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells in the presence and absence of exogenous metabolic activation; THPC induced the aberrations only at toxic concentrations, while the lowest effective doses of THPS in the exchanges and aberrations are lower than those of THPC.[134,246,247] In an in vivo study, THPS did not induce micronuclei in a mouse micronucleus assay,[111,224] and mutations were not induced in silkworms treated with THPC.[216]

The mutagenicity of THP, the primary metabolite and active ingredient of $(HOCH_2)_4P^+$ salts, and of the $CH_2O$-containing 'THPOH', have been poorly investigated. Stated is that THP is not mutagenic in Salmonella typhimurium strains TA100, TA98, TA1535, and TA1537.[99,248] Of note, Mannich-type condensation of THP with amino compounds, which are parts of DNA, is mediated by $CH_2O$.[117,249-251] THPO was not mutagenic in the same strains, the Escherichia coli strain WP2 uvrA, or in the mouse lymphoma assay.[99,111,248] However, the bacterial gene mutation test was not considered acceptable for any of the strains, because of the absence of inadequate, positive controls,[111] and no strains were used to detect cross-linking mutations. The non-genotoxic THPO did not produce chromosomal aberrations in Chinese hamster ovary cells cultured in either the presence or absence of metabolic activation.[99,111]

A dominant lethal assay of THPS using ICR mice at the highest dose (1000 mg/kg) revealed a substantial decrease in the number of pregnant females and an increase in the number of deaths per pregnancy; no differences in the average number of implants per pregnancy in the treatment and control groups were seen.[214,243] THPC was found positive for genotoxicity in the Bacillus subtilis rec-assay, with or without metabolic activation.[216]

An in vitro cytotoxicity assessment of a hydraulic fracturing fluid containing 0.08 mM THPS, using a human gastrointestinal cell line, revealed that the fluid is cytotoxic, with half $IC_{50}$ values ranging from 25 to 51 mM.[252] Among chemicals added to the fluid, THPS was the most toxic ($IC_{50}$ < 0.1 mM). Cytotoxic activity of THP toward the human tumor cell lines HL60, A549, MCF-7, A375, and LoVo ($IC_{50}$ of 58–89 μM) is lower than that of its Cu(I) complexes.[253] The $IC_{50}$ values for the A549 cell line, after 4 and 24 h treatment with (hydroxymethyl)diphenylphosphine $Ph_2PCH_2OH$ and $Ph_2P(O)CH_2OH$ are ~ 74 μM.[254]

In a general toxicity test, aqueous solutions of THPC and THPS at a concentration of 32 μg/mL and adjusted with NaOH to pH 7, showed complete cytolysis of HeLa cells after 3 days, but no cellular damage was observed using 3.2 μg/mL.[215] At pH 7, THPC at 32 μg/mL also causes complete cytolysis of skin fibroblasts from humans, and FM3A and L cells from mice. DL1 and DL1 clones 20 cells derived from a rat normal liver are more sensitive to THPC than the cells mentioned above: complete cytolysis is observed at concentrations of 1.0 and 0.32 μg/mL, respectively. Tests on primary cultured cells from the liver, kidney, brain, and muscle of new-born rats revealed that THPC at pH 7 is cytotoxic above 10 μg/mL to all these cell lines, and 32 μg/mL generally causes complete cytolysis or degeneration. THPC, at 0.285 mM in a phosphate-buffered saline at pH ~ 7.4, exhibited an extremely low cytotoxicity level in red retention of canine epithelial cells.[255] Worth noting, and not mentioned in these studies, is that at pH 7–8 both THPC and THPS are converted to THP (Section 2).

## 5. Conclusions

Quaternary $(HOCH_2)_4P^+$ phosphonium salts and the tertiary phosphine $(HOCH_2)_3P$ are unique water-soluble compounds with interesting, but complicated chemistry. Their extensive use in synthetic chemistry, and proven applications, reveal that these compounds are likely excellent choices for studies in environment-friendly processes. It is bewildering how the salts can be air-stable and used as effective oxygen-scavengers at the same time! The composition and properties of aqueous solutions of the $(HOCH_2)_4P^+$ salts greatly depend on pH and the initial concentration, and these

parameters should be carefully evaluated prior to any application of the salts. Under alkaline conditions, the $(HOCH_2)_4P^+$ cation dissociates to THP and $CH_2O$ and, if the pH of a neutralized solution is not controlled, THP is oxidized by water with liberation of flammable $H_2$ and a pressure increase in a closed container.

The $(HOCH_2)_4P^+$ salts and THP, prepared form $PH_3$ and $CH_2O$, are kinetically unstable in aqueous media, being in rapid equilibria with $CH_2O$, secondary and primary phosphines. In the presence of compounds that react rapidly with formaldehyde "$CH_2O$-scavengers", THP may decompose to $PH_3$, a highly toxic gas that is poorly soluble in water. There are applications of hydroxymethyl phosphorus compounds, in combination with salts of sulfur oxoacids such as $Na_2S_2O_4$, $NaHSO_3$ or $Na_2S_2O_5$, that are able to deformylate $(HOCH_2)_4P^+$ salts and THP and, thus, to cause generation of $PH_3$. The secondary and primary hydroxymethyl phosphines are assumed also to be toxic, and great care should be made when working with these materials.

Both $(HOCH_2)_4P^+$ salts and THP are moderately toxic to rats and mice. The close $LD_{50}$ values for THP and THPC/THPS perhaps indicate that the toxicity of the salts is caused by THP, the primary metabolite of the chloride and sulfate. The oxide THPO, the major final metabolite, is of low acute toxicity. The overall toxicity of $(HOCH_2)_4P^+$ salts and THP may consist of toxicities of other possible degradation products of THP such as BHP and BHPO. The $(HOCH_2)_4P^+$ salts are not carcinogenic to humans.

## References

[1] Hoffman, A. The Action of Hydrogen Phosphide on Formaldehyde. J. Am. Chem. Soc. 1921, 43, 1684-1688.

[2] Reeves, W. A.; Guthrie, J. D. Flameproofing of Cotton with THPC-Resins. US Bur. Agr. and Ind. Chem. Bull., 1953, AIC-364, 1-11.

[3] Reeves, W. A.; Guthrie, J. D. Flameproof Fibrous Aminoethylated Cellulose Derivatives. U.S. Patent 2,668,096, Feb. 2, 1954.

[4] Tattersall, F. Organic Phosphorus Compounds for Textiles. Rubber Plastics Age 1956, 37, 98-103.

[5] Perfect, J. R. W. Flame-Resistant Finishing of Cellulosic Fabrics with Phosphorus-Containing Resins. J. Soc. Dyers Colour. 1958, 74, 829-834.

[6] Sanders, H. J. Government Regulations and Public Emphasis on Safety Provide the Impetus for an Expanding Industry. Chem. Eng. News 1978, 56, 22-36.

[7] Davis, K. P.; Talbot, R. E. Biocidal Water Treatment. Br. Patent 2,145,708, Apr. 3, 1985.

[8] Talbot, R. E.; Cooper, K. G. Biocidal Hydroxyalkyl Phosphines. Br. Patent 2,182,563, May 20, 1987.

[9] Page, S.; Gaylarde, C. Biocide Activity Against Legionella and Pseudomonas. Int. Biodeterior. 1990, 26, 139-148.

[10] Downward, B. L.; Talbot, R. E.; Haack, T. K. Tetrakishydroxymethylphosphonium Sulfate (THPS) - A New Industrial Biocide with Low Environmental Toxicity. Presented at CORROSION 97, New Orleans, LA, March 9-14, 1997; Paper No. 401.

[11] Jones, C.; Downward, B.; Edmunds, S.; Curtis, T.; Smith, F. THPS: A Review of the First 25 Years, Lessons Learned, Value Created and Visions for the Future. Presented at CORROSION 2012, Salt Lake City, UT, March 11-15, 2012; Paper No. C2012-0001505.

[12] Filachione, E. M. Tanning with Tetrakis-(hydroxymethyl)phosphonium Chloride. U.S. Patent 2,732,278, Jan. 24, 1956.

[13] Windus, W.; Happich, W. F. A New Tannage – Tetrakis(hydroxymethyl)phosphonium Chloride-Resorcinol. J. Am. Leather Chem. Assoc. 1963, 58, 638-645.

[14] Jiang, L.; Wu, H.; Shi, K.; Li, Y.; Shao, S. Application of THP Salt in Tanning Process. Zhongguo Pige 2007, 36, 54-57.

[15] Aravindhan, R.; Madhan, B.; Rao, J. R. Studies on Tara-Phosphonium Combination Tannage: Approach towards a Metal Free Eco-benign Tanning System. J. Am. Leather Chem. Assoc. 2015, 110, 80-87.

[16] Jeffery, J. C.; Odell, B.; Stevens, N.; Talbot, R. E. Self Assembly of a Novel Water Soluble Iron(II) Macrocyclic Phosphine Complex from Tetrakis(hydroxymethyl)phosphonium Sulfate and Iron(II) Ammonium Sulfate: Single Crystal X-ray Structure of the Complex $[Fe(H_2O)_2\{RP(CH_2N(CH_2PR_2)CH_2)_2PR\}]SO_4 \cdot 4H_2O$ (R = $CH_2OH$). Chem. Commun. 2000, 101-102.

[17] Gilbert, P. D.; Grech, J. M.; Talbot, R. E.; Veale, M. A.; Hernandez, K. TetrakisHydroxymethylPhosphonium Sulfate (THPS) for Dissolving Iron Sulfides Downhole and Topsides - A Study of the Chemistry Influencing Dissolution. Presented at CORROSION 2002, Denver, CO, April 7-11, 2002; Paper No. 02030.

[18] Wang, Q.; Shen, S.; Badairy, H.; Shafai, T.; Jeshi, Y.; Chen, T.; Chang, F. F. Laboratory Assessment of Tetrakis(hydroxymethyl)phosphonium Sulfate as Dissolver for Scales Formed in Sour Gas Wells. Int. J. Corros. Scale Inhib. 2015, 4, 235-254.

[19] Bajpai, L. S.; Whewell, C. S.; Woodhouse, J. M. Action of Tetrakis(hydroxymethyl)phosphonium Chloride on Wool. Nature 1960, 187, 602-603.

[20] Bajpai, L. S.; Whewell, C. S.; Woodhouse, J. M. The Action of Tetrakis(hydroxymethyl)phosphonium Chloride on Wool and Hair. J. Soc. Dyers Colour. 1961, 77, 193-197.

[21] Sweetman, B. J. The Specificity of Certain Phosphine Derivatives as Reducing Agents for the Disulfide Bond in Wool Keratin. Text. Res. J. 1966, 36, 1096-1101.

[22] Needles, H. L.; Alger, K. W.; Tai, A. The Effect of Tetrakis(hydroxymethyl)phosphonium Chloride (THPC) on Photo-Induced Vapor-Phase Grafting of Monomers on Wool and on the Subsequent Properties of the Grafted Wool. Text. Res. J. 1978, 48, 123-126.

[23] Baldock, C.; De Deene, Y.; Doran, S.; Ibbott, G.; Jirasek, A.; Lepage, M.; McAuley, K. B.; Oldham, M.; Schreiner, L. J. Polymer Gel Dosimetry. Phys. Med. Biol. 2010, 55, R1-R63.

[24] De Deene, Y.; Hurley, C.; Venning, A.; Vergote, K.; Mather, M.; Healy, B. J.; Baldock, C. A Basic Study of Some Normoxic Polymer Gel Dosimeters. Phys. Med. Biol. 2002, 47, 3441-3463.

[25] Venning, A. J.; Brindha, S.; Hill, B.; Baldock, C. Preliminary Study of a Normoxic PAG Gel Dosimeter with Tetrakis(hydroxymethyl)phosphonium Chloride as an Antioxidant. J. Phys. Conf. Ser. 2004, 3, 155-158.

[26] Venning, A. J.; Nitschke, K. N.; Keall, P. J.; Baldock, C. Radiological Properties of Normoxic Polymer Gel Dosimeters. Med. Phys. 2005, 32, 1047-1053.

[27] McAuley, K. B. Fundamentals of Polymer Gel Dosimeters. J. Phys. Conf. Ser. 2006, 56, 35-44.

[28] Duff, D. G.; Baiker, A.; Edwards, P. P. A New Hydrosol of Gold Clusters. J. Chem. Soc., Chem. Commun. 1993, 96-98.

[29] Duff, D. G.; Baiker, A.; Edwards, P. P. A New Hydrosol of Gold Clusters. 1. Formation and Particle Size Variation. Langmuir 1993, 9, 2301-2309.

[30] Duff, D. G.; Baiker, A.; Gameson, I.; Edwards, P. P. A New Hydrosol of Gold Clusters. 2. A Comparison of Some Different Measurement Techniques. Langmuir 1993, 9, 2310-2317.

[31] Chatt, J.; Leigh, G. J.; Slade, R. M. Rhodium(I), Rhodium(III), Palladium(II), and Platinum(II) Complexes Containing Ligands of the Type $PRnQ_{3-n}$ (n = 0, 1, or 2; R = Me, Et, But, or Ph; Q = $CH_2OCOMe$ or $CH_2OH$). J. Chem. Soc., Dalton Trans. 1973, 2021-2028.

[32] DuBois, D. L.; Miedaner, A. Mediated Electrochemical Reduction of $CO_2$. Preparation and Comparison of an Isoelectronic Series of Complexes. J. Am. Chem. Soc. 1987, 109, 113-117.

[33] Harrison, K. N.; Hoye, P. A. T.; Orpen, A. G.; Pringle, P. G.; Smith, M. B. Water Soluble, Zero-Valent, Platinum-, Palladium-, and Nickel-$P(CH_2OH)_3$ Complexes: Catalysts for the Addition of $PH_3$ to $CH_2O$. J. Chem. Soc., Chem. Commun. 1989, 1096-1097.

[34] Ellis, J. W.; Harrison, K. N.; Hoye, P. A. T.; Orpen, A. G.; Pringle, P. G.; Smith, M. B. Water-Soluble Tris(hydroxymethyl)phosphine Complexes with Nickel, Palladium, and Platinum. Crystal Structure of $[Pd\{P(CH_2OH)_3\}_4] \cdot CH_3OH$. Inorg. Chem. 1992, 31, 3026-3033.

[35] Lorenzini, F.; Patrick, B. O.; James, B. R. Serendipitous Syntheses of $Rh(H)_2Cl(PRPh_2)_3$ Complexes, and their Crystal Structures, where R = Me, Cy (cyclohexyl). Inorg. Chim. Acta 2008, 361, 2123-2130.

[36] Jackson, E. The Solvent Extraction Behavior of Platinum(II) with P-50 Oxime in Aqueous Chloride Solutions. Miner. Eng. 1998, 11, 651-656.

[37] Maynard, H. D.; Grubbs, R. H. Purification Technique for the Removal of Ruthenium from Olefin Metathesis Reaction Products. Tetrahedron Lett. 1999, 40, 4137-4140.

[38] Pederson, R. L.; Fellows, I. M.; Ung, T. A.; Ishihara, H.; Hajela, S. P. Applications of Olefin Cross Metathesis to Commercial Products. Adv. Synth. Catal. 2002, 344, 728-735.

[39] Henderson, W.; Petach, H. H.; Sarfo, K. A Novel Polymeric Phosphine Oxide-Derived Support for Enzyme Immobilization. J. Chem. Soc., Chem. Commun. 1994, 245-246.

[40] Cheng, T.-C.; Duan, K.-J.; Sheu, D.-C. Application of Tris(hydroxymethyl)phosphine as a Coupling Agent for β-Galactosidase Immobilized on Chitosan to Produce Galactooligosaccharides. J. Chem. Technol. Biotechnol. 2006, 81, 233-236.

[41] Lim, D. W.; Nettles, D. L.; Setton, L. A.; Chilkoti, A. Rapid Cross-Linking of Elastin-like Polypeptides with (Hydroxymethyl)phosphines in Aqueous Solution. Biomacromolecules 2007, 8, 1463-1470.

[42] Lampe, K. J.; Antaris, A. L.; Heilshorn, S. C. Design of Three-Dimensional Engineered Protein Hydrogels for Tailored Control of Neurite Growth. Acta Biomaterialia 2013, 9, 5590-5599.

[43] Hu, T. Q.; James, B. R.; Yawalata, D.; Ezhova, M. B. New Class of Bleaching and Brightness Stabilizing Agents. Part I: Bleaching of Mechanical Pulps. J. Pulp Pap. Sci. 2004, 30, 233-240.

[44] Hu, T. Q.; James, B. R.; Yawalata, D.; Ezhova, M. B.; Chandra, R. P. A New Class of Bleaching and Brightness Stabilizing Agents. Part II: Bleaching Power of a Bisphosphine. J. Pulp Pap. Sci. 2005, 31, 69-75.

[45] Hu, T. Q.; James, B. R.; Yawalata, D.; Ezhova, M. B. A New Class of Bleaching and Brightness Stabilizing Agents. Part III: Brightness Stabilization of Mechanical Pulps. J. Pulp Pap. Sci. 2006, 32, 131-136.

[46] Chandra, R.; Hu, T. Q.; James, B. R.; Ezhova, M. B.; Moiseev, D. V. A New Class of Bleaching and Brightness Stabilizing Agents. Part IV: Probing the Bleaching Chemistry of THP and BBHPE. J. Pulp Pap. Sci. 2007, 33, 15-22.

[47] Hu, T. Q.; Williams, T.; Schmidt, J. A.; James, B. R.; Cavasin, R.; Lewing, D. Mill Trial of The New Bleaching Agent – THPS. Pulp Paper Can. 2009, 110, 37-42.

[48] Hu, T. Q.; Yu, E.; James, B. R.; Marcazzan, P. The Fate of Phosphorus in the Bleaching of Spruce TMP with the New Bleaching Agent – THPS. Holzforschung 2008, 62, 389-396.

[49] Yuan, Z.; Hu, T. Q.; Schmidt, J. A. Enhanced Brightness and Brightness Stability of Lignocellulosic Materials. World Patent 2007/009221, Jan. 25, 2007.

[50] Moiseev, D. V.; James, B. R. Air-Stability of Aqueous Solutions of (HOCH₂)₃P and (HOCH₂CH₂CH₂)₃P. Inorg. Chim. Acta 2011, 379, 23-27.

[51] Moiseev, D. V.; James, B. R. Conformational Analysis of the 1,3-Oxaphosphorinanes Formed from α,β-Unsaturated Aldehydes and the (Hydroxymethyl)phosphines RP(CH₂OH)₂ (R = Ph or CH₂OH). J. Heterocyclic Chem. 2015, 52, 1518-1530.

[52] Moiseev, D. V.; James, B. R.; Gushchin, A. V. NMR Spectroscopic Studies on the 1:1 Interaction of Tris(hydroxymethyl)phosphine with Cinnamic Acids. Eur. J. Inorg. Chem. 2014, 6275-6280.

[53] Moiseev, D. V.; James, B. R.; Gushchin, A. V.; Malysheva, Y. B. Intermediates and Products in the Reaction of Cinnamaldehyde with (HOCH₂)₃P in Methanol. Phosphorus Sulfur Silicon Relat. Elem. 2016, 191, 1664-1665.

[54] Moiseev, D. V.; James, B. R.; Hu, T. Q. α-Monodeuterated Benzyl Alcohols and Phosphobetaines from Reactions of Aromatic Aldehydes with a Water/D₂O-Soluble Phosphine. Inorg. Chem. 2006, 45, 10338-10346.

[55] Moiseev, D. V.; James, B. R.; Hu, T. Q. Characterization of Secondary and Primary (Hydroxymethyl)Phosphines and Their Oxidation Products: Synergism in Pulp-Bleaching. Phosphorus Sulfur Silicon Relat. Elem. 2012, 187, 433-447.

[56] Flynn, F. F.; Reeves, W. A.; Guthrie, J. D. Production of Tetrakis(hydroxymethyl)phosphonium Chloride. U.S. Patent 2,743,299, Apr. 24, 1956.

[57] Reeves, W. A.; Flynn, F. F.; Guthrie, J. D. Laboratory Preparation of Tetrakis(hydroxymethyl)phosphonium Chloride. J. Am. Chem. Soc. 1955, 77, 3923-3924.

[58] Roitburd, T. Y.; Valetdinov, R. K. Synthesis of Tetrakis(hydroxymethyl)phosphonium Chloride and its Reactions. In Materialy 1-oi Konf. Molodykh Nauchn. Rabotn. Kazani, Sektsiya Khim., Proceedings of the Kazanskaya Gorodskay Konf. Molodykh Nauchn. Rabotn. Kazan, U.S.S.R., May 11-13, 1959; Miropol'skii, L. M., Ed. Akad. Nauk SSSR: Kazan, U.S.S.R., 1960; p 91-97.

[59] Vallat, O.; Balduchelli, Y. Method for Preparing THPX. World Patent 2011/076798, Jun. 30, 2011.

[60] Kumari, K. A Process for the Preparation of Tetra(hydroxymethyl)phosphonium Sulfate. In. Patent 158,897, Feb. 14, 1987.

[61] Feng, Z.; Zhu, K. Preparation of Tetrahydroxymethyl Phosphonium Sulfate by Hydrogen Phosphide from Preparation Process of Sodium Hypophosphite. Chin. Patent 101143877, Mar. 19, 2008.

[62] Katti, K. V.; Singh, P. R.; Reddy, V. S.; Volkert, W. A.; Ketring, A. R. Hydroxyalkyl phosphine compounds for use as diagnostic and therapeutic pharmaceuticals, and method of making them. World Patent 96/30056, Oct. 3, 1996.

[63] Reeves, W. A.; Daigle, D. J.; Donaldson, D. J.; Drake, G. L. Methylol Phosphorus Polymers Used for Flame Retardants. Text. Chem. Color. 1970, 2, 283-285.

[64] Pringle, P. G.; Smith, M. B. Tris(hydroxymethyl)phosphine Platinum Metal Complexes: Catalysts for Water-Based Reactions. Platin. Met. Rev. 1990, 34, 74-76.

[65] Grinshtein, E. I.; Bruker, A. B.; Soborovskii, L. Z. Hydroxymethylation of Phosphine and its Derivatives. Dokl. Akad. Nauk SSSR 1961, 139, 1359-1362.

[66] Bruker, A. B.; Baranaev, M. K.; Grinshtein, E. I.; Novoselova, R. I.; Prokhorova, V. V.; Soborovskii, L. Z. Mechanism and Kinetics of Phosphine Hydroxymethylation. Zh. Obshch. Khim. 1963, 33, 1919-1923.

[67] Grinshtein, E. I.; Bruker, A. B.; Soborovskii, L. Z. Preparation of Tris(hydroxymethyl)phosphine. U.S.S.R. Patent 138,617, 1961.

[68] Raver, K. R.; Bruker, A. B.; Soborovskii, L. Z. Reaction of Aqueous Formaldehyde with Phosphine and 1,1,2,2-Tetrafluoroethylphosphine. Zh. Obshch. Khim. 1962, 32, 588-590.

[69] Soborovskii, L. Z.; Bruker, A. B.; Raver, K. R. Tetrakis(hydroxymethyl)phosphonium Hydroxyde. U.S.S.R. Patent 143,395, 1961.

[70] Stockel, R. F.; O'Brien, S. J.; Weyker, R. G. Feuerhemmende Ausrüstung für Cellulose-Textilien. Ger. Patent 2,151,269, Apr. 19, 1973.

[71] Lin, K. C. Process for Preparing Hydroxymethylated Phosphines. U.S. Patent 3,660,495, May 2, 1972.

[72] Reuter, M.; Orthner, L. Verfahren zur Herstellung von Trioxymethylphosphin. Ger. Patent 1,035,135, Jul. 31, 1958.

[73] Dorfman, Y. A.; Levina, L. V.; Grekov, L. I. α-Hydroxyalkylation, β-Cyanoethylation and β-Alkoxycarbonylethylation of PH₃ in the Presence of Transition Metal Phosphine Complexes. Zh. Obshch. Khim. 1995, 65, 1459-1466.

[74] Hoye, P. A. T.; Pringle, P. G.; Smith, M. B.; Worboys, K. Hydrophosphination of Formaldehyde Catalysed by Tris(hydroxymethyl)phosphine Complexes of Platinum, Palladium or Nickel. J. Chem. Soc., Dalton Trans. 1993, 269-274.

[75] Valetdinov, R. K.; Zuikova, A. N.; Zyablikova, T. A.; Il'yasov, A. V. Reaction of Hydroxymethylphosphines with Aliphatic Aldehydes and Thermal Rearrangement of α-Hydroxyalkylphosphines. Zh. Obshch. Khim. 1979, 49, 1503-1508.

[76] Valetdinov, R. K.; Zuikova, A. N. Tris(α-hydroxyalkyl)phosphines. U.S.S.R. Patent 662,555, May 15, 1979.

[77] Moiseev, D. V.; James, B. R.; Gushchin, A. V. Interaction of PH₃ with Acetaldehyde in Aqueous Media and Chemistry of [HO(Me)CH]₄PCl. Russ. J. Gen. Chem. (Engl. Transl.) 2013, 83, 252-259.

[78] Vail, S. L.; Daigle, D. J.; Frank, A. W. Chemistry of Hydroxymethyl Phosphorus Compounds: Part I. Introduction. Text. Res. J. 1982, 52, 671-677.

[79] Frank, A. W.; Daigle, D. J.; Vail, S. L. Chemistry of Hydroxymethyl Phosphorus Compounds: Part II. Phosphonium Salts. Text. Res. J. 1982, 52, 678-693.

[80] Frank, A. W.; Daigle, D. J.; Vail, S. L. Chemistry of Hydroxymethyl Phosphorus Compounds: Part III. Phosphines, Phosphine Oxides, and Phosphonium Hydroxides. Text. Res. J. 1982, 52, 738-750.

[81] Daigle, D. J.; Frank, A. W. Chemistry of Hydroxymethyl Phosphorus Compounds: Part IV. Ammonia, Amines, and THPOH: A Chemical Approach to Flame Retardancy. Text. Res. J. 1982, 52, 751-755.

[82] Talbot, R. E.; Jones, C. R.; Downward, B. L.; Fidoe, S. D.; Diaz, R.; Hernandez, K. Keeping Pace with the Need for Advanced, High Performance Biocide Formulations of Oil Production Applications. Presented at CORROSION 2006, San Diego, CA, March 12-16, 2006; Paper No. 06663.

[83] Kahrilas, G. A.; Blotevogel, J.; Stewart, P. S.; Borch, T. Biocides in Hydraulic Fracturing Fluids: A Critical Review of Their Usage, Mobility, Degradation, and Toxicity. Environ. Sci. Technol. 2015, 49, 16-32.

[84] Boyer, N. E.; Vajda, A. E. Fireproofing of Polymers with Derivatives of Phosphines and with Halogen-Phosphorus Compounds. Polym. Eng. Sci. 1964, 4, 45-55.

[85] Drake, G. L. Flammability: Yesterday, Today, Tomorrow. Text. Chem. Color. 1976, 8, 184/117-190/123.

[86] Weil, E. D.; Levchik, S. V. Flame Retardants in Commercial Use or Development for Textiles. J. Fire Sci. 2008, 26, 243-281.

[87] Anteunis, M.; Verzele, M.; Dacremont, G. Triesters of Tris-(hydroxymethyl)phosphine oxide. Bull. Soc. Chim. Belges 1965, 74, 622-628.

[88] Ellzey, S. E. Preparation of Pure THP Sulfate. Text. Chem. Color. 1978, 10, 12-12.

[89] Feng, J.; Dong, W.; Yang, X. Preparation and Determination of Tetrakis(hydroxymethyl)phosphonium Sulfate. Yingyong Huagong 2006, 36, 410-413.

[90] Grinshtein, I. E.; Bruker, A. B.; Soborovskii, L. Z. Synthesis of Organophosphorus Compounds from Phosphorus Hydrides. III. Reactions of Ethyl-, Diethyl-, and Methylethylphosphines with Paraformaldehyde. Zh. Obshch. Khim. 1966, 36, 302-306.

[91] Valetdinov, R. K.; Zaripov, S. I.; Khasanov, M. K. Reaction of Alkylbis(hydroxymethyl)phosphines and their Oxides with Isocyanates. Zh. Obshch. Khim. 1973, 43, 1029-1034.

[92] Valetdinov, R. K.; Khasanov, M. K.; Sharifullin, A. S. Synthesis and Properties of Phosphorus-Containing Urethane Elastomers. In Uretanovye Elastomery; Apukhtina, N. P., Mozzhukhina, L. V., Eds. Khimiya: Leningrad, U.S.S.R., 1971, pp 85-88.

[93] Stockel, R. F.; O'Brien, S. J.; Weyker, R. G. Flame-Retardant Finish for Cellulosic Textile Materials. U.S. Patent 3,619,113, Sep. 9, 1971.

[94] Renner, J. N.; Cherry, K. M.; Su, R. S.-C.; Liu, J. C. Characterization of Resilin-Based Materials for Tissue Engineering Applications. Biomacromolecules 2012, 13, 3678-3685.

[95] Markham, R. T.; Dietz, E. A.; Martin, D. R. Trimethylphosphine. In Inorganic Syntheses; Basolo, F., Ed. McGraw-Hill: New York, 1976; Vol. 16, pp 153-155.

[96] Frank, A. W.; Drake, G. L. Use of Aldehydes other than Formaldehyde in THPOH/Ammonia Flame-Retardant Finishes for Cotton. J. Appl. Polym. Sci. 1977, 21, 3087-3097.

[97] Moiseev, D. V.; Patrick, B. O.; James, B. R. New Tertiary Phosphines from Cinnamaldehydes and Diphenylphosphine. Inorg. Chem. 2007, 46, 11467-11474.

[98] Loewengart, G.; Van Duuren, B. L. Evaluation of Chemical Flame Retardants for Carcinogenic Potential. J. Toxicol. Environ. Health 1977, 2, 539-546.

[99] van Esch, G. J. Flame Retardants: Tris(2-butoxyethyl)phosphate, Tris(2-ethylhexyl)phosphate and Tetrakis(hydroxymethyl)phosphonium Salts; Environmental Health Criteria 218; World Health Organization: Geneva, 2000.

[100] Warburton, C. E. Creaseproofing Cotton by in Situ Polymerization of N-Methylolacrylamide (NMA), Acrylamide (AM), and Tetrakis(hydroxymethyl)phosphonium Chloride (THPC). Text. Res. J. 1970, 40, 68-74.

[101] Donaldson, D. J.; Normand, F. L.; Drake, G. L. Effect of pH on THPC-Cyanamide Flame Retardant. Am. Dyest. Rep. 1972, 61, 48, 50-51.

[102] Shamim, A. N. Product Chemistry/Environmental Fate/Ecotoxicity of: Tetrakis (Hydroxymethyl) Phosphonium Sulfate; Document ID: EPA-HQ-OPP-2011-0067-0003; United States Environmental Protection Agency: Washington, DC, 2011.

[103] Ellzey, S. E.; Connick, W. J.; Boudreaux, G. J.; Klapper, H. Nuclear Magnetic Resonance Study of the Formaldehyde-Induced Exchange of Methylol Groups in Tetrakis(hydroxymethyl)phosphonium Chloride and Tris(hydroxymethyl)phosphine. J. Org. Chem. 1972, 37, 3453-3457.

[104] Ellzey, S. E.; Connick, W. J. Novel Process for the Preparation of Tris(hydroxymethyl)phosphine and Tris(hydroxymethyl)phosphine Oxide. U.S. Patent 3,833,661, Sep. 3, 1974.

[105] Reeves, W. A.; Drake, G. L.; Beninate, J. V. Durable and Semidurable Flame Retardants Based on Methylol Phosphorus Compounds. Textilveredlung 1970, 5, 498-505.

[106] Frank, A. W.; Drake, G. L. The Effect of pH on Flame-Retardant Finishes for Cotton Prepared from THPC and Various Bases. Text. Res. J. 1974, 44, 292-298.

[107] Moreau, J. P.; Seal, J. F.; Beninate, J. V. THPS-NH₃ Flame Retardant Finish for Cotton. J. Fire Retard. Chem. 1978, 5, 73-82.

[108] Fodour, L. M. A Study of Some Oxidation Reactions of the Tetrakishydroxymethyl Phosphonium Cation. Ph.D. Dissertation, Cornell University, Ithaca, NY, 1963.

[109] Grayson, M. Phosphonium Compounds. III. Mechanism of Hydroxide Cleavage of Tetrakis(hydroxymethyl)phosphonium Chloride. J. Am. Chem. Soc. 1963, 85, 79-83.

[110] Vullo, W. J. Studies Concerning the Neutralization of Tetrakis(hydroxymethyl)phosphonium Chloride and the Reaction of Tris(hydroxymethyl)phosphine with Formaldehyde. J. Org. Chem. 1968, 33, 3665-3667.

[111] Health Canada Pest Management Regulatory Agency. Tetrakis (Hydroxymethyl) Phosphonium Sulfate; Evaluation Report ERC2010-02; the Health Canada Pest Management Regulatory Agency: Ottawa, Canada, 2010.

[112] Jenkins, A. D.; Wolfram, L. J. The Chemistry of the Reaction between Tetrakis(hydroxymethyl)phosphonium Chloride and Keratin. J. Soc. Dyers Colour. 1963, 79, 55-60.

[113] Rivlin, M.; Eliav, U.; Navon, G. NMR Studies of the Equilibria and Reaction Rates in Aqueous Solutions of Formaldehyde. J. Phys. Chem. B 2015, 119, 4479-4487.

[114] Olkiewicz, M.; Caporgno, M. P.; Font, J.; Legrand, J.; Lepine, O.; Plechkova, N. V.; Pruvost, J.; Seddon, K. R.; Bengoa, C. A Novel Recovery Process for Lipids from Microalgae for Biodiesel Production Using a Hydrated Phosphonium Ionic Liquid. Green Chem. 2015, 17, 2813-2824.

[115] Sedaghat, M.; Bujold, R.; Lepage, M. Severe Dose Inaccuracies Caused by an Oxygen-Antioxidant Imbalance in Normoxic Polymer Gel Dosimeters. Phys. Med. Biol. 2011, 56, 601-625.

[116] Luo, K.; Schroeder, S. L. M.; Dryfe, R. A. W. Formation of Gold Nanocrystalline Films at the Liquid/Liquid Interface: Comparison of Direct Interfacial Reaction and Interfacial Assembly. Chem. Mater. 2009, 21, 4172-4183.

[117] Granzow, A. Kinetic Study of the Reaction of Tetrakis(hydroxymethyl)phosphonium Cation with Urea. J. Am. Chem. Soc. 1977, 99, 2648-2652.

[118] Jayawardhana, D. A.; Sengupta, M. K.; Krishantha, D. M. M.; Gupta, J.; Armstrong, D. W.; Guan, X. Chemical-Induced pH-Mediated Molecular Switch. Anal. Chem. 2011, 83, 7692-7697.

[119] Shao, S.; Jiang, L.; Li, Y.; Shi, K. Effect of pH on the Phosphorous Components in Tetra-Hydroxymethyl Phosphonium Chloride Solution. Adv. Mat. Res. 2012, 560-561, 237-241.

[120] Shao, S.; Shi, K.; Li, Y.; Jiang, L.; Ma, C. Mechanism of Chrome-Free Tanning with Tetra-Hydroxymethyl Phosphonium Chloride. Chin. J. Chem. Eng. 2008, 16, 446-450.

[121] McIlwaine, D.; Richardson, J. Novel Reducing Agents for Producing Chlorine Dioxide. U.S. Patent 2015/0225235, Aug. 13, 2015.

[122] Pepperman, A. B.; Daigle, D. J.; Vail, S. L. Reaction of Tris(hydroxymethyl)phosphine with Substituted Ureas. J. Org. Chem. 1976, 41, 675-678.

[123] Lucken, E. A. C. The Electron Spin Resonance Spectra of Species Resulting from the Action of Hydroxyl Radicals on Trishydroxymethylphosphine and Related Compounds. J. Chem. Soc. A 1966, 1357-1360.

[124] Henderson, W. A.; Streuli, C. A. The Basicity of Phosphines. J. Am. Chem. Soc. 1960, 82, 5791-5794.

[125] Frank, A. W.; Drake, G. L. Displacement of Tertiary Phosphines from Methylolphosphonium Salts by Tributylphosphine. J. Org. Chem. 1971, 36, 549-552.

[126] Taft, R. W. Separation of Polar, Steric, and Resonance Effects in Reactivity. In Steric Effects in Organic Chemistry; Newman, M. S., Ed. John Wiley & Son: New York, 1956, pp 556-675.

[127] Streuli, C. A. Determination of Basicity of Substituted Phosphines by Nonaqueous Titrimetry. Anal. Chem. 1960, 32, 985-987.

[128] Streitwieser, A.; McKeown, A. E.; Hasanayn, F.; Davis, N. R. Basicity of Some Phosphines in THF. Org. Lett. 2005, 7, 1259-1262.

[129] Cline, D. J.; Redding, S. E.; Brohawn, S. G.; Psathas, J. N.; Schneider, J. P.; Thorpe, C. New Water-Soluble Phosphines as Reductants of Peptide and Protein Disulfide Bonds: Reactivity and Membrane Permeability. Biochemistry 2004, 43, 15195-15203.

[130] Frank, A. W.; Drake, G. L. Iodometric Determination of Phosphorus(III) in Flame Retardants for Cotton. I. Development of the Method. Text. Res. J. 1973, 43, 633-638.

[131] Daigle, D. J.; Frank, A. W.; Kullman, R. M. H. Finishing with Ureidophosphorus: a Compound, not a Condensate. J. Fire Retard. Chem. 1979, 6, 276-284.

[132] Frank, A. W. Quaternary Ureidomethyl Phosphonium Salts. U.S. Patent 4,228,100, Oct. 14, 1980.

[133] Frank, A. W. Condensation of Tetrakis(hydroxymethyl)phosphonium Sulfates and Sulfonates with 1,3-Dimethylurea. Phosphorus Sulfur Relat. Elem. 1981, 10, 207-212.

[134] U.S. Department of Health and Human Services. Toxicology and Carcinogenesis of Tetrakis(hydroxymethyl) Phosphonium Sulfate (THPS) (CAS No. 5566-30-8) and Tetrakis(hydroxymethyl) Phosphonium Chloride (THPC) (CAS No. 124-64-1) in F344/N Rats and B6C3F₁ Mice (Gavage Studies); NTP Technical Report No. 296; National Institutes of Health: 1987; pp 290.

[135] Cochrane, F. C.; Petach, H. H.; Henderson, W. Application of Tris(hydroxymethyl)phosphine as a Coupling Agent for Alcohol

Dehydrogenase Immobilization. Enzyme Microb. Technol. 1996, 18, 373-378.

[136] Cooper, K. G.; Talbot, R. E.; Davis, K. P.; Saunders, M. A. Deactivation of Organophosphorus Biocides. Br. Patent 2,231,866, Nov. 28, 1990.

[137] Li, Y.; Wang, M.; Song, H.; Ma, H.; Tian, L. Catalytic Oxidation Synthesis Process and Equipment of Tris(hydroxymethyl)phosphine Oxide Using Phosphine Gas as Raw Material. Chin. Patent 104230989, Dec. 24, 2014.

[138] Filipescu, N.; Kindley, L. M.; Podall, H. E.; Serafin, F. A. Hydroxymethyl Phosphorus Derivatives from Tetrakis(hydroxymethyl)phosphonium Chloride. Reaction with Lead Carbonate and Oxide. Can. J. Chem. 1963, 41, 821-825.

[139] Reuter, M.; Jakob, F. Verfahren zur Herstellung von Trioxymethylphosphinoxyd. Ger. Patent 1,040,549, Oct. 9, 1958.

[140] Calamari, T. A.; Schreiber, S. P.; Reeves, W. A. A Stabilized THPOH Solution with Low Formaldehyde Release. Text. Chem. Color. 1975, 7, 65/27-67/29.

[141] Wagner, G. M.; Hoch, P. E.; Gordon, I. Polymerization Inhibitors for Hydroxy Phosphonium Halides Containing Nitrogen Compound Accelerator. U.S. Patent 3,146,212, Aug. 25, 1964.

[142] IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents; IARC Monographs 4; International Agency for Research on Cancer: Lyon, France, 1974; pp 231-238.

[143] Van Duuren, B. L. Comparison of Potency of Human Carcinogens: Vinyl Chloride, Chloromethylmethyl Ether and Bis(chloromethyl)ether. Environ. Res. 1989, 49, 143-151.

[144] Rao, C. V. Chloromethyl Ether, Bis-. In Encyclopedia of Toxicology; 3 ed.; Wexler, P., Ed. Academic Press, 2014; Vol. 1, pp 894-895.

[145] Lin, K. C. Process for Producing Methyl Phosphine Oxide. U.S. Patent 3,732,316, May 8, 1973.

[146] Bright, J. H. Verfahren zur Herstellung von Bis(hydroxymethyl)methylphosphinoxid. Ger. Patent 2,616,279, Oct. 28, 1976.

[147] Calamari, T. A.; Trask, B. J. Laboratory explosions. Chem. Eng. News 1979, 57, 74-74.

[148] Lutfalla, J. G.; Amalric, C.; Rafard, J. P. Explosive Properties of Tris(hydroxymethyl)phosphine Oxide Trinitrate. Ind. Chim. Belge 1967, 32, (Spec. No.), 623-625.

[149] Manner, V. W.; Cawkwell, M. J.; Kober, E. M.; Myers, T. W.; Brown, G. W.; Tian, H.; Snyder, C. J.; Perriot, R.; Preston, D. N. Examining the Chemical and Structural Properties that Influence the Sensitivity of Energetic Nitrate Esters. Chem. Sci. 2018, 9, 3649-3663.

[150] Hoffman, A. The Action of Hydrogen Phosphide on Formaldehyde. II. J. Am. Chem. Soc. 1930, 52, 2995-2998.

[151] Schenk, C. Etude sur la réactivité du THP (tris(hydroxyméthyl)phosphine) et développement de composés potentiellement efficaces en tant que retardants de flamme. Ph.D. Dissertation, Université de Neuchâtel, Neuchâtel, Switzerland, 2014.

[152] Chance, L. H. Process for Treating Organic Textiles with Flame Retardant Polymers Made from Hydroxymethylphosphorus Compounds and Guanazoles. U.S. Patent 3,914,106, Oct. 21, 1975.

[153] Carlson, R. H. Tetrakis(hydroxymethyl)phosphonium Chloride from Phosphine and Formaldehyde. U.S. Patent 3,666,817, May 30, 1972.

[154] Carlson, R. H. Trishydroxymethyl Phosphine Oxide from Phosphine and Formaldehyde. U.S. Patent 3,636,160, Jan. 18, 1972.

[155] Haas, H. Verfahren zur Herstellung von Trishydroxymethylphosphinoxid. Ger. Patent 1,930,521, Dec. 23, 1970.

[156] Hammann, W. C.; Clampitt, R. B. Organic Phosphorus Compounds. U.S. Patent 3,242,217, Mar. 22, 1966.

[157] Kuznetsov, E. V.; Valetdinov, R. K.; Roitburd, T. Y.; Zakharova, L. B. Syntheses with Phosphine. Tr. Kazakhsk. Khim.-Tekhnol. Inst. 1960, 20-21.

[158] Carretero-González, J.; Castillo-Martíneza, E.; Armand, M. Highly Water-Soluble Three-Redox State Organic Dyes as Bifunctional Analytes. Energy Environ. Sci. 2016, 9, 3521-3530.

[159] Lippsmeier, B.; Hestermann, K. Verfahren zur Herstellung von Hydroxyalkylphosphinoxiden. Ger. Patent 2,511,932, Sep. 30, 1976.

[160] Fidoe, S. D.; Talbot, R. E.; Jones, C. R.; Gabriel, R. Treatment of Iron Sulphide Deposits. World Patent 02/08127, Jan. 31, 2002.

[161] Jones, C. R.; Otter, G. P.; Collins, G. R. Phosphine Compounds and their Use as Tanning Agents, Corrosion Inhibitors and Biocides. World Patent 01/81635, Nov. 1, 2001.

[162] Burrow, R.; Sundah, D. Tanning Leather. World Patent 00/46409, Aug. 10, 2000.

[163] Carlson, R. H. Organophosphorverbindungen, Verfahren zu ihrer Herstellung und ihre Verwendung als Komplexierungsmittel (Sequestrants). Ger. Patent 1,806,886, Feb. 5, 1970.

[164] Carlson, R. H. Synergistic metal sequestrant. U.S. Patent 3,661,960, May 9, 1972.

[165] Nohata, Y. Tetrakis(hydroxymethyl)phosphonium Salts for Preventing Spoilage of Starch-Containing Industrial Materials. Jpn. Patent 2003-137712, May 15, 2003.

[166] Freeland, G. N.; Guise, G. B. The Shrinkproofing of Wool by the Exhaustion of Synthappret BAP and the Effect of Reducing Agents. J. Text. Inst. 1988, 79, 647-654.

[167] Jenkins, A. D.; Wolfram, L. J. Hair Waving Compositions and Method. Br. Patent 976,821, Dec. 2, 1964.

[168] Hueso, J. L.; Sebastian, V.; Mayoral, A.; Uson, L.; Arruebo, M.; Santamaria, J. Beyond Gold: Rediscovering Tetrakis-(Hydroxymethyl)-Phosphonium Chloride (THPC) as an Effective Agent for the Synthesis of Ultra-Small Noble Metal Nanoparticles and Pt-Containing Nanoalloys. RSC Adv. 2013, 3, 10427-10433.

[169] Eguizabal, A.; Uson, L.; Sebastian, V.; Hueso, J. L.; Pina, M. P. Efficient and Facile Tuning of Vulcan XC72 with Ultra-Small Pt Nanoparticles for Electrocatalytic Applications. RSC Adv. 2015, 5, 90691-90697.

[170] Bloom, S. M.; Buckler, S. A.; Lambert, R. F.; Merry, E. V. The Oxidation of Organo-Phosphines by Aqueous Alkali. J. Chem. Soc. D, Chem. Commun. 1970, 870-871.

[171] Harnisch, H. Zur Chemie einfacher Phosphor-Kohlenstoff-Verbindungen. Angew. Chem. 1976, 88, 517-524.

[172] Griffiths, D. V.; Groombridge, H. J.; Salt, M. C. Investigations into the Oxidative Stability of Hydroxymethyl- and Bis(Hydroxymethyl)-Phosphines. Phosphorus, Sulfur Silicon Relat. Elem. 2008, 183, 473-478.

[173] Moiseev, D. V.; James, B. R.; Gushchin, A. V. New Water-Soluble (Hydroxymethyl)triphosphine [(HOCH$_2$)$_2$PCH$_2$CH$_2$]2PCH$_2$OH, a Derived Pd$^{II}$(triphosphine) Complex, and Triphosphine Trioxide. Russ. J. Gen. Chem. (Engl. Transl.) 2011, 81, 1629-1634.

[174] Picklesimer, L. G. THPO Tanned Leather. U.S. Patent 2,993,744, Jul. 25, 1961.

[175] James, B. R. New Chemistry, Including Pulp Bleaching Processes, of the Golden-Aged, Water-Soluble Compound, Tris(hydroxymethyl)phosphine In Catalysis of Organic Reactions; Prunier, M. L., Ed. CRC Press: Boca Raton, 2009, pp 1-14.

[176] Drucker, A.; Grayson, M. Compositions pour ondulations des cheveux, contenant des phosphines tertiaires solubles dans l'eau. Fr. Patent 1,574,239, Jul. 11, 1969.

[177] Kalio, R.; Lönnecke, P.; Hey-Hawkins, E. New Ferrocenylmethylphosphines – Preparation, Characterisation and Coordination Chemistry of PH(CH$_2$Fc)$_2$, P(CH$_2$Fc)$_3$ [Fc = Fe($\eta^5$-C$_5$H$_5$)($\eta^5$-C$_5$H$_4$)] and their Derivatives. J. Organomet. Chem. 2008, 693, 590-600.

[178] Grinshtein, I. E.; Bruker, A. B.; Soborovskii, L. Z. Synthesis of Organophosphorus Compounds from Phosphorus Hydrides. V. Reactions of trifluoroacetone with Phosphorus Hydrides. Zh. Obshch. Khim. 1966, 36, 1138-1141.

[179] LeBlanc, R. B.; LeBlanc, D. A. THPS-Ammonia Precondensate Flame-Retardant for Poly/Cot Blends. Am. Dyest. Rep. 1985, 74, 35-40.

[180] Claiborne, J. L.; Wagner, G. M. Ammonia Curing Device Dhows Promise in FR Treating of 100% Cotton Yarns. Text. Chem. Color. 1979, 11, 30/15-34/19.

[181] Salchner, R.; Schottenberger, H.; Griesser, U.; Lackner, R. Intumescent Coatings. World Patent 2015/042628, Apr. 2, 2015.

[182] Phosphine and Selected Metal Phosphides; Environmental Health Criteria 73; World Health Organization: Geneva, 1988; pp 100.

[183] National Research Council Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 6. The National Academies Press: Washington, DC, 2008.

[184] Lyubimov, A. V.; Garry, V. F. Phosphine. In Hayes' Handbook of Pesticide Toxicology; 3 ed.; Krieger, R., Ed. Academic Press, 2010, pp 2259-2266.

[185] Patnaik, P. Phosphorus and its Compounds. In Comprehensive Guide to the Hazardous Properties of Chemical Substances; 3 ed.; John Wiley & Sons: Hoboken, New Jersey, 2007, p 839.

[186] Nachbur, H.; Maeder, A.; Kern, J. Verfahren zur Flammfestmachen von organischem Fasermaterial. Ger. Patent 2,154,811, Sep. 13, 1973.

[187] Nachbur, H.; Maeder, A. Verwendung von phosphorhaltigen Kondensationsprodukten als Flammschutzmittel für Fasermischungen aus Polyester-Cellulose. Ger. Patent 2,242,709, Mar. 15, 1973.

[188] Nachbur, H.; Maeder, A. Verfahren zur Herstellung von phosphorhaltigen Kondensationsprodukten, die Produkte und ihre Verwendung als Flammschutzmittel. Ger. Patent 2,242,690, Mar. 15, 1973.

[189] Bryan, E.; Veale, M. A.; Talbot, R. E.; Cooper, K. G.; Matthews, N. S. Biocidal Compositions and Treatments. Eur. Patent 0,385,801, Sep. 5, 1990.

[190] Hand, G.; Davis, J.; Woodward, G. Flame Retardant Compositions with Low Formaldehyde Content. World Patent 2017/097894, Jun. 15, 2017.

[191] Kullman, R. M. H.; Pepperman, A. B.; Vail, S. L. Formaldehyde Release in DP and FR Processing. Text. Chem. Color. 1978, 10, 195/161-199/165.

[192] Bayramoglu, E. E.; Yorgancioglu, A.; Onem, E. Analysis of Release of Free Formaldehyde Originated from THP Salt Tannages in Leather by High Performance Liquid Chromatography: Origanum Onites Essential Oil as Free Formaldehyde Scavenger. J. Am. Leather Chem. Assoc. 2013, 108, 411-419.

[193] Shi, J.; Wang, C.; Hu, L.; Xiao, Y.; Lin, W. A Novel Wet-White Tanning Approach Based on Laponite Clay Nanoparticles for Reduced Formaldehyde Release and Improved Physical Performances. ACS Sustainable Chem. Eng. 2019, 7, 1195-1201.

[194] Gordon, I.; Wagner, G. M. Preparation of Tertiary Phosphines. U.S. Patent 3,257,460, Jun. 21, 1966.

[195] Jones, C. R.; Collins, G. R. Tanning Leather. Br. Patent 2,384,006, Jul. 16, 2003.

[196] Xu, X.-J.; Yuan, H.-C.; Chen, H. Formaldehyde Contents Research of Several Aldehyde Tannages and their Modification Products. Pige Kexue Yu Gongcheng 2013, 23, 38-41, 47.

[197] McIlwaine, D. B. Oilfield application for biocides. In Directory of Microbicides for the Protection of Materials; Paulus, W., Ed. Kluwer Academic Publishers: Dordrecht, the Netherlands, 2004, pp 167.

[198] Larsen, J.; Sanders, P. F.; Talbot, R. E. Experience with the Use of Tetrakishydroxymethylphosphonium Sulfate (THPS) for the Control of Downhole Hydrogen Sulfide. Presented at CORROSION 2000, Orlando, FL, March 26-31, 2000; Paper No. 00123.

[199] Ulsamer, A. G.; Beall, J. R.; Kang, H. K.; Frazier, J. A. Overview of Health Effects of Formaldehyde. In Hazard Assessment of Chemicals: Current Developments; Saxena, J., Ed. Academic Press, Inc.: Orlando, FL, 1984; Vol. 3, pp 337-400.

[200] Directory of Microbicides for the Protection of Materials; Paulus, W., Ed. Kluwer Academic Publishers: Dordrecht, the Netherlands, 2004.

[201] Formaldehyde; Environmental Health Criteria 89; World Health Organization: Geneva, 1989.

[202] IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxypropan-2-ol; IARC Monographs 88; International Agency for Research on Cancer: Lyon, France, 2006; pp 39-325.

[203] Duffy, J. J. Source Control: Modification of a Flame Retardant Chemical. Plant Operations Progress 1983, 2, 241-243.

[204] Frank, A. W. Synthesis of Tris(aminomethyl)phosphine Oxide and its Carbon Dioxide Adduct from Tetrakis(hydroxymethyl)phosphonium Salts via their Methyl Carbamate Derivatives. Can. J. Chem. 1981, 59, 27-33.

[205] Tou, J. C.; Westover, L. B.; Sonnabend, L. F. Kinetic Studies of Bis(chloromethyl) Ether Hydrolysis by Mass Spectrometry. J. Phys. Chem. 1974, 78, 1096-1098.

[206] Tou, J. C.; Kallos, G. J. Kinetic Study of the Stabilities of Chloromethyl Methyl Ether and Bis(Chloromethyl) Ether in Humid Air. Anal. Chem. 1974, 46, 1866-1869.

[207] Carson, F. L. Formaldehyde + Hydrochloric Acid Bis-CME: Fact or Fantasy? J. Histotechnol. 1978, 1, 174-175.

[208] Frankel, L. S.; McCallum, K. S.; Collier, L. Formation of Bis(chloromethyl) Ether from Formaldehyde and Hydrogen Chloride. Environ. Sci. Technol. 1974, 8, 356-359.

[209] Kallos, G. J.; Solomon, R. A. Investigations of the Formation of Bis-Chloromethyl Ether in Simulated Hydrogen Chloride-Formaldehyde Atmospheric Environments. Am. Ind. Hyg. Assoc. J. 1973, 34, 469-473.

[210] Tou, J. C.; Kallos, G. J. Study of Aqueous HCl and Formaldehyde Mixtures for Formation of Bis (Chloromethyl) Ether. Am. Ind. Hyg. Assoc. J. 1974, 35, 419-422.

[211] Bock, C. W.; Brendley, W. H.; Hamann, H.; Bhat, K. L. Formation of Bis(chloromethyl)ether in the Vapor Phase: a Computational Investigation. J. Mol. Struct. 2002, 619, 207-228.

[212] Berning, D. E.; Katti, K. V.; Barnes, C. L.; Volkert, W. A. Chemical and Biomedical Motifs of the Reactions of Hydroxymethylphosphines with Amines, Amino Acids, and Model Peptides. J. Am. Chem. Soc. 1999, 121, 1658-1664.

[213] Loewengart, G.; B. L. van Duuren. The Reaction of Guanosine with Tetrakis(hydroxymethyl)phosphonium Chloride. Tetrahedron Lett. 1976, 17, 3473-3476.

[214] Ulsamer, A. G.; Osterberg, R. E.; McLaughlin, J. Flame-Retardant Chemicals in Textiles. Clin. Toxicol. 1980, 17, 101-131.

[215] Nishimura, M.; Umeda, M.; Ishizu, S.; Momotani, H. Effect of Some Flame-Retardants on Various Cultured Mammalian Cells. J. Toxicol. Sci. 1977, 2, 405-416.

[216] National Research Council Toxicological Risks of Selected Flame-Retardant Chemicals. National Academy Press: Washington, DC, 2000.

[217] Zhi, J.-H.; Tang, B.; Li, L.-F.; Wang, L.; Zhang, B.-G. Efficacy and Toxicity of Tetrakis(hydroxymethyl)phosphonium Sulfate in Indoor Air Disinfection. Huanjing Yu Jiankang Zazhi 2007, 24, 156-158.

[218] Grekov, L. I. Development of Catalytic Synthesis of Tris(hydroxymethyl)phosphine. Ph.D. Dissertation, Volgograd State Technical University, Volgograd, Russia, 2000.

[219] Grekov, L. I.; Shkodich, P. E. Study of Toxic Properties and Bactericidal Activity of Tris(hydroxymethyl)phosphine. Izv. Volgograd State Tech. Univ. 2008, 95-98.

[220] Eldefrawi, A. T.; Mansour, N. A.; Brattsten, L. B.; Ahrens, V. D.; Lisk, D. J. Further Toxicologic Studies with Commercial and Candidate Flame Retardant Chemicals. Part II. Bull. Environ, Contam. Toxicol. 1977, 17, 720-726.

[221] Dunn, B. J.; Nichols, C. W.; Gad, S. C. Acute Dermal Toxicity of Two Quarternay Organophosphonium Salts in the Rabbit. Toxicology 1982, 24, 245-250.

[222] Health Canada Pest Management Regulatory Agency. Tributyl Tetradecyl Phosphonium Chloride and Bellacide 350; PRD2018-11; the Health Canada Pest Management Regulatory Agency: Ottawa, 2018.

[223] Deichmann, W. B.; Gerarde, H. W. Toxicology of Drugs and Chemicals. Academic Press: New York, 1969.

[224] Connor, T. H.; Meyne, J.; Legator, M. S. The Mutagenic Evaluation of Tetrakis (Hydroxymethyl) Phosphonium Sulfate Using a Combined Testing Protocol Approach. J. Environ. Pathol. Toxicol. 1980, 4, 145-158.

[225] Oswald, P. R.; Evans, R. A.; Henderson, W.; Daniel, R. M.; Fee, C. J. Properties of a Thermostable β-Glucosidase Immobilized Using Tris(hydroxymethyl)phosphine as a Highly Effective Coupling Agent. Enzyme Microb. Technol. 1998, 23, 14-19.

[226] Drake, G. L.; Perkins, R. M.; Reeves, W. A. Special finishes for textile-flame retardant finishes and soil resistant finishes. Colourage 1971, 18, 35-44, 56.

[227] Laslau, C.; Henderson, W.; Zujovic, Z. D.; Travas-Sejdic, J. Phosphine-Functionalized Polyaniline Nanostructures. Synth. Met. 2010, 160, 1173-1178.

[228] Muralidharan, K.; Reddy, N. D.; Elias, A. J. Syntheses of Novel Exo and Endo Isomers of Ansa-Substituted Fluorophosphazenes and Their Facile Transformations into Spiro Isomers in the Presence of Fluoride Ions. Inorg. Chem. 2000, 39, 3988-3994.

[229] Babu, H. V.; Srinivas, B.; Naik, K. P. K.; Muralidharan, K. Polymerization behaviour of butyl bis(hydroxymethyl)phosphine oxide: Phosphorus containing polyethers for Li-ion conductivity. J. Chem. Sci. 2015, 127, 635-641.

[230] Ramakrishna, T. V. V.; Elias, A. J. Reactions of ferrocene-derived bis(hydroxymethyl) phosphine sulfides FcCH(R)P(S)(CH$_2$OH)$_2$ (R=H, CH$_3$) with cyclic thionylphosphazenes: crystal structures of FcCH$_2$P(S)(CH$_2$O)$_2$PN(NPCl$_2$)[NS(O)Ph] and FcCH$_2$P(S)(CH$_2$O)$_2$PN$_2$P[N(Me)CH$_2$]$_2$[NS(O)Ph] (Fc=ferrocenyl). J. Organomet. Chem. 2001, 637-639, 382-389.

[231] Doblas, S.; Pathuri, G.; Towner, R. A.; Gali, H. Feasibility Evaluation of Detecting Hydroxymethylphosphine Oxide In Vivo by ^{31}P-MRS. Int. J. Biomed. Sci. 2010, 6, 228-232.

[232] IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Some Flame Retardants and Textile Chemicals, and Exposures in the Textile Manufacturing Industry; IARC Monographs 48; International Agency for Research on Cancer: Lyon, France, 1990; pp 95-107.

[233] Aoyama, M. Effect of Anti-Flame Treating Agents on the Skin. Nagoya Med. J. 1975, 20, 11-19.

[234] Hirayama, M. The Antimicrobial Activity, Hydrophobicity and Toxicity of Sulfonium Compounds, and their Relationship. Biocontrol Sci. 2011, 16, 23-31.

[235] Wyllie, M. J.; Turner, H.; Henderson, W. Tris(hydroxymethyl)phosphine, P(CH$_2$OH)$_3$ - A Convenient and Effective New Reagent for the Fixation of Protein Samples for SEM Imaging. Micron 2016, 89, 28-33.

[236] IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide; IARC Monographs 71; International Agency for Research on Cancer: Lyon, France, 1999; pp 1529-1532.

[237] Van Duuren, B. L.; Loewengart, G.; Seidman, I.; Smith, A. C.; Melchionne, S. Mouse Skin Carcinogenicity Tests of the Flame Retardants Tris(2,3-dibromopropyl)phosphate, Tetrakis(hydroxymethyl)phosphonium Chloride, and Polyvinyl Bromide. Cancer Res. 1978, 38, 3236-3240.

[238] Smith, C. J.; Perfetti, T. A. Tumor Site Concordance and Genetic Toxicology Test Correlations in NTP 2-Year Gavage, Drinking Water, Dermal, and Intraperitoneal Injection Studies. Toxicol. Res. Appl. 2018, 2, 1-18.

[239] Pezas, T.; Cogswell, L. Squamous Cell Carcinoma of the Palm after Chronic Organophosphate Exposure. Br. J. Hosp. Med. 2018, 79, 530-531.

[240] Bain, P. A.; Kumar, A. In Vitro Nuclear Receptor Inhibition and Cytotoxicity of Hydraulic Fracturing Chemicals and their Binary Mixtures. Chemosphere 2018, 198, 565-573.

[241] Zeiger, E.; Anderson, B.; Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W. Salmonella Mutagenicity Tests: III. Results from the Testing of 255 Chemicals. Environ. Mutagen. 1987, 9, 1-109.

[242] Zeiger, E. Mutagenicity of 42 Chemicals in Salmonella. Environ. Mol. Mutagen. 1990, 16, 32-54.

[243] Ballantyne, B. Toxicology of Biocides. In General and Applied Toxicology; 3 ed.; Ballantyne, B., Marrs, T. C., Syversen, T., Eds. John Wiley & Sons: Barcelona, 2009; Vol. 6, pp 3207-3232.

[244] Myhr, B.; McGregor, D.; Bowers, L.; Riach, C.; Brown, A. G.; Edwards, I.; McBride, D.; Martin, R.; Caspary, W. J. L5178Y Mouse Lymphoma Cell Mutation Assay Results with 41 Compounds. Environ. Mol. Mutagen. 1990, 16, 138-167.

[245] Schisler, M. R.; Gollapudi, B. B.; Moore, M. M. Evaluation of U.S. National Toxicology Program (NTP) Mouse Lymphoma Assay Data Using International Workshop on Genotoxicity Tests (IWGT) and the Organization for Economic Co-Operation and Development (OECD) Criteria. Environ. Mol. Mutagen. 2018, 59, 829-841.

[246] Loveday, K. S.; Lugo, M. H.; Resnick, M. A.; Anderson, B. E.; Zeiger, E. Chromosome Aberration and Sister Chromatid Exchange Tests in Chinese Hamster Ovary Cells in Vitro: II. Results with 20 Chemicals. Environ. Mol. Mutagen. 1989, 13, 60-94.

[247] Anderson, B. E.; Zeiger, E.; Shelby, M. D.; Resnick, M. A.; Gulati, D. K.; Ivett, J. L.; Loveday, K. S. Chromosome Aberration and Sister Chromatid Exchange Test Results with 42 Chemicals. Environ. Mol. Mutagen. 1990, 16, 55-137.

[248] MacGregor, J. T.; Diamond, M. J.; Mazzeno, L. W.; Friedman, M. Mutagenicity Tests of Fabric-Finishing Agents in Salmonella typhimurium: Fiber-Reactive Wool Dyes and Cotton Flame Retardants. Environ. Mutagen. 1980, 2, 405-418.

[249] Daigle, D. J.; Pepperman, A. B.; Reeves, W. A. The Role of Formaldehyde in the Production of Tris(diphenylaminomethyl)phosphine. Text. Res. J. 1971, 41, 944-945.

[250] Daigle, D. J.; Reeves, W. A.; Donaldson, D. J. Reaction of THPOH with Secondary Amines. Text. Res. J. 1970, 40, 580-581.

[251] Daigle, D. J.; Donaldson, D. J. Formaldehyde: The Key to Polymerization between THPOH and $NH_4OH$. J. Appl. Polym. Sci. 1970, 14, 248-249.

[252] Payne, M. E.; Chapman, H. F.; Cumming, J.; Leusch, F. D. L. In Vitro Cytotoxicity Assessment of a Hydraulic Fracturing Fluid. Environ. Chem. 2015, 12, 286-292.

[253] Marzano, C.; Pellei, M.; Colavito, D.; Alidori, S.; Lobbia, G. G.; Gandin, V.; Tisato, F.; Santini, C. Synthesis, Characterization, and in Vitro Antitumor Properties of Tris(hydroxymethyl)phosphine Copper(I) Complexes Containing the New Bis(1,2,4-triazol-1-yl)acetate Ligand. J. Med. Chem. 2006, 49, 7317-7324.

[254] Komarnicka, U. K.; Starosta, R.; Kyzioł, A.; Płotek, M.; Puchalska, M.; Jeżowska-Bojczuk, M. New Copper(I) Complexes Bearing Lomefloxacin Motif: Spectroscopic Properties, in Vitro Cytotoxicity and Interactions with DNA and Human Serum Albumin. J. Inorg. Biochem. 2016, 165, 25-35.

[255] Chowhan, M. A.; Han, W. W.; Schneider, L. W. Pharmaceutical Compositions with Phosphonium Antimicrobial Agents U.S. Patent 2011/0269719, Nov. 3, 2011.