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Oxidative decontamination of chemical warfare agent VX and its simulant using *N,N*-dichlorovaleramide

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ABSTRACT:

The optimized conditions have been reported for efficient, operationally simple and safe oxidative decontamination of chemical warfare agent *O*-ethyl *S*-2-(*N,N*-diisopropylaminoethyl) methylphosphonothioate (VX) and its non-toxic simulant *O,S*-diethyl methylphosphonothioate (OSDEMP). A positive chlorine bearing reagent *N,N*-dichlorovaleramide (NCV) was tested successfully to effect decontamination of these compounds. These compounds were found to undergo instantaneous reaction with NCV in acetonitrile-water medium to form non-toxic products. The reaction was monitored by gas chromatograph (GC) and the products were identified by gas chromatograph coupled with mass spectrometer (GC-MS) & nuclear magnetic resonance (NMR) spectroscopy. The reagent is cheap, easy to synthesize from commercially available raw materials and it has a shelf life of more than one year.

Keywords: VX, *N, N*-dichloro valeramide, active chlorine, decontamination, NMR and GC-MS.

INTRODUCTION:

The massive and highly diverse family of organophosphorus compounds have a variety of uses as key intermediates or components used in the synthesis of different important organic compounds having huge economic and societal importance (viz. pesticides [1], herbicides[2], fungicides [3], insecticides [4], acaricides[5], fire retardants [6], metal extractants [7], surfactants [8], detergents [9], drugs [10] and lubricant additives [11], etc).

Alongside these peaceful uses, they have also been used for the manufacture of highly toxic chemical warfare agents (CWA) [12]. Owing to their ease of synthesis and toxic effects on life forms, these CWAs confer a great tactical/psychological advantage as weapons of mass destruction [13, 14]. In spite of the continued efforts of the world community to ostracize the CWAs, they continue to pose a constant threat to the civilized world [15]. They have been repeatedly used during military conflicts [16] and terror attacks [17]. Among all chemical warfare agents reported to date [18], *O*-ethyl *S*-2-(*N,N*-diisopropylaminoethyl) methylphosphonothioate (VX) and its analogues are the most toxic[19]. According to the Acute Exposure Guideline Level three (AGEL-3) the lethal dose of VX is 0.0096 mg/m^3 for a ten minute exposure to humans [20]. Hence it is ten times more toxic than sarin [21] (the chemical warfare agent used during attack on the Tokyo subway in 1995 [22]). Like other organophosphorus chemical warfare agents, it rapidly inhibits acetylcholinesterase (AChE) [23] enzyme by phosphorylating its active site. This leads to the accumulation of neurotransmitter acetylcholine, over-stimulation of cholinergic receptors and finally breakdown of neuromuscular function [24] takes place. Hence, VX has been rightly classified as a nerve agent [25] and it has been enlisted in Schedule 1.A.3 of the Chemical Weapons Convention (CWC) [26].

Hence, for the safe and effective management of accidental and intentional release of this chemical; efficient decontamination is a mandatory requirement. In order to achieve this goal, several physical, chemical and physico-chemical decontamination techniques have been developed. They make use of various chemical reactions (viz. hydrolytic or solvolytic [27-30] and oxidative reactions [31, 32]).

Although pure VX is a persistent chemical at room temperature, a 95% pure sample of VX decomposes at a rate of 5% a month at 71°C. The hydrolysis of VX is highly dependent on pH [32]. It is quite

water-soluble below its pKa of 7.9 owing to protonation of nitrogen. Hence above this pH it is less soluble in water. Its half-life is 100 days at pH 2 or 3 at 25°C. It undergoes biphasic reaction and at pH 14 its half-life is 1.3 min. [33]. It is calculated that VX is approximately 1,500 times slower in evaporating than nerve agent GB [34]. Due to low volatility and high stability, VX can persist for months under average weather conditions [35, 36]. It is extremely toxic by absorption through skin and eye [37]. VX has a tendency to rapidly penetrate skin without causing any injury [38]. As compared to the G-agents, the vivo persistence of VX is substantially higher. This undermines the efficacy of treatment with oximes since the later have shorter persistence in comparison to the agent itself [39]. Due to these reasons, immediate decontamination of the smallest drop of VX is very necessary.

The formation of up to about 10% of *S*-2-(*N,N*-diisopropylaminoethyl) methylphosphonothioic acid (also known as EA-2192) is another important aspect of basic hydrolysis of VX[32]. Since this compound is equally toxic as VX [40], so its formation is not desirable. Although and enzymatic [41] degradation of VX is fast and safe, the enzymes are not only expensive, difficult to produce and have poor shelf life [42]. The micellar [35] decontamination methods on the other hand are very sensitive to the reaction conditions[43].

Many of the oxidative decontaminants utilize the oxidative power of positively charged chlorine species [32]. These decontaminants include hypochlorites or their equivalents. Other prominent oxidative decontaminating reagents reported for the oxidation of to date include hydrogen peroxide [44], peroxymonosulfates [45], nanomaterials [46], self-decontaminating materials [47], inorganic oxidants [48], photocatalysts [49], iodosobenzoates [50], chloramides [51] and household chemicals [52]. We have reported the oxidative degradation of OSDEMP (a non-toxic simulant of VX) and sulfur mustard using positive chlorine bearing decontaminants [53-56]. By far the oxidative methods are easy to implement as they instantly convert the sulfur containing CWAs to their corresponding innocuous oxidation products.

In the present work *N,N*-dichlorovaleramide (NCV) was first tested for the decontamination of OSDEMP, a non-toxic simulant of VX. Thereafter decontamination of highly toxic chemical warfare agent

VX (figure 1) was attempted with this reagent. The the extent of decontamination reactions was monitored using $^{31}P\{^{1}H\}$ NMR spectroscopy. Whereas, gas chromatograph coupled with flame photometric detector working in sulfur mode (GC-FPD(S)) a more sensitive analytical technique was also used to ascertain complete disappearance of VX/OSDEMP. The products were identified by phosphorus edited proton nuclear magnetic resonance spectrometer (NMR) spectroscopy and gas chromatography mass spectrometry (GC-MS). Although (GC-FPD(S)) provided information regarding progress of the reaction, rapid identification of the products in the reaction mixture was achieved by using GC-MS and NMR spectroscopy (performed without and with standard addition of ethyl methylphosphonic acid (EMPA) to the NMR tube). The GCFPD(S) and GC-MS require aggressive experimental conditions and suffer from memory effects. Moreover, the non-volatile analytes had to be converted into their volatile derivatives prior to analysis by these two techniques. In order to overcome these problems, NMR spectroscopy was also used as a complimentary technique. It allowed rapid analysis of the reaction mixtures with minimal sample preparation and memory effects. Being a soft analytical technique it does not induce any further chemical reactions during analysis and the sample can be recovered as it is a non-destructive technique as well. . Nucleus specific observation of the analytes also imparted selectivity to the NMR experiments [57-65]. Complete decontamination of VX/OSDEMP was ensured by absence of reactant and concomitant formation of non-toxic products.

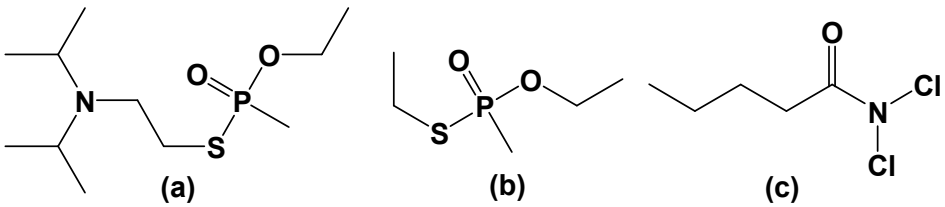

Figure 1. The chemicals (a) *O*-ethyl *S*-2-(*N,N*-diisopropylaminoethyl) methylphosphonothioate (VX) (b) *O,S*-diethyl methylphosphonothioate (OSDEMP) and (c) decontaminant *N,N*-dichloro valeramide (NCV) selected for the study.

EXPERIMENTAL:

2.1 Materials: The chemicals valeramide, 3-trimethylsilyl propionic acid-d_4 (TSP), chloroform-d_1, and acetonitrile-d_3 were purchased from Sigma Aldrich Chemical Company, Milwaukee, USA. Acetonitrile and glacial acetic acid of AR grade were purchased from S.D. Fine-Chem Ltd, Mumbai, India. Sodium

hypochlorite was prepared by passing chlorine gas at flow of 1gmin^{-1} in NaOH solution (15%, 100 mL) for 30 min. at 5 $^{\circ}$C.

2.2 Instruments used and conditions of analysis:

Identification of the products of the decontamination reaction was performed on GC (Agilent 7890) coupled with flame photometric detector (FPD) working in sulfur mode. Whereas, GC (Agilent 7890) coupled with 5975C mass selective detector (MSD) working in EI mode (Agilent Technologies, San Jose, CA, USA) was used for identification of the products. Chromatographic separation was achieved using the following conditions: column HP-5 (30 m × 0.250 mm × 0.25 μm) with a temperature program of 50 $^{\circ}$C for 2 min followed by a linear gradient to 250 $^{\circ}$C at 10 $^{\circ}$C min^{-1}, and hold at 250 $^{\circ}$C for 5 min. The injector temperature was maintained at 250 $^{\circ}$C while the transfer line was heated to 280 $^{\circ}$C. The EI analysis was performed at 70eV with ion source temperature at 230 $^{\circ}$C and emission current of 400 μA. All NMR spectra were recorded on Bruker AV III 600 MHz spectrometer equipped with a 5 mm broadband observe probe head (BBFO) fitted with an actively shielded single axis Z-gradient and automated tuning and matching accessory. All NMR experiments[66] were carried out at 25 ˚C after equilibrating the samples for 5 minutes at this temperature. The NMR spectra were acquired and processed using Topspin 3.2 software.

2.3 Synthesis of O,S-diethyl methylphosphonothioate (OSDEMP), VX and N, N-dichloro valeramide (NCV):

The target compounds *O,S*-diethyl methyl phosphonothioate and VX and NCV were synthesized by as methods reported earlier [55, 56]. Structure and purity of all the compounds was confirmed by ^{1}H, ^{31}P{^{1}H}, ^{31}P-^{1}H HMQC NMR spectroscopy and GC-MS. The active chlorine content of NCV was found to be 44% [67]. Freshly synthesized NCV was stored in a stoppered glass vial at room temperature. In order to determine its shelf life, active chlorine was determined by iodometry once in a month for a period of one year. A marginal decrease of active chlorine was observed from 44.10 to 42.4%.

2.4 Reaction of VX and OSDEMP with NCV:

The reaction was carried out in NMR tube using $CD_3CN:D_2O$ (5:1) to study the role of solvents and reaction time by observing the disappearance of the signal of VX (at 57.13 ppm). In order to ascertain the complete degradation of VX under the optimized conditions, a test-tube containing OSDEMP or VX (1.0 equivalent), in 6mL $CH_3CN:H_2O$ (5:1) NCV (2.0 equivalents) were added. Samples were withdrawn at 5 minute time intervals from the reaction mixture. Experiments were performed to ascertain the complete degradation of VX. This was performed by extracting one 500 µL aliquot of the reaction mixture with two 200 µL aliquots of hexane. The hexane layers were pooled and dried using anhydrous sodium sulfate and the dry extracts were taken in 5 mm NMR sample tubes. To this solution a 200 µL aliquot of $CDCl_3$ was added and it was subjected to NMR, GC-FPD(S) and/or GC-MS analysis. In order to identify the degradation products formed during the reaction, a 600 µL aliquot was taken in a test tube and concentrated near to dryness under a gentle purge of dry nitrogen (5 $mLmin^{-1}$) on a dry bath (50 $^{\circ}C$). The residues were reconstituted in 600 µL $CDCl_3$ and analyzed by NMR spectroscopy. Another 500 µL aliquot was cooled to 5 $^{\circ}C$ and freshly prepared ethereal solution of diazomethane was added slowly to the other portion till a faint yellow color persisted. It was then concentrated to 50 µL under a gentle stream of nitrogen. The resulting solution was concentrated to near to dryness under a gentle purge of dry nitrogen (5 $mLmin^{-1}$) and injected into GC-FPD(S) and/or GC-MS (under the conditions specified in section 2.2).

Results and discussion:

The $^{31}P\{^1H\}$ NMR experiments on the reactions carried out in different solvents (viz. chloroform, dichloromethane, benzene, tetrahydrofuran, acetonitrile, water, ethyl acetate and their admixtures clearly showed that a mixture of $CH_3CN:H_2O$ (5:1) was best suited composition. A vigorous reaction ensued at room temperature with observable warming of the solution and concomitant disappearance of the $^{31}P\{^1H\}$ NMR signal of VX. Due to high specific capacity of water, the endogenous heat was handled efficiently by this solvent system. This solvent system also led to instantaneous reaction and homogeneous solution of the reaction. This helped in efficient monitoring of the reaction products by GC/GC-MS and solution state

NMR techniques. The extent of reaction and the optimum reaction conditions were established by these experiments. The complete absence of VX and EA2192 were confirmed by GC-FPD(S) and/or GC-MS analysis of the hexane extracts and diazomethane derivatives present in the reaction mixture (figure 2-4). Alongside the $^{31}P\{^{1}H\}$ NMR experiments, they also helped to ascertain the identities of the degradation products. These experiments clearly showed that methyl derivatives of (2-(diisopropylamino)ethanesulfonate (i.e. MDIES) and ethyl methylphosphonate (i.e. EMMP) were present in the reaction mixture. The decontaminant NCV was converted to methyl derivatives of valeric acid (MVA) and valeramide (MVAmide) respectively. The extracted ion chromatograms were checked with an ion-command of m/z 114 on the GC-MS data recorded in full scan mode (m/z 40-400). No peaks corresponding to VX or the methyl ester of EA-2192 were observed in the extracted ion chromatograms. This not only indicated 100% decontamination of VX, it was also indicative of the absence of methyl ester of its toxic degradation product EA-2192.

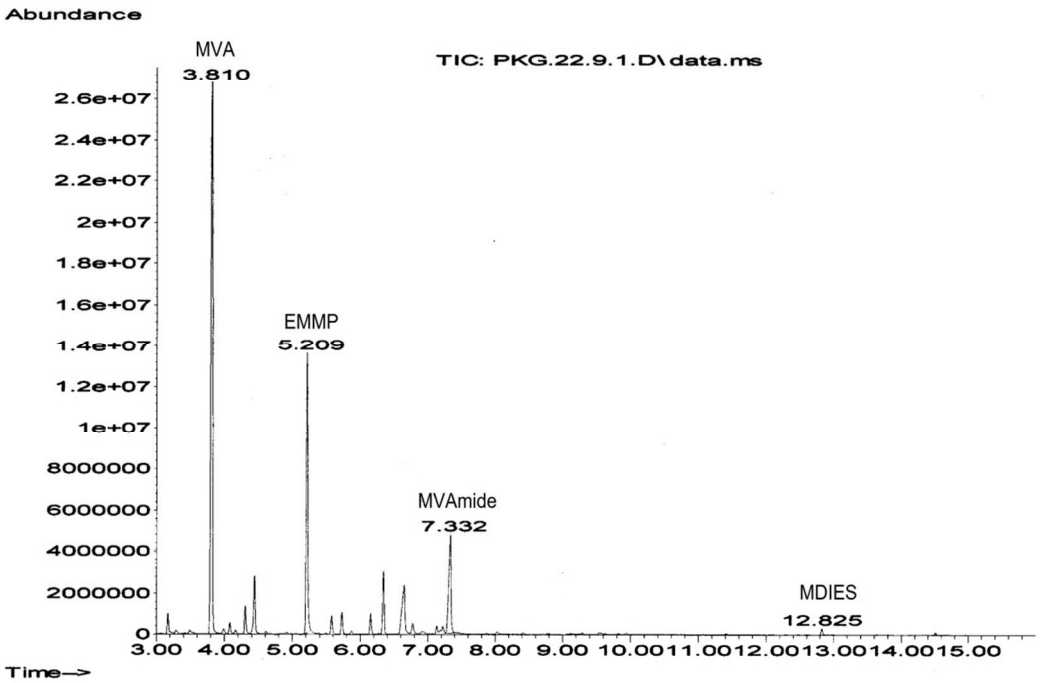

Figure 2. The GC-MS total ion chromatogram of the reaction mixture clearly showing the methylated reaction products N-methyl valeric acid (MVA), ethyl methyl methylphosphonate (EMMP), methyl (2-(diisopropylamino)ethanesulfonate (MDIES)and valeramide (MVAmide).

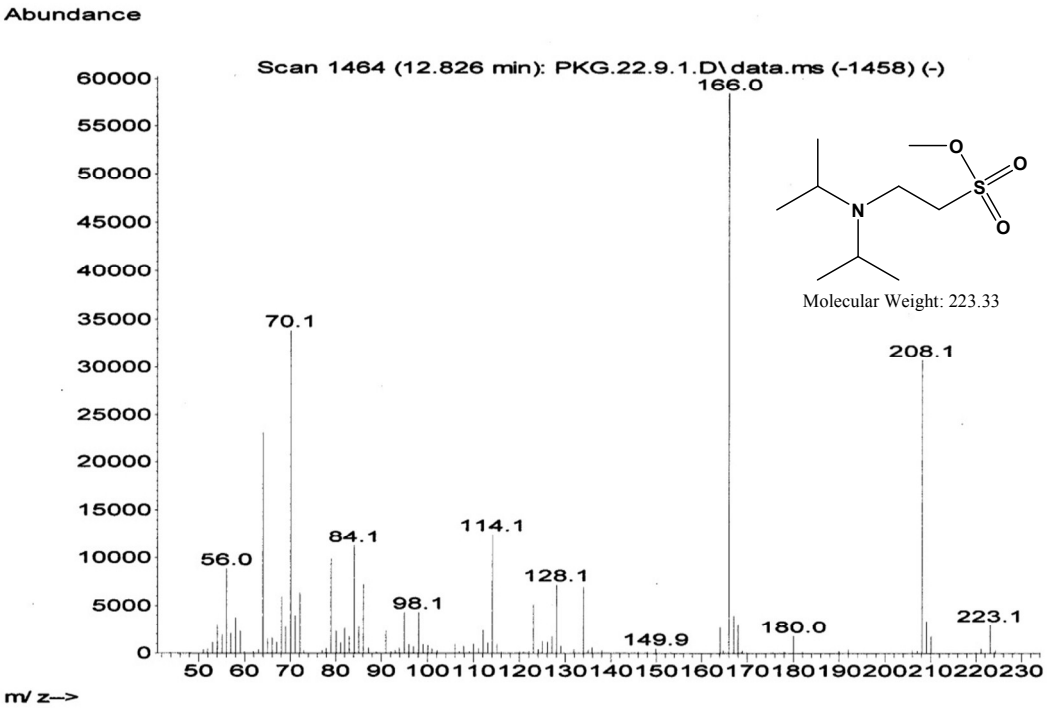

Figure 3. GC-EI-MS spectrum of methyl 2-(diisopropylamino)ethanesulfonate (MDIES) decontaminated product of VX. Eluting at 12.82 mins from the GC column.

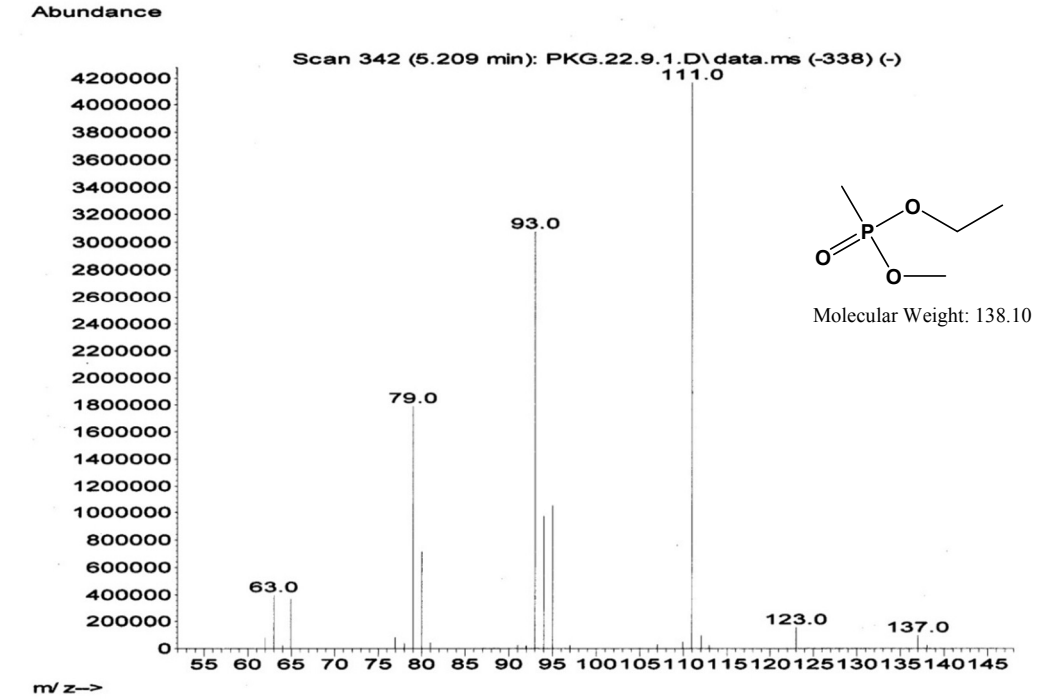

Figure 4. GC-EI-MS spectrum of ethyl methyl methylphosphonate (EMMP) decontaminated product of VX. Eluting at 5.21 mins from the GC column.

The $^{31}P\{^{1}H\}$, ^{31}P NMR experiments were carried out on VX and the the second fraction of the reaction mixture clearly indicated absence of VX (at 57.12 ppm, figure 5) and exclusive formation of *O*-ethyl methylphosphonate (EMPA, 30.06 ppm, figure 6 and 7) as the only organophosphorus degradation

product. The presence of EMPA and absence of degradation product EA-2192 was also confirmed by ^{1}H–^{31}P HSQC experiments on the reaction mixture (figure 7).

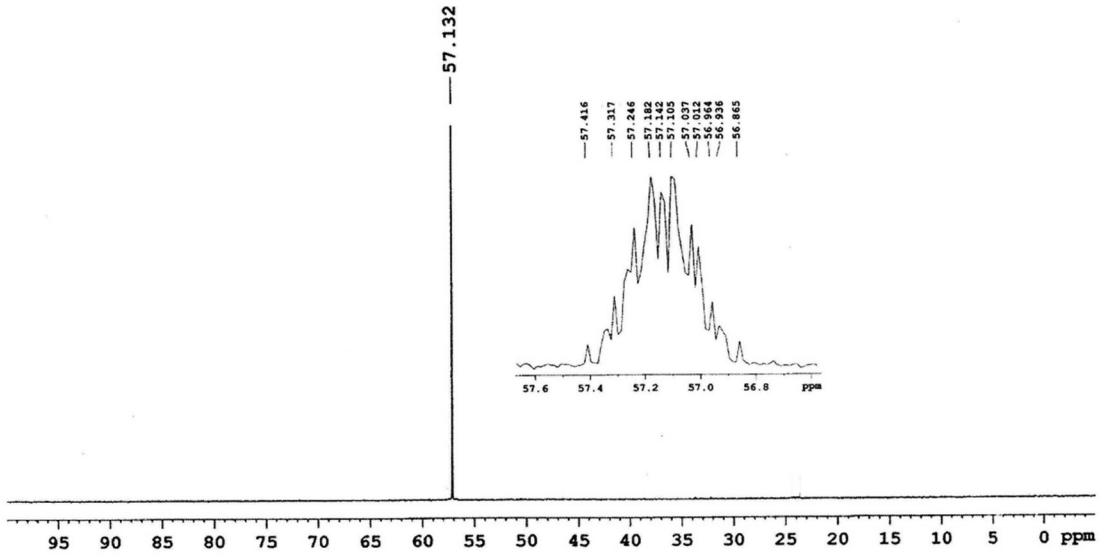

Figure 5. The purity of VX was ascertained from $^{31}P\{^{1}H\}$-NMR (inset ^{31}P-NMR) spectrum of VX recorded prior to reaction.

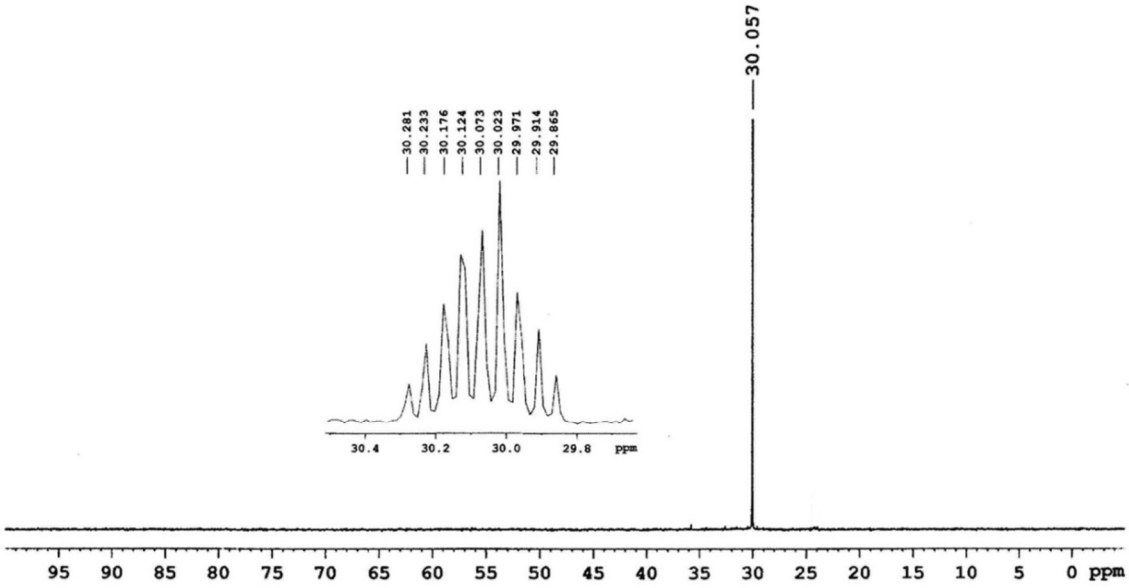

Figure 6. $^{31}P\{^{1}H\}$-NMR (inset ^{31}P-NMR) spectrum of *O*-ethyl methylphosphonic acid (EMPA) recorded after decontamination using NCV. Identity of the analyte was further confirmed by standard addition of EMPA to the reaction mixture. The change in chemical shift and absence of signal at 57.13 ppm clearly demonstrates the absence of VX.

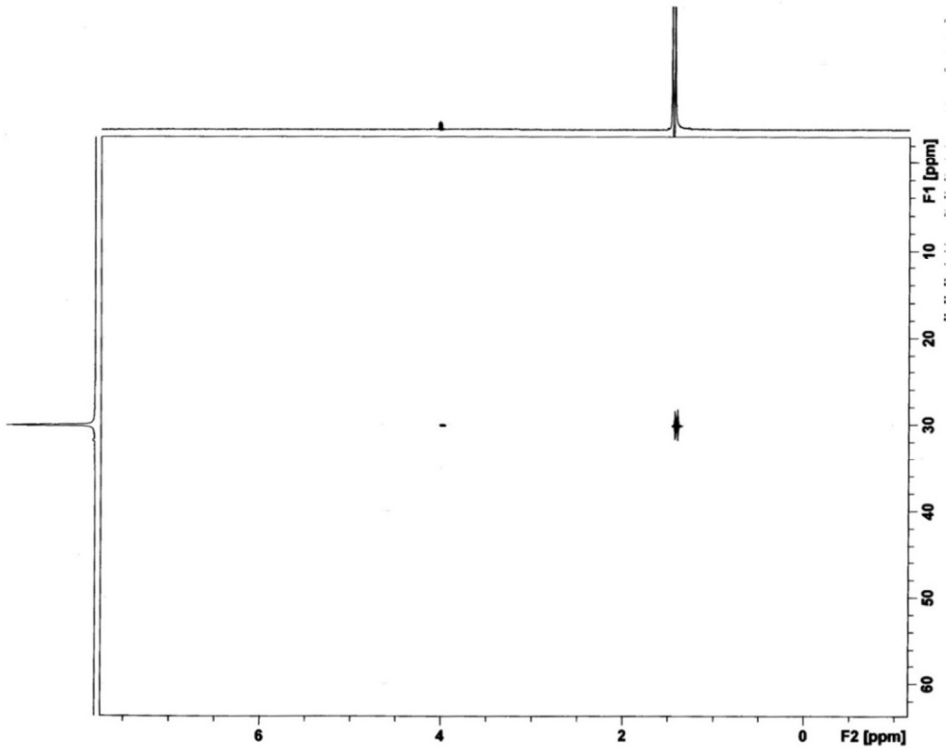

Figure 7. $^{1}H–^{31}P$ HSQC NMR spectrum of the reaction mixture after decontamination of VX is shown. *O*-ethyl methylphosphonic acid (EMPA) is observed as the only phosphorus containing product. This was further confirmed by standard addition of EMPA to the reaction mixture.

Similar sample preparation procedure was used to study the decontamination products of OSDEMP by GC-MS. The hexane extract did not show the presence of OSDEMP. When the aqueous fraction was analyzed after methylation, ethyl methyl methylphosphonate (EMMP) was found to be present. The samples were also subjected to ^{31}P, $^{31}P\{^{1}H\}$ and $^{1}H–^{31}P$ HSQC NMR experiments. The results clearly indicated complete degradation of the OSDEMP into *O*-ethyl methylphosphonic acid (EMPA).

On the basis of the identified major degradation products valeric acid (VA), ethyl methylphosphonate (EMP), (2-(diisopropylamino)ethanesulfonate (DIES) and valeramide (VAmide) and reported literature [31, 68], plausible mechanism of the reaction is proposed below (Figure 8). The reaction is initiated by attack of the electrophilic Cl^{+} on the lone pair of electrons of bivalent sulfur of VX [31]. This leads to the formation of sulfonium cation intermediate (b) and subsequently the nucleophilic attack of water on phosphorus atom of (b) leads to cleavage of the P-S bond of VX gives protonated ethyl methylphosphonate (EMPA) (c) and 2-(*N,N*-diisopropylamino)ethanesulfenyl chloride (d). Removal of

proton from intermediate (c) gives ethyl methylphosphonate (EMPA). Furthermore in the step (iii) hydrolysis S-Cl bond and subsequent removal of HCl forms intermediate (d) which further hydrolysis to form (e). In the step (iv) again the lone pair of electrons present on sulfur atom of (e) attacks on positive chlorine to form a specie (f). This happens due to the presence of positive charge and vacant d-orbitals on the sulfur atom in (f) and lone pair of oxygen moiety of water molecule attacks on this sulfur and leads to the formation of unstable dicationic specie (g). This specie gets converted into intermediate (h). Elimination of HCl from intermediate (h) in the step (vii) produces sulfinic acid derivative (i). Furthermore repetition of steps iv-vii leads to the formation of sulfonic acid product 2-(*N,N*-diisopropylamino) ethanesulfonate (j).

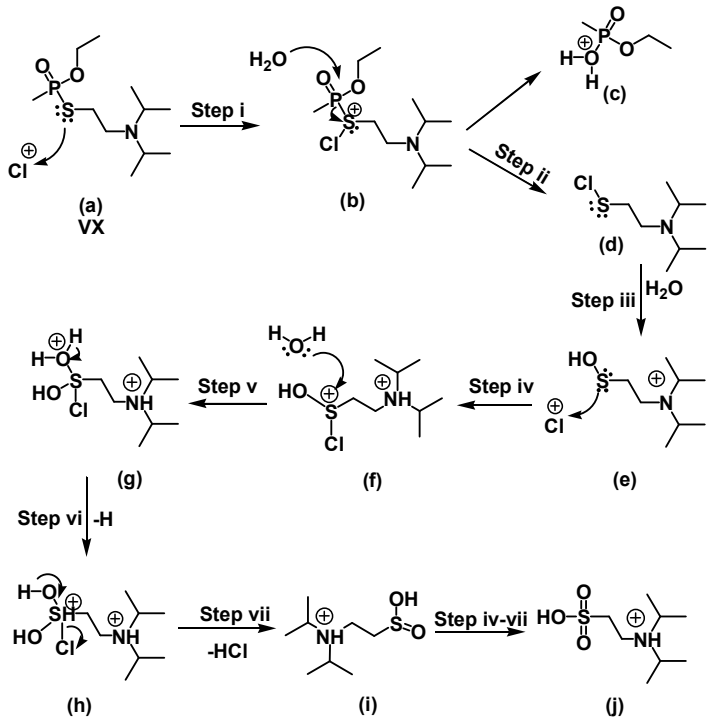

Figure 8: Proposed mechanism of oxidative decontamination of VX using the reagent NCV.

Conclusion:

In conclusion, the study reveals that NCV works as an effective decontaminating agent against OSDEMP and VX to form non-toxic products at room temperature. This reagent has advantage over earlier reported reagent in terms of ease of synthesis, cost, effectiveness, decontamination efficiency and stability.

Author contributions:

PKG was responsible for conception of the study, synthesis of NCV, reaction monitoring by

GC/GC-MS and drafting of manuscript. AM was responsible for sample preparation, acquisition of NMR experiments, interpretation of experimental data, drafting and editing the manuscript. GR synthesized VX for the study.

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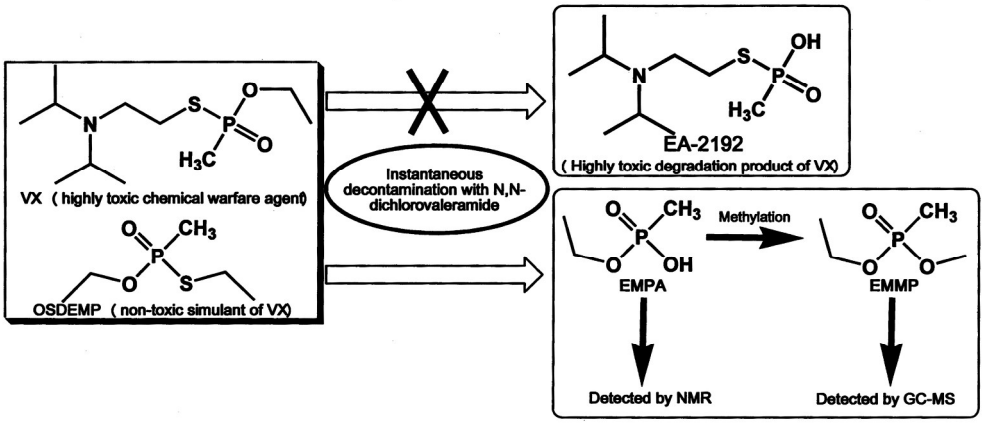

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