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REVIEW

ELECTRONIC SUPPORTING INFORMATION (ESI)

Advice from the Scientific Advisory Board of the Organisation for the Prohibition of Chemical Weapons on riot control agents in connection to the Chemical Weapons Convention

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Figure S1. Members of the SAB at its Twenty-First Session (The Hague, 23 June 2014), whom endorsed the report containing the initial advice on RCAs. From left to right: (Back Row) Dr Muhammad Zafar-Uz-Zaman (Pakistan), Dr Augustin Baulig (France), Professor David Gonzalez (Uruguay), Mr Francois Mauritz van Straten (South Africa), Mr Valentin Rubaylo (Russian Federation), Dr Michael Geist (Germany); (Middle Row) Dr Koji Takeuchi (Japan), Professor Djafer Benachour (Algeria), Professor Roberto Martínez-Álvarez (Spain), Professor Ferruccio Trifirò (Italy), Mr Cheng Tang (China), Mr William Kane (United States of America), Dr Veronica Borrett (Australia), Dr Syed Raza (India), Dr Jonathan E. Forman (OPCW Science Policy Adviser), Mr Stian Holen (OPCW Secretary to the SAB); (Front Row) Professor Slawomir Neffe (Poland), Professor Mohammad Abdollahi (Islamic Republic of Iran), Dr Christopher M. Timperley (United Kingdom, SAB Vice-Chair), Professor Alejandra Graciela Suárez (Argentina, SAB Chair), John Sequeira (OPCW Director of Administration and Acting Director-General on 23 June), Professor Mongia Said Zina (Tunisia), Dr Nicia Maria Fusaro Mourão (Brazil), Professor Slavica Vučinič; (Serbia), Professor Flerida Cariño (Philippines), Professor Paula Vanninen (Finland), Professor Volodymyr Zaitsev (Ukraine).

Figure S2. Members of the SAB at its Twenty-Fifth Session (The Hague, 27 March 2017) whom endorsed the report containing the updated advice on RCAs, together with invited participants. From left to right: (Back Row) Professor Andrew Wang (Guest, University of North Carolina, USA), Professor Ponnadurai Ramasami (Mauritius), Mr Valentin Rubaylo (Russian Federation), Dr Koji Takeuchi (Japan), Dr Pal Åas (Norway), Dr Zrinka Kovarik (Croatia); (Middle Row) Dr Evandro De Souza Nogueira (Brazil), Professor Volodymyr Zaitsev (Ukraine), Dr Robert Mikulak (USA), Professor Roberto Martínez-Álvarez (Spain), Dr Augustin Baulig (France), Mr Francois Mauritz van Straten (South Africa), Dr Christophe Curty (Switzerland), Dr Mark Cesa (Guest, IUPAC Past President); (Front Row) Ms Farhat Waqar (Pakistan), Dr Jonathan E. Forman (OPCW Science Policy Adviser and SAB Secretary), Dr Veronica Borrett (Australia), Professor David Gonzalez (Uruguay), Dr Renate Becker-Arnold (Germany), Professor Mongia Said Zina (Tunisia), Dr Christopher M. Timperley (United Kingdom, SAB Chair), Ambassador Ahmet Uzümcü (OPCW Director-General), Professor Ferruccio Trifirò (Italy), Dr Syed Raza (India), Mr Cheng Tang (China, SAB Vice-Chair), Professor Isel Pascuel Alonso (Cuba), Professor Mohammad Abdollahi (Islamic Republic of Iran).

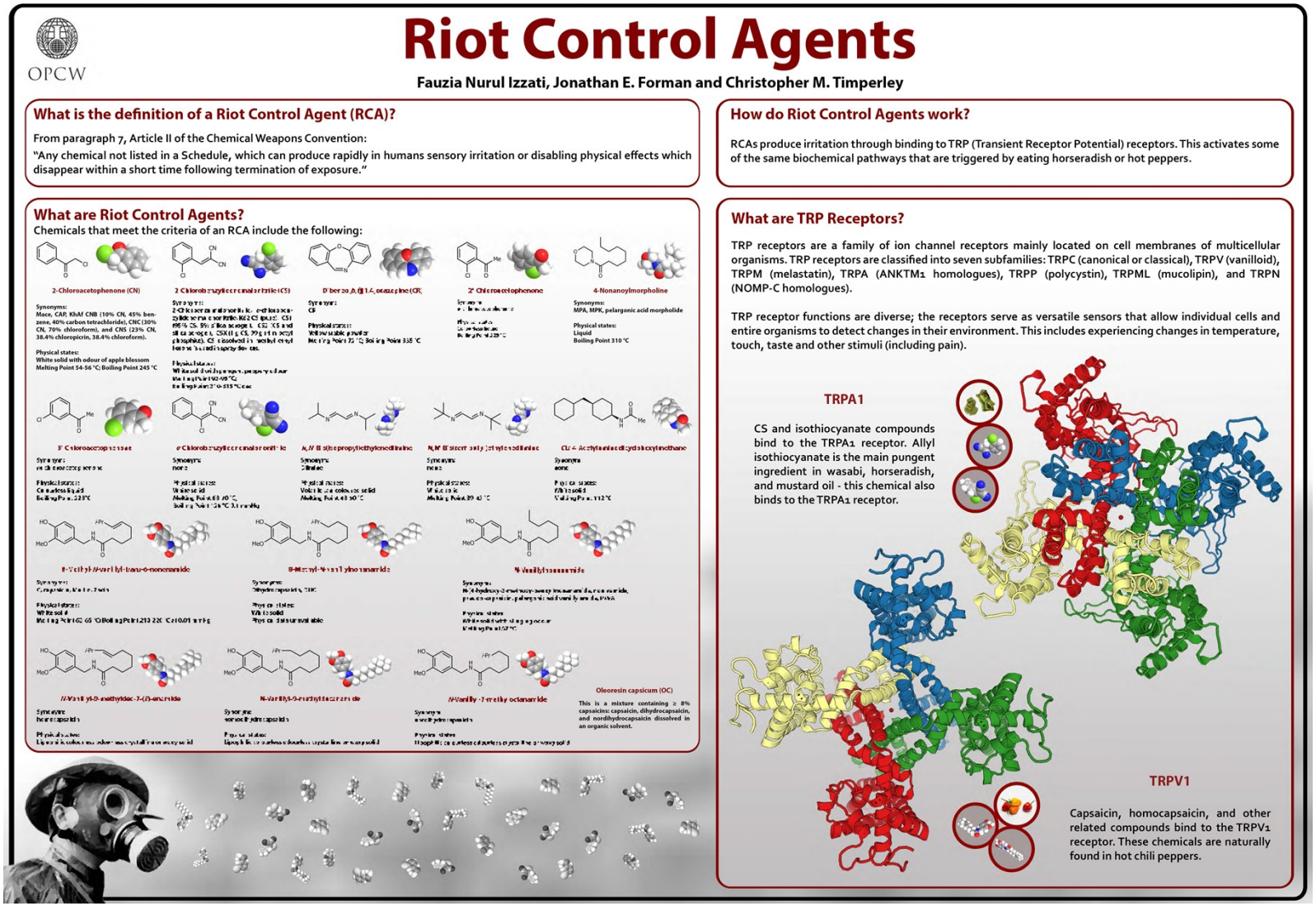
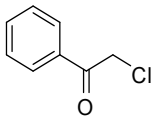
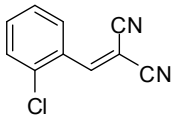
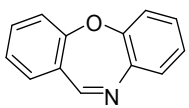
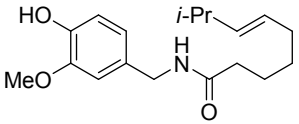
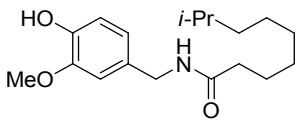
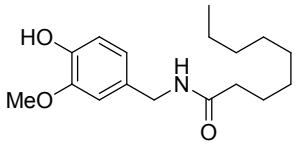
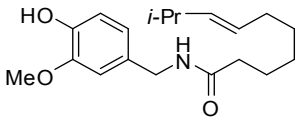


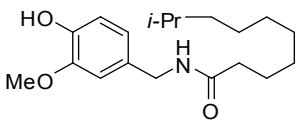
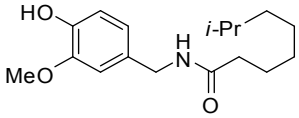
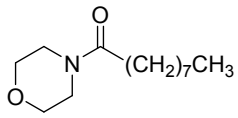
Figure S3. Poster summarising the SAB advice, giving the definition of a RCA, chemical structures, and their action on the human TRPA1 and/or TRPV1 ion channels.

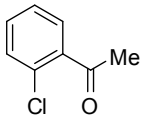
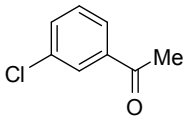
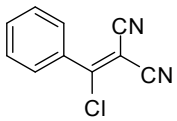
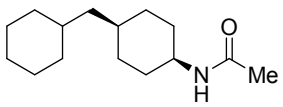
Table S1. List of chemicals that meet the RCA definition[a]

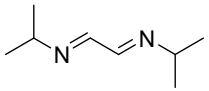
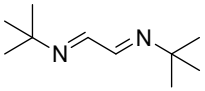
Chemical name and CAS number	Physical state	Notes	Physiological effect
2-Chloroacetophenone (CN)  *Synonyms*: Mace, CAP, KhAf CNB (10% CN, 45% benzene, 40% carbon tetrachloride), CNC (30% CN, 70% chloroform), and CNS (23% CN, 38.4% chloropicrin, 38.4% chloroform)[b] CAS 532-27-4	White solid with odour[1] of apple blossom Mp 54-56 °C Bp 245 °C	Sparingly soluble in water, dissolves in chloroform and other organic solvents. Stable and does not decompose on heating or detonation; its lachrymatory effects are soon lost by condensation to the solid state soon after dispersion: non-persistent and not hydrolysed readily.[1-3]	Immediately irritates eyes (at 0.3 mg/m^3) and upper respiratory passages.[4-25] High concentrations cause irritation, lachrymation, blepharospasm, conjunctivitis, headache, dizziness, tingling and pain in the nose and throat; and burning and itching of tender skin, especially areas wet by perspiration.[6] High concentrations cause blisters with effects similar to sunburn – blisters are harmless and usually disappear in a few hours. Some individuals experience nausea after exposure. ICt_{50} 80 mg/m^3.[2] LCt_{50} 7000 mg min/m^3 from solvent and 14,000 mg min/m^3 from a thermal grenade.[2] Rapid detoxification – effects disappear in minutes. Limit of supportability is 4.5 mg/m^3 in air.[3] One source provides these figures: threshold for eye irritation 1 mg/m^3, effective concentration ICt_{50} 20-50 mg min/m^3, and estimated lethal concentration 8500-25,000 mg min/m^{-3}.[25] Animal studies show that toxic effects of CN are more severe than those of CS.[24] CN has been superseded as an RCA by CS which is safer to use.
2-Chlorobenzylidenemalononitrile (CS)  *Synonyms*: 2-Chlorbenzalmalononitrile, *o*-chloro-benzylidene malononitrile, K62 CS (pure), CS1 (95% CS, 5% silica aerogel), CS2 (CS and silica aerogel), CSX (1 g CS, 99 g trioctyl phosphite). CS dissolved in methyl ethyl ketone is used in spray devices CAS 2698-41-1	White solid with pungent peppery odour Mp 93-95 °C Bp 310-315 °C dec.	CS is the most common RCA, known as "tear gas".[25-35] Different forms have different persistency. CS is sparingly soluble in water (~0.008 weight % at 25 °C). Dispersed as a solid aerosol.[36] Thermal breakdown products have been studied.[37-40]	CS aerosol irritates the eyes, nose, and throat within 20-60 s. It causes temporary disablement: tears, coughing, breathing difficulty, chest tightness, involuntary closing of eyes, dizziness, stinging of moist skin, and mucous formation in the nose.[6,13,14,22,25,37-79] The copious saliva flow induced by CS is said to require 'towels rather than handkerchiefs'.[6] Eye effects at 1-5 mg/m^3. LCt_{50} 61,000 mg min/m^3 and ICt_{50} 10-20 mg/m^3.[2] One source provides these figures: threshold for eye irritation 0.004 mg/m^3, effective concentration ICt_{50} 4-20 mg min/m^3, and estimated lethal concentration 25,000-100,000 mg min/m^{-3}.[25] Exposure to fresh air dissipates effects in 5-10 min, with skin rash persisting ~1 day after heavy exposures. No lasting health effects when used in open areas in high dilution. Rarely, high concentrations reduce lung function temporarily[68] or burn skin that heals rapidly.[69,70] 'Hepatic dysfunction and urinary abnormalities' and allergic dermatitis following repeated exposure of humans have been reported.[6] CS is metabolised in animals[71-76] and humans[77] to products of low toxicity. Some analogues of CS also irritate humans.[78,79]

Dibenzo[*b,f*][1,4]oxazepine (CR)  *Synonyms*: CR CAS 257-07-8	Yellow stable powder[80-89] Mp 72 °C Bp 335 °C	Insoluble in water. Soluble in benzene, chloroform, and carbon tetrachloride. Stable in hot aqueous acid or alkali. CR is dissolved in 80 parts of propylene glycol and 20 parts of water to form a 0.1% CR solution for riot control.[2,4] CR does not degrade in water and persists for a long time in the environment.[86,87] It is thermally stable at temperatures below 200 °C.[89]	Exposure causes symptoms similar to CS.[6,16,18-20,22] CR irritates the eyes (~10 × CS)[90,91] and has a low acute toxicity. It has a wide safety ratio (IC_{50}/TC_{50} > 350). The concentration that irritates the eye is 0.01 mg/m^3 but no irritation is experienced when this falls below 0.001 mg/m^3. IC_{50} 0.15 mg/m^3 and threshold effects on respiratory system at 0.002 mg/m^3 and the eyes at 0.004 mg/m^3.[2,4] CR irritates the oral cavity causing burning pain and malaise, and the nose producing nasal discharge and obstruction. Delivered as an aerosol, CR irritates eyes causing stinging, the feeling of a foreign body in the eye, and involuntary eyelid spasm (blepharospasm). As concentrations increase, severity and duration of symptoms increase; ~0.5 mg CR can immediately irritate the skin and cause it to redden. Blistering is not seen: the redness quickly disappears following washing with water. Information on likelihood of long-term effects after exposure is unavailable, but findings to date give no cause for concern.[92-97]
Oleoresin capsicum Resin containing about 8% capsaicins: capsaicin, dihydrocapsaicin, and nordihydrocapsaicin.[98-101] Capsaicin is main capsaicinoid in chillies, then dihydrocapsaicin. The latter two compounds are about twice as potent to sensory nerves as the minor capsaicinoids: homocapsaicin and nordihydrocapsaicin *Synonyms*: OC CAS 8023-77-6	A mixture of products in an organic solvent[102,103] that degrades naturally in the environment.[104]	Obtained by grinding chilli peppers (e.g. dried *Capsicum frutescenes*), extracting them with an organic solvent, and removing the solvent to give the wax-like oleoresin.[98-105] Pepper spray contains this resin emulsified in aqueous propylene glycol.	In minute quantities, it produces an intense burning sensation of the eyes and tender skin.[21,65] Considered safe, although concentrates cause some respiratory distress, lachrymation, and mucosal burning.[105] Chemical constituents do not appear to be carcinogenic. Sprays in toxic solvents can cause eye damage.[106,107] A study of the inhalation toxicity of oleoresin capsicum from *Capsicum frutescenes var. Nagahari* in mice indicated this mixture, containing 40% capsaicinoids, to be the most suitable and environmentally-friendly compound from a natural source to be used as an ingredient for tear gas munitions.[108] Human volunteer studies have been reported.[109,110] The pharmacology and physiological effects of capsaicin have been reviewed.[111-115] One source provides these figures: threshold for eye irritation 0.002 mg/m^3 and estimated lethal concentration > 100,000 mg min/m^{-3}.[25]
8-Methyl-*N*-vanillyl-*trans*-6-nonenamide  *Synonyms*: C, capsaicin, Moitin, Zacin CAS 404-86-4	White solid Mp 62-65 °C Bp 210-220 °C at 0.01 mmHg	Active component of cayenne pepper, isolated from *Capsicum* species.[116-131] Used in pain management[132-135] and as a pest deterrent. For riot control it has been disseminated in solution[136] or as a particulate smoke,[137] but can thermally degrade.[138]	Stimulates sensory nerves [132,133] to effect changes in systemic blood pressure and respiration.[139] Capsaicin inhalation causes violent coughing,[140-143] nasal irritation,[144] a burning sensation in the mouth,[145] and penetrates the skin[146] to cause erythema and pain.[147] Capsaicin readily enters human tissue and cells due its high lipophilicity.[148-150] Repeat applications to skin result in progressively diminished response until the area becomes insensitive. The metabolism of capsaicin *in vitro* has been studied[151] and its acute toxicity in several animal species measured.[152] Its toxicology is not fully known, but no evidence was found for carcinogenicity or mutagenicity in humans.

8-Methyl-*N*-vanillylnonanamide  *Synonyms*: Dihydrocapsaicin, DHC CAS 19408-84-5	White solid Physical data unavailable	Isolated from *Capsicum* species[98-102] (see the entry on capsicum oleoresin).	Causes eye, skin and respiratory irritation.[4,65] Prolonged or repeated exposure can cause diarrhoea and/or liver damage. Its metabolism has been studied *in vitro*.[151] Its toxicology in humans has not been fully studied. No evidence for carcinogenicity or mutagenicity in humans found.
***N*-Vanillylnonanamide**  *Synonyms*: *N*-(4-hydroxy-3-methoxy-benzyl)nonanamide, nonivamide, pseudocapsaicin, pelargonic acid vanillylamide, PAVA CAS 2444-46-4	White solid with stinging odour Mp 57 °C	Found naturally in chillies,[100,101] but commonly produced commercially by synthesis.[153-164] More heat stable than capsaicin. Used under the name 'PAVA' in pepper sprays and as a food additive in spicy flavourings.	It causes eye, skin and respiratory irritation, skin sensitisation and allergy.[4,65] Inhalation can cause cough, headache, nausea and vomiting. As with other capsaicinoids, the effects disappear within 15-35 min upon removal to fresh air. Taste tests - irritancy tests - have been reported, with no ill-effects being noted afterwards.[154,155] The toxicology in humans has not been fully investigated. No evidence for carcinogenicity or mutagenicity in humans was found.
***N*-Vanillyl-9-methyldec-7-(*E*)-enamide**  *Synonyms*: Homocapsaicin CAS 58493-48-4	Lipophilic colourless odourless crystalline or waxy solid	Accounts for ~1% of the total capsaicinoids in an oleoresin capsicum extract.[98-102]	Biological action similar to oleoresin capsicum of which it is a constituent.[4,65] Modest pungency – approximately half that of capsaicin. It causes a burning sensation in the mouth upon swallowing that fades after a short time. The toxicology in humans has not been fully investigated. No evidence for carcinogenicity or mutagenicity in humans was found.

_N_-Vanillyl-9-methyldecanamide  *Synonyms*: Homodihydrocapsaicin CAS 20279-06-5	Lipophilic colourless odourless crystalline or waxy solid	Accounts for about 1% of the total capsaicinoids in an oleoresin capsicum extract.[98-102]	Biological action similar to oleoresin capsicum of which it is a constituent.[4,65,153] It has high pungency – it has a stronger burning sensation than pepper spray. It causes a burning sensation in the mouth upon swallowing that fades after a short while.
_N_-Vanillyl-7-methyloctanamide  *Synonyms*: Nordihydrocapsaicin CAS 28789-35-7	Lipophilic colourless odourless crystalline or waxy solid	Accounts for about 7% of the total of capsaicinoids in oleoresin capsicum extract.[98-102]	Biological action similar to oleoresin capsicum of which it is a constituent.[4,65,153] It has a high pungency. It causes a burning sensation in the mouth upon swallowing that fades after a short time.
4-Nonanoylmorpholine  *Synonyms*: MPA, MPK, nonanoyl morpholide, pelargonic morpholide CAS 5299-64-9	Liquid[165,166] Bp 310 °C	Used as solvent and co-irritant in CS and CR mixtures. Used alone - low effectiveness, even at the highest permitted concentration (MPA is generally less irritant than capsaicin[167]). Insoluble in water, but soluble in organic solvents (e.g. acetone).	Mixed with CS or CR it causes sensory irritation for 15-30 min.[11,12] Such irritant mixtures are effective against dogs and people under the influence of alcohol and drugs. Human volunteers exposed to 4-nonanoylmorpholine experienced transient effects including: irritation, cough, a burning sensation of the nose (with rhinorrhoea), throat, respiratory tract and eyes, with lachrymation, substernal pain and dyspnoea (difficult or laboured breathing).[6,12] Nausea has been reported and vomiting if the subject has eaten prior to exposure.[6] Headaches sometimes occurred 1 h after exposure, and for one subject the headache persisted for 1 week.[6] Generally, all symptoms were relieved immediately by movement to fresh air. Occasional and mild transient conjunctivitis was sometimes observed. Physical examination of the volunteers after exposure revealed no significant changes.

2'-Chloroacetophenone  *Synonyms*: *o*-chloroacetophenone CAS 2142-68-9	Colourless liquid Bp 229 °C	Commercially available.[153] Almost insoluble in water. Soluble in organic solvents.	Inhalation causes eye and skin irritation, cough, shortness of breath, headache, nausea and vomiting.[153] The toxicology in humans has not been fully investigated. No evidence for carcinogenicity or mutagenicity in humans was found.
3'-Chloroacetophenone  *Synonyms*: *m*-chloroacetophenone CAS 99-02-05	Colourless liquid Bp 228 °C	Commercially available.[153] Almost insoluble in water. Soluble in organic solvents.	Inhalation causes eye and skin irritation, cough, shortness of breath, headache, nausea and vomiting.[153] The toxicology in humans has not been fully investigated. No evidence for carcinogenicity or mutagenicity in humans was found.
α–Chlorobenzylidenemalononitrile  *Synonyms*: None CAS 18270-61-6	White solid Mp 68-70 °C Bp 126 °C/0.1 mmHg	Commercially available.[153] Very sparingly soluble in water. Soluble in common organic solvents.	Exposure causes a burning sensation, cough, wheezing, laryngitis, shortness of breath, headache, nausea and vomiting.[153] The toxicology in humans has not been fully investigated. No evidence for carcinogenicity or mutagenicity in humans was found.
***Cis*-4-Acetylaminodicyclohexylmethane** 	White solid Mp 112 °C	"These compounds have two advantages over currently used riot control agents such as CS and CN. One, the compounds are more potent at low concentrations and two, they provide residual activity over a long period of time".[168]	Potent irritant of mucous membranes. In humans produces a running nose, a choking sensation, and uncontrollable coughing (the *trans* isomer is essentially inactive) which disappear within a short time after termination of exposure. Irritant to mice, dogs and guinea pigs, but these tests were not configured to reveal if there were other toxic effects that caused permanent harm. The *cis* isomer is 10-30 times more effective an animal irritant than the *trans* isomer.[168]

Synonyms: None CAS 37794-87-9 (*trans* CAS 37794-48-2)			
***N,N'*-Bis(isopropyl)ethylenediimine**  *Synonyms:* Diimine CAS *E,E* 28227-41-0 CAS *Z,Z* 185245-09-4 CAS *E,Z* 185245-08-3 CAS no defined stereochemistry 57029-91-1	Volatile tan-coloured solid Mp 48-50 °C	Soluble in organic solvents. Environmental persistence is poor. Disseminated by smoke or explosive munitions.[169]	Compound is a "fast acting riot control agent capable of irritating exposed personnel within minutes of dissemination. Inhalation of as little as 5 mg can lead to irritation and congestion. Diimine is not considered to be a skin irritant, but eye exposure to as little as 15 mg can lead to watering and irritation. The lethal dose to the average man is unknown, but is calculated to be very high; diimine is regarded as non-toxic".[170] The effects last from 5 min to 1 h, and there is little effect on the skin.
***N,N'*-Bis(*tert*-butyl)ethylenediimine**  *Synonyms*: None CAS 30834-74-3 CAS *E,E* 28227-42-1	White solid Mp 39-43 °C	Mentioned in a patent as having "excellent utility in inducing non-lethal physiological action on people subjected to its vapours".[170]	"During the course of handling this chemical during filtration from ether its lachrymatory powers were noted. The experimenter was overcome with severe lachrymation, coughing and discharges from the nose and mouth, along with stomach cramps. The attack occurred even though the reaction and recovery of the product were being carried out in a well ventilated hood. The attack symptoms subsided in about 5 min, and the experimenter proceeded with the rest of the experiment. The experimenter has not observed any side effects from this exposure once the effects of the initial exposure had subsided".[170]

a. *Toxicological measurements*

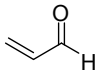
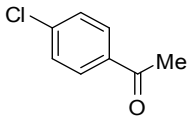
Median lethal dose (LCt_{50}) of a vapour or aerosol: The LCt_{50} is the dose - concentration of the chemical multiplied by the time of exposure - that is lethal to half a population of exposed unprotected personnel at a given breathing rate. It varies with the breathing rate of the person. If individuals breathe quicker, they inhale more of the chemical in the same time, increasing the dose received. The higher the LCt_{50} figure, the less acutely toxic the chemical agent. The ICt_{50} is similarly the dose that incapacitates half a population of exposed unprotected personnel.

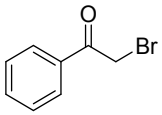
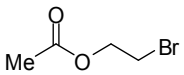
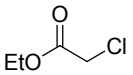
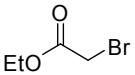
b. CN mixed with chloropicrin (a toxic chemical in Schedule 3A.04 of the Chemical Weapons Convention) would not meet the definition of a RCA as defined by Article II(7) of the Convention.

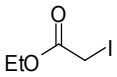
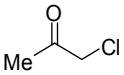
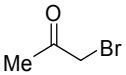
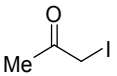
RSC Advances

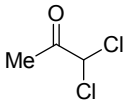
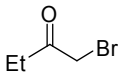
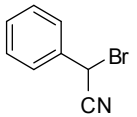
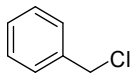
REVIEW

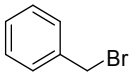
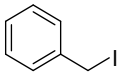
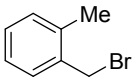
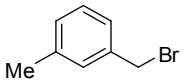
Table S2. List of toxic chemicals that have been researched for use as potential RCAs[a]

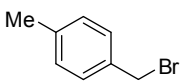
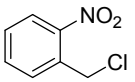
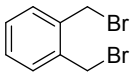
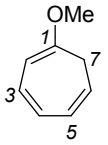
Name and CAS number	Physical state	Notes	Physiological effect
Acrolein  *Synonyms*: Papite, 2-propenal CAS 107-02-8	Colourless or yellow liquid with a pungent odour. Partly miscible with water but miscible with organic solvents. Bp 53 °C	Used in 1916 in World War I. Readily polymerises to an amorphous resin that lacks irritancy. Produced during overcooking of food and is the component in barbeque smoke[171] that has a piercing disagreeable acrid smell and irritates the eyes.[171-175] Acrolein reacts avidly with proteins.[175]	One source states that acrolein is detectable by the human eyes, nose, throat or lower respiratory tract at a concentration of 2.8 mg/m^3 and that some individuals can detect it at even lower concentrations.[172] Irritation of the eyes and nose is prominent at a concentration of 7.7 mg/m^3. Lachrymation does not become prominent until the concentration reaches 10 mg/m^3.[172] Elsewhere it is stated that the minimum concentration causing lachrymation in humans is 7 mg/m^3 and that the limit of insupportability is 50 mg/m^3.[3] Another source states that humans cannot tolerate concentrations of acrolein in air of 5 mg/m^3 or higher for > 2 min, while at > 20 mg/m^3 the outcome may be lethal.[173] Low concentrations irritate the eyes, skin, and mucous membranes, and can cause dose-dependent delayed lung damage (pulmonary oedema).[174]
4'-Chloroacetophenone  *Synonyms*: *p*-chloroacetophenone CAS 99-91-2	Colourless liquid. Bp 232 °C	Commercially available.[153] Practically insoluble in water, soluble in organic solvents.	Highly irritating to the eyes and mucous membranes.[174] Its toxicological profile is the same for 2- and 3-chloroacetophenone except that this isomer may be fatal if inhaled.[153]

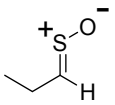
2-Bromoacetophenone  *Synonyms*: ω–bromoacetophenone CAS 70-11-1	White solid with an irritating odour that decomposes on exposure to light. Mp 50 °C[176] Bp 260 °C dec.	Commercially available[153] with similar physiological properties to 2-chloro-acetophenone (see entry in Table S1).	The lachrymatory power of 2-bromoacetophenone is stated to be less than that of 2-chloroacetophenone; however it is still a potent lachrymator.[3,174] It is highly irritating to the skin, eyes and mucous membranes, and can cause severe eye damage and skin burns.[153] This vesicant action appears, from the limited data available, to be greater than that of 2-chloroacetophenone.
2-Bromoethyl acetate  *Synonyms*: Bromoethyl acetate CAS 927-68-4	Colourless liquid Bp 159 °C	Available commercially containing <3% acetic anhydride.[153] Combustible and emits toxic fumes when on fire.	Extremely destructive to tissue of the mucous membranes and upper respiratory tract, eyes, and skin, causing burns.[153] Inhalation causes cough, shortness of breath, and headache. No evidence of a carcinogenic effect; a possible human mutagen, but relevant information is scarce.
Ethyl chloroacetate  *Synonyms*: Ethyl 2-chloroacetate CAS 105-39-5	Colourless liquid having a fruity odour Bp 144 °C	Available commercially. Used to a limited extent in World War I.[3] Manufactured for the preparation of two other substances with increased 'aggressiveness' (i.e. irritancy): ethyl bromoacetate and ethyl iodoacetate.	Lachrymator. Toxic in contact with skin and if inhaled or swallowed. The liquid or vapour can cause serious eye damage.[153]
Ethyl bromoacetate  *Synonyms*: Weisskreuz, White Cross CAS 105-36-2	Colourless flammable liquid with a fruity odour Bp 159 °C	Ethyl bromoacetate was the first chemical employed in warfare as a vapour (at the end of 1914 during World War I).[3] Used in hand grenades and shells. Because of its relatively high boiling point and low volatility, it could be used in shells without producing a visible cloud on bursting. Once used in joke-type toys before it was banned for this purpose and has also been used illicitly as a preservative in alcoholic beverages.	Highly irritating to human eyes and nose.[177] Extremely destructive to the mucous membranes and upper respiratory tract, eyes, and skin; the neat liquid can cause eye and skin burns. Inhalation of vapour can cause coughing, wheezing, inflammation and oedema of the respiratory passages, a burning sensation, shortness of breath, headache, nausea and vomiting. Limit of insupportability for a human is 40 mg/m^3 in air.[3] Minimum concentration capable of irritating the eyes is 10 mg/m^3. The compound is a toxic alkylating agent and may be fatal if inhaled in sufficient quantity.

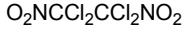
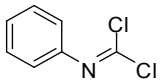
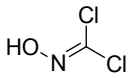
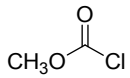
Ethyl iodoacetate  *Synonyms*: KSK CAS 623-48-3	Dark brown liquid and invisible vapour with a fruity smell resembling "pear drops" Bp 179-180 °C	Ethyl iodoacetate was used in World War I in shells, especially mixed with chloropicrin (10%).[3]	Stinging of eyes: immediate lachrymation and blepharospasm. Irritates nasal mucosa but usually not the skin when encountered as the vapour; liquid splashes may irritate the skin. Limit of insupportability is 15 mg/m^3 in air.[3] Minimum concentration that irritates the eyes is 1.4 mg/m^3. Toxic alkylating agent. May be fatal if inhaled in sufficient quantity.
Chloroacetone  *Synonyms*: CA, A-Stoff, Tonite CAS 78-95-5	Liquid with a very pungent odour Mp -45 °C Bp 120 °C dec.	Used in World War I mixed with bromoacetone (1:4, viz Martonite). Prepared by the action of chlorine on diketene or acetone.[174] Darkens and resinifies on prolonged exposure to light. May be stabilised by addition of 0.1% water or 1.0% calcium carbonate.	Intensely irritating to eyes, skin, and mucous membranes. Eye contact with ~1 mg can cause pain and irritation.[169] Lowest concentration irritating the eyes is 18 mg/m^3 in air.[3] Skin contact with 15-50 mg can produce redness, rash, itching, and/or local discomfort.[169] A lethal dose by inhalation can be ~10,000 mg. It is a toxic alkylating agent and may be fatal if inhaled in sufficient quantity.
Bromoacetone  *Synonyms*: BA, BC, B-Stoff CAS 598-31-2	Liquid with a pungent odour Bp 137 °C	Used in World War I in shells and hand grenades and prepared by bromination of acetone.[174] Turns a violet colour rapidly even in the absence of air. Sparingly soluble in water, soluble in many organic solvents.	Violent lachrymator. Lowest concentration irritating eyes is 1 mg/m^3.[3] Inhalation of 2-5 mg can cause coughing, nose and throat irritation.[169] Skin contact with 20-30 mg can produce irritation, itching, swelling and discomfort. Skin exposure to 50-100 mg may lead to blisters. Lethal dose through inhalation is 2000-5000 mg. An alkylating agent that may be fatal if inhaled in sufficient quantity.
Iodoacetone  *Synonyms*: 2-iodo-2-propanone CAS 3019-04-3	Pale yellow liquid Bp 163 °C	Used to produce other organic chemicals.	Potent lachrymator[178] and strong irritant that is toxic by inhalation and skin absorption. An alkylating agent that may be fatal if inhaled in sufficient quantity.

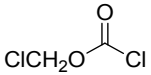
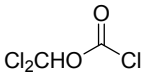
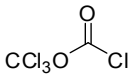
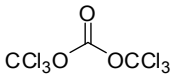
1,1-Dichloroacetone  *Synonyms*: 1,1-dichloro-2-propanone CAS 513-88-2	Colourless liquid Bp 117-118 °C	Commercially available.[153]	Fast-acting irritant capable of causing casualties within minutes.[169] Eye contact with ~3 mg can cause pain. Skin contact with 12-50 mg can cause redness, rash, itching, and/or local discomfort. Inhalation of ~5 mg can cause severe nose and throat irritation and discomfort. Lethal dose through inhalation can be ~10,000 mg. A toxic alkylating agent that may be fatal if inhaled in sufficient quantity.[153]
1-Bromo-2-butanone  *Synonyms*: bromomethyl ethyl ketone CAS 816-40-4	Colourless liquid Bp 145-146 °C	Employed in World War I in place of bromoacetone whose production during the war was limited by a need to reserve acetone for the explosives industry.[3]	Causes a burning sensation, cough, wheezing, laryngitis, shortness of breath, headache, nausea, and vomiting. Harmful by inhalation, in contact with skin, and if swallowed. Minimum concentration irritating the eyes is 1.6 mg/m^3.[3] Limit of insupportability 11 mg/m^3. Alkylating agent that may be fatal if inhaled in sufficient quantity.
Bromobenzyl cyanide  *Synonyms*: BBC, CA, Calmite, Larmine CAS 5798-79-8	Yellow solid; crude material used in World War I was a heavy yellow liquid with a penetrating bitter-sweet smell of rotting fruit Mp 25 °C Bp 242 °C dec.	One of first tear agents used in World War I. Less effective than 2-chloroacetophenone (CN) and viewed as obsolete. Decomposes when heated, does not burn; at > 242 °C it gives PhC(CN)=C(CN)Ph and hydrobromic acid. Bromobenzyl cyanide is insoluble in water, soluble in organic liquids; slow rate of hydrolysis, giving complex products.[3]	Irritating to skin and eyes.[6,179] Relatively non-toxic. Estimated LCt_{50} is 8000-11,000 mg min/m^3 and ICt_{50} ~30 mg min/m^3. Detoxified rapidly at low doses. Minimum concentration causing lachrymation is 0.3 mg/m^3 in air and the limit of insupportability is 30 mg/m^3.[3,169] Inhalation of 15-30 mg can cause severe irritation, coughing, sore throat, congestion, and nasal discharges within minutes. Lethal dose through inhalation ranges from 2000-6000 mg. Inhalation of ~900 mg per litre of air over 30 min can result in death.
Benzyl chloride  *Synonyms*: α-chlorotoluene CAS 100-44-7	Colourless liquid with an unpleasant odour Bp 179 °C	Used in World War I. Made by chlorination of toluene. Soluble in and fairly stable to water; it is decomposed by prolonged boiling in water (to benzyl alcohol and hydrochloric acid).	Intensely irritating to skin, eyes and mucous membranes.[180,181] Limit of insupportability: 85 mg/m^3 of air.[3] Overexposure causes irritation (eyes, skin, and nose), weakness, irritability, headache, skin damage, and lung damage.[174] Toxic alkylating agent: may cause permanent injury or death after short exposures. Can cause nerve damage and is carcinogenic.

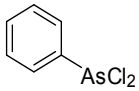
Benzyl bromide  *Synonyms*: Cyclite, T-Stoff CAS 100-39-0	Colourless lachrymatory liquid with an aromatic odour[182] Mp -3 to -1 °C Bp 198-199 °C	Used in World War I. Made from bromine, toluene and ultraviolet light, or hydrobromic acid and dibenzyl ether. Insoluble, and slowly decomposed, in water, but soluble in organic solvents.	Intensely irritating to skin, eyes, and mucous membranes. Minimum concentration irritating the eyes is 4 mg/m^3.[3] Limit of insupportability is 60 mg/m^3 in air. Large doses depress the central nervous system.[174] Can damage permanently lungs, liver, kidneys and nervous system through its alkylating action, and may be fatal if inhaled in sufficient quantity.
Benzyl iodide  *Synonyms*: Fraisinite CAS 620-05-3	White intensely lachrymatory solid[183-185] Mp 24 °C Bp 226 °C dec.	One of the most potent lachrymators. Allegedly used in 1915 in World War I. Insoluble in water, soluble in organic solvents. Barely decomposed by water.	Irritates skin, eyes, nose and throat, causing coughing and wheezing. Minimum concentration irritating eyes is 2 mg/m^3 in air.[3] Maximum concentration supportable for not more than 1 min is 25-30 mg/m^3 in air. An alkylating agent that may be fatal if inhaled in sufficient quantity.
2-Methylbenzyl bromide  *Synonyms*: *o*-xylyl bromide CAS 89-92-9	White solid with odour when dilute of elder blossom Mp 21 °C Bp 223-234 °C	Commercially available. Mixture with 3- and 4-isomers used in World War I and known as "T-Stoff". Practically insoluble in water, soluble in organic solvents.[174]	Powerful lachrymator.[186,187] Minimum concentration capable of irritating is 1.8 mg/m^3 in air. Limit of insupportability is 15 mg/m^3.[3] May be fatal if inhaled, swallowed, or absorbed through the skin, principally through its alkylating action.
3-Methylbenzyl bromide  *Synonyms*: *m*-xylyl bromide CAS 620-13-3	Colourless liquid Mp not available Bp 212-215 °C dec.	Commercially available. Mixture with 3- and 4-isomers used in World War I and known as T-Stoff. Practically insoluble in water, soluble in organic solvents.[174]	Powerful lachrymator. Minimum concentration capable of irritating is 1.8 mg/m^3 in air. Limit of insupportability is 15 mg/m^3.[3] May be fatal if inhaled, swallowed, or absorbed through the skin, principally through its toxic alkylating action.

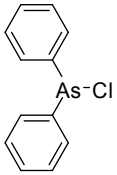
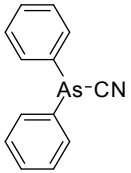
4-Methylbenzyl bromide  *Synonyms*: *p*-xylyl bromide CAS 104-81-4	Colourless liquid Mp 38 °C Bp 218-220 °C	Commercially available. Mixture with 3- and 4-isomers used in World War I and known as T-Stoff. Practically insoluble in water, soluble in organic solvents.[174]	Same as above. May be fatal if inhaled, swallowed, or absorbed through the skin, principally through its toxic alkylating action.[3]
2-Nitrobenzyl chloride  *Synonyms*: Cedenite CAS 612-23-7	White solid Bp 48-49 °C	Commercially available. Used in World War I mixed with the isomer 4-nitrobenzyl chloride under the name of "Cedenite".	More powerful irritant than benzyl chloride.[3] Lower limit of irritation is 1.8 mg/m^3 in air. The compound is vesicant and can cause severe skin burns.
1,2-Bis(bromomethyl)benzene  *Synonyms*: *o*-xylylene dibromide CAS 91-13-4	White solid Mp 91-92 °C[188]	Commercially available. Impurity in methylbenzyl bromide (xylyl bromide). Mixture (*o*, *m*, and *p*) used for chemical warfare during World War I.[3]	A powerful and persistent lachrymator:[189,190] "the vapours attack the eyes horribly".[191] Causes severe skin burns and eye damage.[153] A potent alkylating agent that can cause death if inhaled in sufficient quantity.
1-Methoxy-1,3,5-cycloheptatriene  *Synonyms*: CH, CHT, GG, MCHT, tropilidene	Colourless mobile liquid with an irritating odour Bp 44 °C/10 mmHg	Researched in the 1980s as a sensory irritant. Formed by heating the 7-methoxy isomer, with the 3-methoxy isomer being an intermediate, and usually not obtained pure, but as a mixture with both these isomers.[192-196] The 1-methoxy isomer predominates as it is the most stable.[197] Miscible with organic solvents and in water (0.6 mg/ml at 16 °C). Dispersal device for forcing egress of humans from spaces has been patented.[198]	1-Methoxy compound (CH) is a potent lachrymator - other isomers less active - and at 20 mg/m^3 causes powerful irritation within 1 min sufficient to cause flight from the contaminated area.[198] Two subjects exposed to 100 mg/m^3 wearing clothes and a gas mask reported a strong burning sensation under the arms, in the crotch and other sweaty parts of the body. Both subjects were forced to leave the zone within 20 min. When the subjects were exposed to fresh air, the compound evaporated from clothing within minutes and the skin condition abated within 20 min. Slight reddening of the skin disappeared within 1 h. Other trials showed CH to cause lachrymation, temporary eye closure, blurred vision 'lasting several minutes after exposure' with

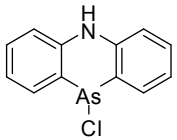
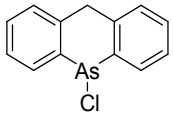
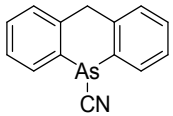
CAS 1728-32-1			'complete resolution by 15 min after leaving the chamber'.[6] Dermal irritation also reported.[6] No apparent effect on urine and blood, and study of CH on human cells indicated no evidence for a carcinogenic or mutagenic effect. Studies on small mammals however indicate some carcinogenic potential.[199,200]
(*Z*,*E*)-Propanethial *S*-oxide  *Synonyms*: *syn*-Propanethial *S*-oxide, thiopropanol *S*-oxide CAS 32157-29-2	Pale yellow unstable liquid	Lachrymator released upon slicing onions (*Allium cepa*) due to the action of the enzyme allinase on *S*-(1-propenyl)cysteine sulfoxide present in onions.[201] Can be produced by synthesis but degrades quickly to non-lachrymatory product/s. A related lachrymator, *syn*-butanethiol *S*-oxide has been found in another onion species (*Allium siculum*).[202]	Intense and painful lachrymator, but unstable - it decomposes quickly at room temperature.[203-205] Effects are temporarily disabling and rapidly reversible upon entering fresh air. It is unlikely the compound could be isolated in large enough quantities and stabilised sufficiently long enough to constitute a riot control agent, but this possibility in future cannot be discounted based upon an analysis of the scientific literature to date. Toxicity data on it and its decomposition products are unavailable.
Trichloronitromethane CCl_3NO_2 *Synonyms*: Acquinite, chloropicrin, chloropicrine, G8, Klop (mixed with chlorine), klorpikrin, NC, nitrochloroform, PG (mixed with phosgene), picfume, larvicide 100, PS CAS 76-06-2	Colourless volatile liquid with an intense pungent and stinging odour[206] Bp 112 °C	Used extensively as a chemical warfare agent in World War I. Now used as an insecticide and fumigant to disinfect cereal and grain,[207] and in synthesis (especially to make methyl violet dye). First prepared from picric acid and bleach powder and later by addition of sodium hypochlorite to nitromethane.[3] Practically insoluble in water (0.16 g/l at 25 °C).[174] Miscible with most organic solvents. Semi-persistent.	Cumulative toxicity. Causes irritation of eyes, skin, and respiratory system, lachrymation, cough, lung damage, nausea, vomiting.[6,174] At 8 mg/m^3 in air, can be detected; at 16 mg/m^3, produces coughing and lachrymation; and at 120 mg/m^3, 30 to 60 min exposure can be fatal.[3,207] Inhalation of ~5 mg can cause irritation and pain to nose and throat.[169] Eye contact with ~3 mg, and skin contact with ~10 mg, can cause irritation and pain. Lethal dose through inhalation is 2000-2500 mg. Lowest irritant concentration is 9 mg/m^3 for 10 min and LCt_{50} is 2000 mg min/m^3.[2] Induces sister chromatid exchanges in cultured human lymphocytes but is not considered carcinogenic.[208] Chloropicrin is listed in Schedule 3A.04 of the Chemical Weapons Convention.
Tribromonitromethane CBr_3NO_2 *Synonyms*: Bromoacquinite, bromopicrin, nitrobromoform CAS 464-10-8	White solid or semi-liquid with a strong biting odour Mp 10 °C Bp 127 °C/118 mmHg	Patented as a fumigant and soil sterilant.[209] Can persist in the environment for several days to weeks. Disseminated from aerosols, smoke generating or explosive munitions, or sprayed in solvents.[169]	One reference states: "bromopicrin is a violent riot control agent, which has been banned by most agencies".[169] It is similar to trichloronitromethane in its toxic action. It is a powerful irritant. Eye contact with ~1 mg can irritate. Inhalation of 5-10 mg can cause nose and throat irritation with congestion within minutes.[169] Lethal dose through inhalation is ~1200 mg, but usually ranges from 1500-2200 mg. Skin contact with ~4 mg can irritate, and 10-25 mg can cause sores and lesions.

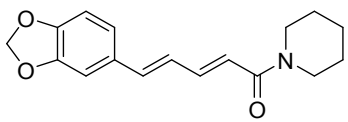
1,1,2,2-Tetrachloro-1,2-dinitroethane  *Synonyms*: None CAS 67226-85-1	White solid Mp 142 °C	Insoluble in water. Soluble in organic solvents (e.g. benzene, ethanol, ether, and ligroin).	One reference states: "tetrachlorodinitroethane is toxic to mice at one-sixth the concentration for chloropicrin. It produces lachrymation in man at one-eighth the concentration that chloropicrin does. It is not stable when exploded in a three-inch shell, but would probably stand up satisfactorily if dissolved in chloropicrin."[210]
Phenylimidocarbonyl chloride  *Synonyms*: Green Cross I, K-Stoff, phenyl carbylamine chloride; phenylimidophosgene CAS 622-44-6	Pale yellow, pungent liquid with an onion-like odour[211-213] Bp 209-212 °C	From reaction of chlorine with phenyl isothiocyanate; 4- and 2,4-di-chlorinated products that co-form have similar properties, but are less irritant. The phenylimidocarbonyl chloride is obtained by distillation. Used during World War I in projectiles with sulfur mustard to mask garlic odour of the latter. Insoluble in water and soluble in most organic solvents. Persistent.	The property of producing in animals corneal ulcers, which do not, however, tend to permanent blindness, undoubtedly identifies the compound as the "blinding gas" of World War I. Physiological symptoms are mainly those from a mild lung irritant: nausea, sometimes vomiting, throat soreness, chest tightness, and stomach pain.[214] Cough and bronchitis develop later. Lachrymation is not prominent. It irritates the lung, nose, eyes and throat. 3 mg/m^3 causes involuntary weeping and ~800 mg/m^3 for 1-2 min harms respiratory organs, and 3 mg irritates.[48] Limit of insupportability is 30 mg/m^3 in air.
Phosgene oxime  *Synonyms*: CX, Fosgen oksim, dichloroformoxime CAS 1794-86-1	White solid with a penetrating odour Mp 40 °C Bp 129 °C dec.	Prepared from trichloronitromethane and hydrochloric acid. One of the most violent irritants known. Extremely unstable though, and unlikely to be used militarily. Soluble in water and only slowly hydrolysed.	Solid or liquid (melted or dissolved in organic solvents) has a severe destructive and burning action on the lung, skin and eyes.[215] Inhalation toxicity similar to phosgene. Skin contact causes immediate itching and pain. Vapour in the eye causes immediate lachrymation. Corneal damage develops over 24 h and dims vision. Irritating concentration Ct is 0.17 mg min/m^3 and intolerable Ct is 3 mg min/m^3. Lowest irritant concentration after a 10 s exposure is 1 mg/m^3.[3] Effects become unbearable after 1 min at 3 mg/m^3. Estimated LCt_{50} is 3200 mg min/m^3.
Methyl chloroformate  *Synonyms*: none found CAS 79-22-1	Colourless liquid with an irritating odour Bp 71 °C	Available commercially. Used in World War I mixed with other chemicals.[3] Because of its strongly irritant properties it has been used in insecticidal preparations*, e.g.* in "Zyklon B" with hydrocyanic acid. Hydrolysed readily by cold water.	Powerful lachrymator.[153] Causes severe skin burns and eye damage. Harmful if swallowed and in contact with the skin, and fatal if inhaled.[216] Its physiological effects are very similar to those of phosgene, causing a delayed and irreversible lung damage (pulmonary oedema). The delay from inhalation of a lethal dose to death can be in the order of days.

Chloromethyl chloroformate  *Synonyms*: K Stoff, Palite CAS 22128-62-7	Colourless liquid with an irritating odour Bp 107 °C	Commercially available. A mixture with dichloromethyl chloroformate was used in World War I under the name "K Stoff" and "Palite".[3] Hydrolysed readily by cold water.	Powerful lachrymator.[3] Minimum concentration producing lachrymation is 2 mg/m^3 in air. Limit of insupportability is 50 mg/m^3 in air. Causes severe skin burns and damage, and toxic if inhaled.[153] The toxicity to humans is 'probably of the same order as that of phosgene' and death can result from inhalation of a sufficiently large dose, through irreversible lung damage and an incurable build-up of fluid on the damaged tissue (pulmonary oedema).[217]
Dichloromethyl chloroformate  *Synonyms*: K Stoff, Palite CAS 22128-63-8	Colourless liquid with an intensely irritating odour Bp 110 °C	Commercially available. Used mixed with chloromethyl chloroformate in World War I under name of "K Stoff" and "Palite".[3] Hydrolysed readily by cold water.	Less irritating than methyl chloroformate, but more toxic. Limit of insupportability is 75 mg/m^3 in air. Inhalation of a sufficient dose can cause a life-threatening and delayed pulmonary oedema, which in severe cases can lead to death.
Trichloromethyl chloroformate  *Synonyms*: diphosgene, Perstoff CAS 503-38-8	Colourless liquid with a smell of new mown hay Bp 127-128 °C	Not easily hydrolysed by water and therefore semi-persistent.	Action similar to phosgene. Lethal on inhalation, causing cough, lachrymation, chest pain, difficulty breathing, and delayed lung damage. It irritates the throat at a concentration of 13 mg/m^3 and causes coughing at a concentration of 25 mg/m^3.[218] Inhalation toxicity is cumulative.[3] Irreversible effects appear within 0-24 h depending on inhaled dose. The LCt_{50} is 3200 mg min/m^3 (same as phosgene). Its vapour is heavier than air and remains in low-lying areas. It has no effect on the skin.
Bis(trichloromethyl) carbonate  *Synonyms*: triphosgene CAS 32315-10-9	White solid Mp 78-79 °C Bp 205-206 °C	Not easily hydrolysed by cold water and therefore semi-persistent.[153]	Irritant vapour but physiological action similar to phosgene. Lethal upon inhalation, causing cough, lachrymation, chest pain, difficulty breathing, and delayed lung damage. Effects appear in 0-24 h depending on dose. LCt_{50} is 3200 mg min/m^3 (same as phosgene).[3]

Methyldichloroarsine $MeAsCl_2$ *Synonyms*: methyldick, MD, Medikus CAS 593-89-5	Colourless volatile liquid with a burning odour Bp 132-133 °C	Probably used in World War I in small quantities.[3] Hydrolysed rapidly by water.	Liquid and vapour irritate eyes, respiratory tract and damage the lung.[219] Exposure of skin to vapour and liquid may produce severe blistering. Inhalation of vapour and liquid may lead to systemic toxicity and death (the toxicity of methyldichloroarsine to animals approaches that of phosgene).[220] It can cause irreversible corneal damage. Lower limit of irritation is 2 mg/m^3 of air.[3] Maximum concentration a normal person can breathe for no more than 1 min is 25 mg/m^3 in air. Vapour has a vesicant action akin to sulfur mustard that presents several hours after exposure.
Ethyldichloroarsine $EtAsCl_2$ *Synonyms*: ethyldick, ED CAS 598-14-1	Colourless liquid with a fruity but biting and irritating odour Bp 153 °C	Widely used in projectiles in World War I as a volatile agent with a short duration of effectiveness that acted more quickly than diphosgene or sulfur mustard. It was used as a delayed casualty agent that caused vomiting and blistering.[3] Hydrolysed rapidly by water.	Extremely irritating action on nose, eyes, and throat, and causes painful skin wounds.[219] The vapour causes profound respiratory difficulties, faintness, prolonged paralysis, and anaesthesia of extremities. Minimum concentration capable of perceptible irritant action is 1.5 mg/m^3 in air.[3] Maximum concentration supportable by a human for ~1 min is 5-10 mg/m^3. Vesicant action on skin is perceptible at 1 mg/m^3. ICt_{50} and LCt_{50} are 25 and 3000-5000 mg min/m^3.[48]
Phenyldichloroarsine  *Synonyms*: dichlorophenylarsine, MA, PD, Pfiffikus, Sternite CAS 696-28-6	Colourless liquid that turns yellow gradually Bp 255 °C	Used in World War II and often found in abandoned “Red Canister” munitions.[221]	Instant irritation and pain in eyes, nose, throat and respiratory tract. Effects include sneezing, coughing, salivation, nasal congestion, and suffocation. These persist 5-20 min after retreat. It also produces systemic effects: headache, perspiration, chills, nausea, vomiting, cramps, and depression, malaise and misery. These appear ~30 min after exposure and persist for several hours. 1.0-2.5 mg/m^3 irritates nose and throat; 50 mg/m^3 is intolerable in 30 s.[219] ICt_{50} is 16 mg min/m^3 as vomiting agent.[3] LCt_{50} is 2600 mg min/m^3. Maximum concentration a human can support for ~1 min is 16 mg/m^3 of air.[3] Phenyldichloroarsine is a vesicant upon contact with human skin[222-224] and a marked swelling occurs within 15 min and increases throughout a period of from 6 to 8 h. It is accompanied by a rapid hyperaemia (an excess of blood in the vessels supplying then skin) and from 3 to 6 h by extensive haemorrhages.[224] The exposed area becomes white and hard, appearing like dead skin. The hardening of the skin and the translucent white colour gradually replace the capillary haemorrhage until only a small hyperaemia area is left surrounding the burn.

Diphenylchloroarsine (DA)  *Synonyms*: Clark I CAS 712-48-1	White solid Mp 41-45 °C Bp 333 °C dec.[3]	Used in World War II and caused surprise as it was able to penetrate the respirators then in use.[3] Nowadays found in old and abandoned[221,225-227] and sea dumped[228,229] munitions.	Produces irritation, burning and pain in the eye, nose, throat and respiratory tract. Effects include sneezing, coughing, salivation, congestion, and suffocation.[3,219,230-238] 1.5-2.5 mg/m^3 irritates the nose and throat; 50 mg/m^3 is intolerable in 30 s. Other irritancy data for humans: 0.12 mg/m^3 (just detectable), 0.24 mg/m^3 (nasal irritation after 2 min), 0.6 mg/m^3 (induced marked nasal irritation without sneezing), and 1.2 mg/m^3 (became intolerable, with or without the eyes protected, and produced severe irritation of the respiratory tract).[234] The ICt_{50} for humans is 22-150 mg min/m^3 and the LCt_{50} is 13,000 mg min/m^3.[3] Diphenylchloroarsine also produces systemic effects: headache, perspiration, chills, nausea, vomiting, cramps, depression and malaise. Systemic effects can start about 30 min after the beginning of exposure and persist for several hours. Solid and liquid material can cause small blisters on the skin. Ingestion may cause severe injury and death. No abnormal sensation was felt when a saturated solution of diphenylchloroarsine was applied to the flexor surface of the human forearm for 10 to 20 min.[234] Afterwards, the skin was coloured red and a papular erythema had developed. A warm solution applied for 10 min produced a more marked erythema, and after 30 h, a blister formed. After an application lasting 30 min, the results were 'similar but more intense'. Diphenylchloroarsine is less vesicant in action than either phenyldichloroarsine or sulfur mustard.[2,3,234]
Diphenylcyanoarsine (DC)  *Synonyms*: Clark II CAS 23525-22-6	White solid with odour of garlic/bitter almonds Mp 32-35 °C Bp 377 °C calc.[3]	Used towards the end of World War II alone and mixed with diphenylchloroarsine.[3] Found in abandoned "Red Canister" munitions[221] and in old munitions[225-227] including those historically dumped at sea.[228,229] Combustible vapours can form an explosive mixture with air.	Irritates the nose and provokes sneezing.[219,230-238] Inhalation, ingestion or skin contact may cause severe injury or death. Minimum concentration detectable by odour is 0.005-0.010 mg/m^3 in air.[3] A human can tolerate a maximum concentration of 0.25 mg/m^3 for no more than 1 or 2 min. ICt_{50} 30 mg min/m^3 for a 30 s exposure and LCt_{50} 10,000 mg min/m^3. Nearly impossible to build up a vapour concentration of DC that would be lethal in a short time, but the compound once it enters the body can cause systemic poisoning.

10-Chloro-5,10-dihydrophenarsazine  *Synonyms*: Adamsite, DM CAS 578-94-9	Bright yellow ('canary yellow') crystalline solid Mp 195 °C Bp 410 °C calc.[3]	Used in World War I.[3] Insoluble in water and difficultly soluble in many organic solvents. When heated it forms an inflammable odourless vapour that is invisible except when viewed near the source. Non-persistent.[3]	Produces sneezing, burning and an aching pain in the chest, throat, nose, and gums in 1-5 min.[11,12] Recovery usually rapid, but irritant effects may increase for several minutes in fresh air. Systemic effects include headache, perspiration, chills, nausea, vomiting, and cramps.[12] These start about 30 min after the beginning of exposure and persist for several hours.[219] 0.1-2.5 mg/m^3 irritates nose and throat, 50 mg/m^3 is intolerable in 30 s. ICt_{50} is estimated as 22-150 mg min/m^3 and LCt_{50} as 13,000 mg min/m^3. Hydrolyses in the body to phenarsazine oxide which is hepatotoxic (at least in rats[239]).
10-Chloro-5,10-acridarsine  *Synonyms*: Excelsior CAS 25093-02-1	Pale yellow solid Mp 110 °C[240]	Potent sternutator and analogue of Adamsite developed during World War II and researched afterwards as a potential chemical warfare agent.[240]	Potent skin irritant[237] and said to be 10 times as active an irritant as diphenylcyanoarsine (but this may be an exaggeration; the primary data this claim was based on could not be located). 2 mg/m^3 is intolerable after 1 min. Human toxicology apparently has not been studied (no information was found); the compound is expected to have systemic toxicity like the other arsenicals.[2,3] The dust in air causes a severe burning of the face, the lips and the tongue.[235,237,241]
5(10*H*)Acridarsinecarbonitrile  *Synonyms*: Arsacridine cyanide CAS 23395-81-5	White solid Mp 115 °C[240]	Researched as a sternutator after World War II like Excelsior.[240]	A sensory irritant said to be more powerful in its sternutatory action - nasal irritancy - than its 10-chloro analogue Excelsior.

Trialkyl-lead compounds $XPbR_3$ R = Me, Et, *n*-Pr X = leaving group e.g. Cl, Br, I, $MeC_6H_4SO_2NH$ CAS various numbers	White solids	Study of the sternutatory properties of organolead salts was conducted during World War II.[242-248] Those having the generic structure shown left produced sternutation.	Irritated nose, throat and chest of human volunteers in chamber trials. Activity decreased R = *n*-Pr > Et > Me and potent compounds were obtained when X was a group derived from an organic acid.[242-248] Sternutation wore off rapidly on retreating from a contaminated atmosphere. Lead salts cause neurological damage. Triethyl-lead fluoroacetate $FCH_2CO_2PbEt_3$ has sternutatory and convulsant action; it is poisonous.[247]
Piperine  *Synonyms*: piperoylpiperidine CAS 94-62-2	Beige-yellow solid Mp 130 °C	Principal irritant occurring naturally in black pepper,[249-257] used as a spice throughout the world.[258-268]	Irritates the nose to provoke sneezing and throat to cause coughing.[249-268] It irritates the mouth when ingested.[263] Its irritant action has been linked to its ability to activate both TRPA1[269] and TRPV1 receptors.[269-271] Toxicology in humans by the aerosol route does not appear to have been reported.

a. *Toxicological measurements*

Lower limit of irritation: The minimum concentration of the chemicals listed that provokes a painful sensation at those surfaces it acts on (conjunctiva of the eyes, the nasal mucosa and the pharynx, the throat, the skin etc.) is sometimes referred to as the "lower limit of irritation" or "the threshold value of pathological sensitivity".[3] Experiments historically involved human volunteers and the dose of the chemical in vapour or particulate form - depending on whether it was a liquid or a solid respectively – was increased until the appearance of signs of the specific irritant action of the chemical, generally lachrymation (causing a flow of tears) or sternutation (causing sneezing), in all or nearly all of the participants. The minimum concentration causing irritation is generally expressed in milligrams of substance per cubic metre of air (mg/m^3). The lower limits of irritation for some of the compounds listed in the table, in order of decreasing potency, are: diphenylchloroarsine (0.1) > chloroacetophenone (0.3) > ethyldichloroarsine (1) > chloropicrin (2) > trichloromethyl chloroformate (5 mg/m^3).[3] This illustrates the fact that the lower limit of irritation of the compounds listed may vary between fairly wide limits, and that the irritant potency of a chemical is a function of its structure. The substance with the greatest irritant potency, among those examined for use in chemical warfare and/or potentially in law enforcement, is arguably diphenylcyanoarsine.

Limit of insupportability (or intolerability): This is the maximum concentration of a chemical a human can tolerate for 1 min without observable injury. This characteristic can only be determined for those chemicals that have a predominantly irritant action. For lachrymators, the limit of insupportability is the point at which, after abundant lachrymation, a condition of photophobia, burning of the eyes and inability to keep the eyes open is reached. For sternutators, insupportability is often taken to be the stage when, after the production of sneezing, other symptoms such as coughing, retrosternal pain, headache etc., appear and produce the sensation of having reached a limit beyond which it would be unwise to proceed. The limits of insupportability for some of the compounds in the table, in order of decreasing potency, are: diphenylchloroarsine (1) > chloroacetophenone (4.5) > ethyldichloroarsine (10) > trichloromethyl chloroformate (40) > chloropicrin (50 mg/m^3).[3] Thus, among these, the chemical having the lowest limit of insupportability is diphenylchloroarsine, and that having the highest is chloropicrin.

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Supplementary references to Tables S1 and S2

1. Discovery of CN and its irritancy: C. Graebe, *J. Chem. Soc.*, 1871, **24**, 222-223.
2. Anonymous, *Potential Military Chemical/Biological Agents and Compounds*, US Army Field Manual No. 3-9, Washington D.C., USA, 12 December 1990.
3. M. Sartori, *The War Gases – Chemistry and Analysis*, Third Edition, D. Van Nostrand Co. Inc., New York: USA, 1943.
4. E. J. Olajos and H. Salem, *J. Appl. Toxicol.*, 2001, **21**, 355-391.
5. J. P. Sanford, *Annu. Rev. Med.*, 1976, **27**, 421-429.
6. Human volunteer trials of RCAs: M. Brown, *Military Med.*, 2009, **174**, 1041-1048.
7. B. Ballantyne, *Toxicol. Rev*., 2006, **25**, 155-197.
8. B. Ballantyne, Riot control agents in military operations, civil disturbance control and potential terrorist activities, with particular reference to peripheral chemosensory irritants, in: *Chemical Warfare Agents: Toxicology and Treatment;* T. C. Marrs, R. L. Maynard and F. R. Siddell (Eds.); Second Edition, Wiley, Chichester, UK, 2007, Chapter 26, pp. 659-666.
9. T. F. Watkins, J. C. Cackett and R. G. Hall, *Chemical Warfare, Pyrotechnics and the Fireworks Industry*, Pergamon Press, London, UK, 1968, p. 7.
10. M. Dixon, Reactions of lachrymators with enzymes and proteins, in: R. T. Williams (ed.), *The Biochemical Reactions of Chemical Warfare Agents*, Cambridge University Press, Cambridge, UK, 1948, pp. 39-49.
11. Inhalation studies with chloroacetophenone, diphenylaminochloroarsine, and pelargonic morpholide – animal exposures: C. L. Punte, T. A. Ballard and J. T. Weimer, *Am. Ind. Hyg. Assoc. J*., 1962, **23**, 194-198.
12. Inhalation studies with chloroacetophenone, diphenylaminochloroarsine, and pelargonic morpholide – human exposures: C. L. Punte, P. J. Gutentag, E. J. Owens and L. E. Gongwer, *Am. Ind. Hyg. Assoc. J*., 1962, **23**, 199-202.
13. C. W. Chung and A. L. Giles, *J. Immunol.*, 1972, **109**, 284-293.
14. B. Ballantyne and D. W. Swanston, *Arch. Toxicol.*, 1978, **40**, 75-95.
15. R. C. Malhotra and P. Kumar, *Def. Sci. J.*, 1987, **37**, 281-296.
16. K. Husain, P. Kumar and R. C. Malhotra, *Indian J. Med. Res. (B)*, 1991, **94**, 76-79.
17. P. Kumar, P. Kumar, K. Zachariah, R. Vijayaraghavan, G. P. Rai and N. Singh, *Bull. Environ. Contam. Toxicol*., 1993, **50**, 69-76.
18. S. C. Pant and P. Kumar, *Funct. Dev. Morph*., 1993, **3**, 181-184.
19. P. Kumar, S. J. S. Flora, S. C. Pant, A. S. Sachan, S. P. Saxena and S. D. Gupta, *J. Appl. Toxicol*., 1994, **14**, 411-416.
20. P. Kumar, R. Vijayaraghavan, S. C. Pant, A. S. Sachan and R. C. Malhotra, *Human Exp. Toxicol*., 1995, **14,** 404-409.
21. G. M. Recer, T. B. Johnson and A. K. Gleason, *Regul. Toxicol. Pharmacol.*, 2002, **36**, 1-11.
22. P. G. Blain, *Toxicol. Rev.*, 2003, **22**, 103-110.
23. A. K. Nigam, M. V. S. Suryanarayana, P. K. Gutch, S. P. Sharma, L. N. S. Tomar and R. Vijayaraghavan, *J. Hazard. Mat*., 2010, **184**, 506-514.
24. J. P. de Torres, V. Correa, J. Rosquete and T. Febles, *Respiratory Med. Extra*, 2006, **2**, 13-15.
25. L. J. Schep, R. J. Slaughter and D. I. McBride, *R. Army Med. Corps.*, 2015, **161**, 94-99.
26. Discovery of CS and its irritancy: B. B. Corson and R. W. Stoughton, *J. Am. Chem. Soc.*, 1928, **50**, 2825-2827.
27. H. G. Sturz and C. R. Noller, *J. Am. Chem*. Soc., 1949, **71**, 2949-2949.
28. G. R. N. Jones, *Nature (London)*, 1972, **235**, 257-261.
29. J. S. Knapp, *US Patent* 3,963,770 (1976).
30. J. Rosin, *US patent* 3,549,684 (1970).
31. A. Pande, K. Ganesan, A. K. Jain, P. K. Gupta and R. C. Malhotra, *Org. Proc. Res. Dev.*, 2005, **9**, 133-136.
32. Tear gas (CS), in: *Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 16*, Committee on Acute Exposure Guidelines Levels; Committee on Toxicology, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies; National Research Council of the National Academies Press, Washington D.C., USA, 2004, Chapter 7, pp. 309-399.
33. Y. Dimitroglou, G. Rachiotis and C. Hadjichristodoulou, *Int. J. Environ. Res. Public Health*, 2015, **12**, 1397-1411.
34. P. Arbak, I. Baser, O. O. Kumbasar, F. Ulger, Z. Kilicaslan and F. Evyapan, *The Scientific World Journal* 2014, ID 963638, 5 pages.
35. E. M. Summerhill, G. W. Hoyle, S. E. Jordt, B. J. Jugg, J. G. Martin, S. Matalon, S. E. Patterson, D. J. Prezant, A. M. Sciuto, E. R. Svendsen, C. W. White and L. A. Veress, *Ann. Am. Thorac. Soc.*, 2017, **14**, 1060-1072.
36. D. H. Finn, M. A. P. Hogg and D. Crichton, *US Patent* 967,660 (1964).
37. T. A. Kluchinsky, P. B. Savage, M. V. Sheely, R. J. Thomas and P. A. Smith, *J. Microcolumn Separations*, 2001, **13**, 186-190.
38. T. A. Kluchinsky, M. V. Sheely, P. B. Savage and P. A. Smith, *J. Chromatogr. A*, 2002, **952**, 205-213.
39. P. K. Gutch, S. K. Raza and R. C. Malhotra, *J. Thermal Analysis Calorimetry*, 2003, **71**, 593-599.
40. J. J. Hout, G. L. Hook, P. T. LaPuma and D. W. White, *J. Occupat. Environ. Hyg.*, 2010, **7**, 352-357.
41. B. Ballantyne and F. W. Beswick, *Medicine Sci. Law*, 1972, **12**, 121-128.
42. K. H. Kemp and W. B. Wilder, *Medicine Sci. Law*, 1972, **12**, 113-120.
43. B. Ballantyne and S. Callaway, *Medicine Sci. Law*, 1972, **12**, 43-65.

44. R. W. Brimblecombe, D. M. Green and A. W. Muir, *Br. J. Pharmacol.* 1972, **44**, 561-576.
45. C. L. Punte, J. T. Weimer, T. A. Ballard and J. L. Wilding, *Toxicol. Appl. Pharmacol.*, 1962, **4**, 656-662.
46. C. L. Punte, E. J. Owens and P J Gutentag, *Arch. Environ. Health*, 1963, **6**, 366-374.
47. E. J. Owens and C. L. Punte, *Am. Ind. Hyg. Assoc. J.*, 1963, **24**, 262-264.
48. F. W. Beswick, P. Holland and K. H. Kemp, *Brit. J. Industr. Med.*, 1972, **29**, 298-306.
49. J. E. Cotes, J. M. Dabbs, M. R. Evans and P. Holland, *Quart. J. Exp. Physiol.*, 1972, **57**, 199-206.
50. T. J. Cole, J. E. Cotes, G. R. Johnson, H. de V. Martin, J. W. Reed and M. J. Saunders, *Quart. J. Exp. Physiol.*, 1977, **62**, 341-351.
51. E. Shmunes and J. S. Taylor, *Arch. Dermatol.*, 1973, **107**, 212-216.
52. I. Solomon, I. Kochba, E. Eizenkraft and N. Maharshak, *Arch. Toxicol.*, 2003, **77**, 601-604.
53. M. A. Alieva, *Sud. Med.* Ekspert, 1955, **38**, 33-36.
54. Y. Alarie, *Arch. Environ. Health*, 1966, **13**, 433-449.
55. D. G. Upshall, *Toxicol. Appl. Pharm.*, 1973, **24**, 45-59.
56. B. Ballantyne and D. W. Swanston, *Acta Pharm. Toxicol.*, 1973, **32**, 266-277.
57. B. Ballantyne, M. F. Gazzard, D. W. Swanston and P. Williams, *Arch. Toxicol.*, 1974, **32**, 149-168.
58. B. Ballantyne and W. G. Johnston, *Medicine Sci. Law*, 1974, **14**, 93-97.
59. B. Ballantyne and W. G. Johnston, *Medicine Sci. Law*, 1974, **14**, 44-50.
60. B. Ballantyne. *Military Medicine*, 1979, **144**, 691-694.
61. E. Worthington and P. A. Nee, *J. Accid. Emerg. Med.*, 1999, **16**, 168-170.
62. Y. G. Karagama, J. R. Newton and C. J. R. Newbegin, *J. Roy. Soc. Med.*, 2003, **96**, 172-174.
63. R. V. Babakhanian, E. S. Bushuev, L. K. Gustyleva, Yu. A. Ignat'ev and G. N. Kul'bitskii, *Sud. Med. Ekspert.*, 1996, **39**, 28-29.
64. A. A. Ivanov, *Sud. Med. Ekspert.*, 1998, **41**, 27-28.
65. S. Debarre, L. Karinthi, S. Delamanche, C. Fuché, P. Desforges and J. H. Calvet, *Human Exp. Toxicol.*, 1999, **18**, 724-730.
66. Y. J. Kim, A. R. Payal and M. K. Daly, *Survey of Ophthalmology*, 2016, **61**, 434-442.
67. R. J. Haar, V. Iacopino, N. Ranadive, S. D. Weiser and M. Dandu, *BMC Public Health*, 2017, 17:831.
68. R. J. Thomas, P. A. Smith, D. A. Rascona, J. D. Louthan and B. Gumpert, *Mil. Med.*, 2002, **167**, 136-139.
69. A. M. B. Zekri, W. W. K. King, R. Yeun and W. R. J. Taylor, *Burns*, 1995, **21**, 586-589.
70. J. Hardwicke and U Satti, *Injury Extra*, 2006, **37**, 133-134.
71. S. A. Cucinell, K. C. Swentzel, R. Biskup, H. Snodgrass, S. Lovre, W. Stark, L. Feinsilver and F. Vocci, *Fed. Proc.*, 1971, **30**, 86-91.
72. L. Frankenberg and B. Sőrbo, *Arch. Toxicol.*, 1973, **31**, 99-108.
73. L. Leadbeater, *Toxicol. Appl. Pharmacol.*, 1973, **25**, 101-110.
74. L. Leadbeater, G. L. Sainsbury and D. Utley, *Toxicol. Appl. Pharmacol.*, 1973, **25**, 111-116.
75. J. M. Harrison, T. D. Inch, I. W. Lawston, R. V. Ley and G. L. Sainsbury, *J. Labelled Comp. Radiopharm.*, 1978, **14**, 141-148.
76. K. Brewster, J. M. Harrison, L. Leadbeater, J. Newman and D. G. Upshall, *Xenobiotica*, 1987, **17**, 911-924.
77. J. R. Riches, R. W. Read, R. M. Black, J. M. Harrison, D. A. Shand, E. V. Tomsett, C. R. Newsome, N. C. Bailey, N. Roughley, M. R. Gravett, S. J. Stubbs and R. R. McColm, *J. Chromatogr. B*, 2013, **928**, 125-130.
78. P. K. Gutch, P. Kumar, M. V. S. Suryanarayana and R. C. Malhotra, *Defence Sci. J.*, 2005, **55**, 447-457.
79. P. K. Gutch and R. K. Srivastava, *Defence Sci. J.*, 2012, **62**, 319-323.
80. Discovery of CR and its irritancy: R. Higginbottom and H. Suschitsky, *J. Chem. Soc.*, 1962, **0**, 2367-2370.
81. Anonymous, *BMJ*, 7 July 1973, 5-5.
82. H. Fakhraian, Y. Nafary, A. Yarahmadi and H. Hadj-Ghanbary, *J. Heterocyclic Chem.*, 2008, **45**, 1469-1471.
83. H. Fakhraian and Y. Nafary, *J. Heterocyclic Chem.*, 2009, **46**, 988-992.
84. V. G. Noskov, L. N. Kalinina, M. N. Noskova, Yu L. Kruglyak, O. G. Strukov, A. P. Bezrukov and V. K. Kurochkin, *Pharm. Chem. J.*, 1997, **31**, 431-434.
85. V. G. Noskov, Yu. L. Kruglyak, O. G. Strukov and V. K. Kurochkin, *Pharm. Chem. J.*, 1997, **31**, 492-493.
86. A. V. Kovalev, S. I. Tolmachev, L. A. Mukovskii and Yu. A. Khrustaleva, *Sud. Med. Ekspert*, 2012, **55**, 15-18.
87. A. V. Kovalev, S. I. Tolmachev, L. A. Mukovskii and Yu. A. Khrustaleva, *Sud. Med. Ekspert.*, 2012, **55**, 38-41.
88. N. Zaware and M. Ohlmeyer, *Heterocyclic Commun.*, 2014, **20**, 251-256.
89. T. Xue, Q. Z. Cui, Y. H. Han, S. Wang and Y. Y. Mao, *Anal. Methods,* 2016, **8**, 3824-3830.
90. D. M. Green, D. J. Balfour and A. Muir, *Toxicology*, 1979, **12**, 151-153.
91. B. Ballantyne and D. W. Swanston, *Acta Pharmacol.*, 1974, **35**, 412-423.
92. J. M. Harrison, T. D. Inch, D. G. Upshall, *J. Labelled Comp. Radiopharm.*, 1977, **14**, 375-380.
93. H. F. Colgrave, R. F. Brown and R. A. Cox, *Br. J. Exp. Path.,* 1979, **60**, 130-141.
94. M. C. French, J. M. Harrison, T. D. Inch, L. Leadbeater, J. Newman, D. G. Upshall and G. M. Powell. *Xenobiotica*, 1983, **13**, 345-359.
95. B. Furnival, J. M. Harrison, J. Newman and D. G. Upshall, *Xenobiotica,* 1983, **13**, 361-372.
96. M. C. French, J. M. Harrison, J. Newman, D. G. Upshall and G. M. Powell, *Xenobiotica*, 1983, **13**, 373-381.
97. J. M. Harrison, R. J. Clarke, T. D. Inch and D. G. Upshall, *Experientia*, 1978, **34**, 698-699.
98. R. Mathur, R. S. Dangi, S. C. Dass and R. C. Malhotra, *Current Science*, 10 August 2000, **79**, 287-288.
99. A. Tiwari, M. P. Kaushik, K. S. Pandey and R. S. Dangi, *Current Science*, 25 May 2005, **88**, 1545-1546.
100. Capsicum content and pungency in different Capsicum spp. cultivars: S. Sanatombi and G. J. Sharma, *Not. Bot. Hort. Agrobot. Cluj.*, 2008, **36**, 89-90.
101. V. S. Govindarajan and M. N. Sathyanarayana, *Critical Reviews in Food Science and Nutrition*, 1991, **29**, 435-474.
102. I. Perucka and W. Oleszek, *Food Chemistry*, 2000, **71**, 287-291.

103. K. Sutoh, K. Kobata and T. Watanabe, *J. Agric. Food Chem.*, 2001, **49**, 4026-4030.
104. R. T. Sterner, A. D. Ames and B. A. Kimball, *Int. Biodeterioration & Biodegradation*, 2002, **49**, 145-149.
105. R. T. Sterner and B. A. Kimball, *Int. Biodeterioration & Biodegradation*, 2005, **56**, 188-191.
106. C. G. Smith and W. Stopford, *NCMJ*, September/October 1999, **60**, 268-274.
107. J. M. Holopainen, J. A. O. Moilanen, T. Hack and T. M. T. Tervo, *Toxicol. Appl. Pharmacol.*, 2003, **186**, 155-162.
108. P. Kumar, U. Deb and M. P. Kaushik, *Inhal. Toxicol.*, 2012, **24**, 659-666.
109. R. V. Babakhanian, G. N. Binat, V. D. Isakov and L. A. Mukovskii, *Sud. Med. Ekspert.*, 2001, **44**, 9-11.
110. J. Prescott and N. Swain-Campbell, *Chem. Senses*, 2000, **25**, 239-246.
111. M. F. Yeung and W. Y. M. Tang, *Hong Kong Med. J.*, 2015, **21**, 542-552.
112. M. de Lourdes Reyes-Escogido, E. G. Gonzalez-Mondragon and E. Vaquez-Tzompantzi, *Molecules*, 2011, **16**, 1253-1270.
113. R. Arora, N. S. Gill, C. Chauhan and A. C. Rana, *Int. J. Pharm. Sci. Drug Res.*, 2011, **3**, 280-286.
114. J. O'Neill, C. Brock, A. E. Olesen, T. Andressen, M. Nilsson and A. H. Dickenson, *Pharmacol. Rev.*, 2012, **64**, 939-971.
115. V. Fattori, M. S. N. Hohmann, A. C. Rossaneis, F. A. Pinho-Ribeiro and W. A. Verri Jr., *Molecules*, 2016, **21**, 844 (33 pages).
116. R. Q. Thompson, M. J. Pennino, M. J. Brenner and M. A. Mehta, *Talanta*, 2006, **70**, 315-322.
117. C. F. Bucholz, *Almanach oder Taschenbuch für Scheidekünstler und Apotheker* (Weimar), 1816, **37**, 1-30.
118. C. F. Thresh, *Pharmaceut. J.*, 1876, **315**, 21-21.
119. C. F. Thresh, *The Analyst*, 1876, **1**, 148-149.
120. E. K. Nelson, *J. Ind. Eng. Chem.*, 1910, **2**, 419-421.
121. E. K. Nelson, *J. Am. Chem. Soc.*, 1919, **41**, 1115-1121.
122. E. K. Nelson, *J. Am. Chem. Soc.*, 1919, **41**, 2121-2130.
123. E. K. Nelson, *J. Am. Chem. Soc.*, 1920, **42**, 597-599.
124. W. L. Scoville, *J. Pharm. Assoc.*, 1912, **1**, 453-454.
125. E. H. Wirth and E. N. Gathercoal, *J. Am. Pharm. Assoc.*, 1924, **13**, 217-219.
126. A. Lapworth and F. A. Royle, *J. Chem. Soc., Trans.*, 1919, **115**, 1109-1116.
127. S. Kobayashi, *Scientific Papers – Institute of Physical and Chemical Research Tokyo*, 1927, **6**, 166-184.
128. N. A. Lange, H. L. Ebert and L. K. Youse, *J. Am. Chem. Soc.*, 1929, **51**, 1911-1924.
129. E. Späth and S. F. Darling, *Ber.*, 1930, **63**, 737-743.
130. L. Crombie, S. H. Dandegaonker and K. B. Simpson, *J. Chem. Soc.*, 1955, **0**, 1025-1027.
131. C. Cooksey, *Royal Society of Chemistry Historical Group Newsletter and Summary of Papers*, A. Simmons (ed.), Summer 2018, **No. 74**, 26-31.
132. C. C. Toh, T. S. Lee and A. K. Kiang, *Brit. J. Pharmacol.*, 1955, **10**, 175-182.
133. N. Jancsó and A. Jancsó-Gábor, *Archiv für Experimentalle Pathologie und Pharmakologie*, 1959, **236**, 142-145.
134. D. J. Bennett and G. W. Kirby, *J. Chem. Soc. (C)*, 1968, **0**, 442-446.
135. J. L. Y. Chen, *US patent 5,094,782* (1992).
136. H. Yan, Z. Wang and J. Wang, *Ind. Eng. Chem. Res.*, 2012, **51**, 2808-2813.
137. M. P. Kulkarni, U. G. Phapale, N. G. Swarge and M. R. Somayajulu, *Def. Sci. J.*, 2006, **56**, 369-375.
138. D. E. Henderson and S. K. Henderson, *J. Agric. Food Chem.*, 1992, **40**, 2263-2266.
139. Y. Alairie and L. W. Keller, *Environ. Physiol. Biochem.*, 1973, **3**, 169-181.
140. J. G. Collier and R. W. Fuller, *Br. J. Pharmacol.*, 1984, **81**, 113-117.
141. M. Fujimura, Y. Kamio, S. Sakamoto, T. Bando, S. Myou and T. Matsuda, *Clinical Autonomic Research*, 1992, **2**, 397-401.
142. H. A. Hutchings, S. Morris, R. Eccles and M. S. M. Jawad, *Respiratory Medicine*, 1993, **87**, 379-382.
143. I. Satia, N. Tsamandouras, K. Holt, H. Badri, M. Woodhead, K. Ogungbenro, T. W. Felton, P. M. O'Byrne, S. J. Fowler and J. A. Smith, *J. Allergy Clin. Immunol.*, 2017, **139**, 771-779.
144. A. M. Sanico, S. Atsuta, D. Proud and A. Togias, *J. Allergy Clin. Immunol.*, 1997, **100**, 632-641.
145. B. G. Green, *Pain*, 1996, **68**, 245-253.
146. B. M. Magnusson and L. O. D. Koskinen, *Int. J. Pharmaceutics*, 2000, **195**, 55-62.
147. R. W. Foster and K. M. Weston, *Pain*, 1986, **25**, 269-278.
148. J. W. Lambert and A. K. Sum, *J. Phys. Chem. B*, 2006, **110**, 2351-2357.
149. J. Swain and A. K. Mishra, *J. Phys. Chem. B*, 2015, **119**, 12086-12093.
150. A. Torrecillas, M. Schneider, A. M. Fernández-Martínez, A. Ausili, A. M. de Godos, S. Corbalán-García and J. C. Gómez-Fernández, *ACS Chem. Neurosci.*, 2015, **6**, 1741-1750.
151. M. Halme, M. Pesonen, H. Salo, M. Söderström, M. Pasanen, K. Vähäkangas and P. Vanninen, *J. Chromatogr. B*, 2016, **1009-1010**, 17-24.
152. T. Glinsukon, V. Stitmunnaithum, C. Toskulkao, T. Buranawuti and V. Tangkrisanavinout, *Toxicon*, 1980, **18**, 215-220.
153. Aldrich Chemical Company Material Safety Data Sheet, accessed online in 2013.
154. E. C. S. Jones and F. L. Pyman, *J. Chem. Soc.*, 1925, **0**, 2588-2598.
155. A. H. Ford-Moore and J. W. C. Phillips, *Rec. Trav. Chim.*, 1934, **53**, 847-859.
156. D. B. Bradner and M. L. Sherrill, *US patent 1,503,631* (1944).
157. A. A. L. Challis and G. R. Clemo, *J. Chem. Soc.*, 1947, **0**, 613-618.
158. D. Amos, *Aust. J. Chem.*, 1965, **18**, 2049-2052.
159. I. J. Chen, *US patent 5,221,692* (1993).
160. H. L. Constant and G. A. Cordell, *J. Nat. Prod.*, 1996, **59**, 425-426.
161. B. Wang, F. Yang, Y. F. Shan, W. W. Qiu and J. Tang, *Tetrahedron*, 2009, **65**, 5409-5412.
162. J. Patocka and K. Kuca, *Mil. Med. Sci. Lett. (Voj. Zdrav. Listy)*, 2011, **80**, 72-79.
163. J. M. Janusz, B. L. Buckwalter, P. A. Young, T. R. LaHann, R. W. Farmer, G. B. Kasting, M. E. Loomans, G. A. Kerckaert, C. S. Maddin, E. F. Berman, R. L. Bohne, T. L. Cupps and J. R. Milstein, *J. Med. Chem.*, 1993, **36**, 2595-2604.
164. C. S. J. Walpole, R. Wrigglesworth, S. Bevan, E. A. Campbell, A. Dray, I. F. James, M. N. Perkins, D. J. Reid and J. Winter, *J. Med. Chem.*, 1993, **36**, 2362-2372.
165. D. B. Collum, S. C. Chen and B. Ganem, *J. Org. Chem.*, 1978, **43**, 4393-4394.

166. L. M. Rice, C. H. Grogan, B. H. Armbrecht and E. E. Reid, *J. Am. Chem. Soc.*, 1954, **76**, 3730-3731.
167. S. Franke, *Textbook of Military Chemistry*, Volume 1, Military Publisher of the German Democratic Republic, Berlin, East Germany, 1977, p. 270.
168. R. N. Knowles and W. J. Arthur, *US patent 3,686,415* (1972).
169. J. Ledgard, Preparation of lachrymator, disabling, and irritant substances, in: *A Preparatory Manual of Chemical Warfare Agents*, Paranoid Publications Group, USA, 2007, Chapter 3, Section 2, p. 64.
170. J. M. Kliegman and R. K. Barnes, *US patent 3,652,672* (1972).
171. P. W. Atkins. *Molecules*, Scientific American Library, New York, USA, 1987, p. 123.
172. F. P. Underhill, Acrolein, in: The Physiological Action of Miscellaneous Gases, in: *The Medical Department of the United States Army in the World War, Volume XIV Medical Aspects of Gas Warfare*; Maj. Gen. M. W. Ireland (ed.), Washington D.C., USA, 1926, Chapter XIII, pp. 419-420.
173. Acrolein, *Concise International Chemical Assessment Document 43*, World Health Organisation, Geneva, 2002.
174. *The Merck Index - An Encyclopedia of Chemicals, Drugs and Biologicals*; Fourteenth Edition, Merck Inc., Whitehouse Station, NJ, USA, 2006.
175. J. Cai, A. Bhatnagar and W. M. Pierce, *Chem. Res. Toxicol.*, 2009, **22**, 708-716.
176. W. Taylor, *J. Chem. Soc.*, 1937, **0,** 304-308.
177. W. H. Perkin and B. F. Duppa, *J. Chem. Soc.*, 1859, **11**, 22-30.
178. R. R. Renshaw and J. C. Ware, *J. Am. Chem. Soc.*, 1925, **47**, 2989-2995.
179. K. Sisido, N. Nozaki, M. Nozaki and K. Okano, *J. Org. Chem.*, 1954, **19**, 1699-1703.
180. F. S. Kipping and F. P. Kipping, *Perkin and Kipping's Organic Chemistry Part II*, W. & R. Chambers Ltd., London, UK, 1933, p. 380.
181. V. M. Clark and A. R. Todd, *J. Chem. Soc.*, 1950, **0**, 2023-2030.
182. M. Nakajima and J. P. Anselme, *J. Org. Chem.*, 1983, **48**, 2492-2496.
183. R. S. Drago, J. Gaul, A. Zombeck and D. K. Straub, *J. Am. Chem. Soc.*, 1980, **102**, 1033-1038.
184. P. D. Bartlett and J. E. Leffler, *J. Am. Chem. Soc.*, 1950, **72**, 3030-3025.
185. M. Filipan-Litvić, M. Litvić and V. Vinković, *Tetrahedron*, 2008, **64**, 5649-5656.
186. M. S. Newman, *J. Am. Chem. Soc.*, 1940, **62**, 2295-2300.
187. S. Wawzonek and R. E. Karll, *J. Am. Chem. Soc.*, 1948, **70**, 1666-1666.
188. A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.*, 1951, **73,** 1668-1673.
189. R. W. Hay, A. L. Galyer and G. A. Lawrence, *J. Chem. Soc.*, 1976, **0**, 939-942.
190. R. E. Gawley, S. R. Chemburkar, A. L. Smith and T. V. Anklekar, *J. Org. Chem.*, 1988, **53**, 5381-5383.
191. E. Grimaux, *J. Chem. Soc.*, 1872, **25**, 816-818.
192. E. Weth and A. S. Dreiding, *Proc. Chem. Soc.*, 1964, **59**, 59-60.
193. T. Nozoe and K. Takahashi, *Bull. Chem. Soc. Japan*, 1965, **38**, 665-674.
194. H. W. Yurrow and S. Sass, *Anal. Chem. Acta*, 1987, **194**, 323-327.
195. G. E. Langford, *US Patent 4,978,806* (1990).
196. V. G. Noskov, N. Yu. Kuritsyna, G. L. Syrova, M. A. Sokal'skii, M. N. Noskova, Yu. G. Kruglyak and V. K. Korochkin, *Pharm. Chem. J.*, 1997, **31**, 494-496.
197. W. H. Donovan and W. E. White, *J. Org. Chem.*, 1996, **61**, 969-977.
198. G. A. Grant, *US Patent 4,598,096* (1986).
199. J. C. Asquith, J. Dewey, C. G. Lee, B. C. Morris, T. D. Webber, *Mutation Res.*, 1990, **230**, 71-80.
200. J. Cole, M. C. Diot, F. N. Richmond and B. A. Bridges, *Mutation Res.*, 1990, **230**, 81-91.
201. M. H. Brodnitz and J. V. Pascale, *J. Agr. Food Chem.*, 1971, **19**, 269-272.
202. R. Kubec, R. B. Cody, A. J. Dane, R. A. Musah, J. Schrami, A. Vattekkatte and E. Block, *J. Agric. Food Chem.*, 2010, **58**, 1121-1128.
203. E. C. Block, J. Z. Gillies, C. W. Gillies, A. A. Bazzi, D. Putman, L. K. Revelle, D. Wang and X. Zhang, *J. Am. Chem. Soc.*, 1996, **118**, 7492-7501.
204. E. Block, R. E. Penn and L. K. Revelle, *J. Am. Chem. Soc.*, 1979, **101**, 2200-2201.
205. C. E. Eady, T. Kamoi, M. Kato, N. G. Porter, S. Davis, M. Shaw, A. Kamoi and S. Imai, *Plant Physiol.,* 2008, **147**, 2096-2106.
206. M. Halme, M. Pesonen, T. Grandell, M. Kuula, M. Pasenen, K. Vähäkangas and P. Vanninen, *J. Sep. Sci.*, 2015, **38**, 3383-3389.
207. C. D. S. Tomlin (ed.), *The Pesticide Manual*, Thirteenth Edition, British Crop Protection Council, Hampshire UK, 2003, p. 168.
208. S. E. Sparks, G. B. Quistad and J. E. Casida, *Chem. Res. Toxicol.*, 1997, **10**, 1001-1007.
209. G. A. Burk, *US Patent 3,159,686* (1964).
210. W. L. Argo, E. M. James and J. L. Donnelly, *J. Phys. Chem.*, 1919, **23**, 578-585.
211. E. Sell, G. Zierold, *Ber*., 1874, **7**, 1228-1234.
212. J. U. Nef, *Ann.*, 1892, **270**, 267-335.
213. D. P. Murphy, *J. Org. Chem.*, 1964, **29**, 1613-1615.
214. R. S. Bly, G. A. Perkins and W. L. Lee, *J. Am. Chem. Soc.*, 1922, **44**, 2896-2903.
215. E. Gryszkiewicz-Trochimouski, E. Dymowski and E. Schmidt, *Bull. Chim. Soc. Fr.,* 1948, **0**, 597-598.
216. F. P. Underhill, Methylchloroformate, in: The Physiological Action of Miscellaneous Gases, in: *The Medical Department of the United States Army in the World War, Volume XIV Medical Aspects of Gas Warfare*; Maj. Gen. M. W. Ireland (ed.), Washington D.C., USA, 1926, Chapter XIII, p. 416.
217. F. P. Underhill, Chloromethylchloroformate, in: The Physiological Action of Miscellaneous Gases, in: *The Medical Department of the United States Army in the World War, Volume XIV Medical Aspects of Gas Warfare*; Maj. Gen. M. W. Ireland (ed.), Washington D.C., USA, 1926, Chapter XIII, p. 416.
218. F. P. Underhill, Trichlormethylchloroformate, in: The Physiological Action of Miscellaneous Gases, in: *The Medical Department of the United States Army in the World War, Volume XIV Medical Aspects of Gas Warfare*; Maj. Gen. M. W. Ireland (ed.), Washington D.C., USA, 1926, Chapter XIII, p. 417.
219. K. E. Jackson, *Chem. Rev.*, 1935, **17**, 251-292.

220. F. P. Underhill, Dichlormethylarsine, in: The Physiological Action of Miscellaneous Gases, in: *The Medical Department of the United States Army in the World War, Volume XIV Medical Aspects of Gas Warfare*; Maj. Gen. M. W. Ireland (ed.), Washington D.C., USA, 1926, Chapter XIII, p. 412.
221. S. Hanaoka, K. Nomura and S. Kudo, *J. Chromatogr.* A, 2005, **1085**, 213-223.
222. K. E. Jackson, *Chem. Rev.*, 1939, **25**, 67-119.
223. E. L. McGown, T. van Ravenswaay and C. R. Dumlao, *Toxicol. Pathol.*, 1987, **15**, 149-156.
224. F. P. Underhill, Dichlorphenylarsine, in: The Physiological Action of Miscellaneous Gases, in: *The Medical Department of the United States Army in the World War, Volume XIV Medical Aspects of Gas Warfare*; Maj. Gen. M. W. Ireland (ed.), Washington D.C., USA, 1926, Chapter XIII, pp. 413-414.
225. S. Hanaoka, E. Nagasawa, K. Nomura, M. Yamazawa and M. Ishizaki, *Appl. Organomet. Chem.*, 2005, **19,** 265-275.
226. M. Hempel, B. Daus, C. Vogt and H. Weiss, *Environ. Sci. Technol.*, 2009, **43**, 6989-6995.
227. T. Arao, Y. Maejima and K. Baba, *Environ. Sci. Technol.*, 2009, **43**, 1097-1101.
228. T. Missiaen, M. Söderström, I. Popescu and P. Vanninen, *Science of the Total Environment*, 2010, **408**, 3536-3553.
229. N. Neimikoski, M. Söderström and P. Vanninen, *Anal. Chem.*, 2017, **89**, 11129-11134.
230. A. A. Fries and C. J. West, Arsenic derivatives, in: *Chemical Warfare*, First Edition, McGraw-Hill Company Inc., New York, USA, 1921, Chapter X, pp. 180-189.
231. F. Flury, *Zeitschrift für die gesamte experimentelle medizin einschliesslich experimentelle chirurgie*, 1921, **13**, 523-579.
232. D. C. Walton and W. A. Eldridge, *J. Pharm. Exp. Ther.*, 1935, **35**, 241-256.
233. V. N. Aleksandrov, Irritant toxic agents (Sternites), in: *Otravlyayushchiye Veshchestva* (translates into English as "Toxic Agents"), Moscow, Order of the Red Banner of Labour Military Publishing, House of the Ministry of Defence USSR, Russia, 1969, 191 pages.
234. F. P. Underhill, Diphenylchlorarsine, in: The Physiological Action of Miscellaneous Gases, in: *The Medical Department of the United States Army in the World War, Volume XIV Medical Aspects of Gas Warfare*; Maj. Gen. M. W. Ireland (ed.), Washington D.C., USA, 1926, Chapter XIII, pp. 415-416.
235. G. T. Morgan, *Organic Compounds of Arsenic and Antimony*, Monographs on Industrial Chemistry, E. Thorpe (ed.); Longmans, Green, and Co.; London, UK, 1918.
236. G. W. Raiziss and J. L. Gavron, *Organic Arsenical Compounds*, American Chemical Society Monograph Series, The Chemical Catalog Company Inc., New York, USA, 1923.
237. F. G. Mann. *The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, Bismuth and Silicon*, Interscience Publishers Ltd., London, UK, 1950.
238. N. V. Sidgwick, Group V B. Arsenic, antimony, bismuth, in: *The Chemical Elements and Their Compounds*, Volume 1, Clarendon Press, Oxford, 1950, pp. 758-803.
239. B. Ballantyne, *Toxicology*, 1978, **10**, 341-361.
240. C. L. Hewett, L. J. Lermit, H. T. Openshaw, A. R. Todd, A. H. Williams, F. N. Woodward, *J. Chem. Soc.*, 1948, **0**, 292-295.
241. W. Gump and H Stoltzenberg, *J. Chem. Soc.,* 1931, **53**, 1428-1432.
242. H. McCombie and B. C. Saunders, *Nature (London)*, 1949, **159**, 491-494.
243. B. C. Saunders, G. J. Stacey, *J. Chem. Soc.*, 1949, **0**, 919-925.
244. R. Heap and B. C. Saunders, *J. Chem. Soc.,* 1949, **0**, 2983-2988.
245. B. C. Saunders, *J. Chem.* Soc., 1950, **0**, 684-687.
246. R. Heap, B. C. Saunders and G. J. Stacey, *J. Chem. Soc*., 1951, **0**, 658-664.
247. B. C. Saunders. *Some Aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine*, Cambridge University Press, Cambridge, UK, 1957, p. 16, 84 and pp. 118-119.
248. H. Gilman, S. M. Spatz and M. J. Kolbezen, *J. Org. Chem.*, 1953, **18**, 1341-1351.
249. W. R. Dunstan and H. Garnett, *J. Chem. Soc.*, *Trans.*, 1895, **67**, 94-100.
250. E. Ott and K. Zimmermann, *Ann.*, 1921, **425**, 314-337.
251. E. Ott and F. Eichler, *Ber.*, 1922, **55**, 2653-2663.
252. H. Rheinboldt, *Ber.*, 1923, **56**, 1228-1229.
253. H. Staudinger and H. Schneider, *Ber.*, 1923, **56**, 699-711.
254. H. Staudinger and F. Müller, *Ber.*, 1923, **56**, 711-715.
255. L. Lohaus and H. Gall, *Ann.*, 1935, **517**, 278-289.
256. R. Grewe, W. Freist, H. Neumann and S. Kersten, *Chem. Ber.*, 1970, **103**, 3752-3770.
257. R. A. Olsen and G. O. Spessard, *J. Agric. Food Chem.*, 1981, **29**, 942-944.
258. D. G. Barceloux, *Dis. Mon.*, 2009, **55**, 380-390.
259. T. J. Zachariah and V. A. Parthasarathy, Black pepper, in: *Chemistry of Spices*; V. A. Parthasarathy, B. Chempakam and T. J. Zachariah (eds.), CABI, Wallingford, Oxfordshire, England, 2008, pp. 21-40.
260. L. Gorgani and M. Mohammadi, G. D. Najapour and M. Nikzad, *Comprehensive Reviews in Food Science and Food Safety*, 2017, **16**, 124-140.
261. E. A. Correa, E. D. Högestätt, O. Sterner, F. Echeverri and P. M. Zygmunt, *Bioorg. Med. Chem.*, 2010, **18**, 3299-3306.
262. C. Dawid, A. Henze, O. Frank, A. Glabasnia, M. Rupp, K. Büning, D. Orlikowski, M. Bader and T. Hofmann, *J. Agric. Food Chem.*, 2012, **60**, 2884-2895.
263. H. T. Lawless and D. A. Stevens, *Perception & Psychophysics*, 1988, **43**, 72-78.
264. T. S. Ribeiro, L. Freire-de-Lima, J. O. Previato, L. Mendonça-Previato, N. Heise and M. E. Freire-de-Lima, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3555-3558.
265. R. A. Rather and M. Bhagat, *Front. Cell. Dev. Biol.* 2018, 6:10.
266. R. Venkatasamy, L. Faas, A. R. Young, A. Raman and R. C. Hider, *Bioorg. Med. Chem.*, 2004, **12**, 1905-1920.
267. C. Dawid, A. Henze, O. Frank, A. Glabasnia, M. Rupp, K. Büning, D. Orlikowski, M. Bader and T. Hofmann, *J. Agric. Food Chem.*, 2012, **60**, 2884-2895.
268. S. K. Okwute and H. O. Egharevba, *Int. J. Chem.*, 2013, **5**, 99-122.
269. Y. Okamura, M. Narukawa, Y. Iwasaki, A. Ishikawa, H. Matsuda, M. Yoshikawa and T. Watanabe, *Biosci. Biotechnol. Biochem.*, 2010, **74,** 1068-1072.
270. F. N. McNamara, A. Randall and M. J. Gunthorpe, *Br. J. Pharmacol.*, 2005, **144**, 781-790.
271. E. A. Correa, E. D. Högestätt, O. Sterner, F. Echeverri and P. M. Zygmunt, *Bioorg. Med. Chem.*, 2010, **18**, 3299-3306.

