University of Hradec Králové
Faculty of Science
Department of Chemistry

Toxicology of non-lethal chemical weapons

Bachelor Thesis

Student: Michaela Dohnalová
Study programme: B1407 Chemistry
Field of study: Toxicology and analysis of pollutants
Supervisor: Mgr. Eugenie Nepovimová, Ph.D.

Hradec Králové July 2020

Univerzita Hradec Králové
Přírodovědecká fakulta

Zadání bakalářské práce

Autor:	**Michaela Dohnalová**
Studium:	S17CH094BP
Studijní program:	B1407 Chemie
Studijní obor:	Toxikologie a analýza škodlivin
Název bakalářské práce:	**Toxikologie neletálních chemických zbraní**
Název bakalářské práce AJ:	Toxicology of non-lethal chemical weapons

Cíl, metody, literatura, předpoklady:

The aim of this Bachelor Thesis is to review non-lethal chemical weapons. Within the first part, definition, history and classification of such chemicals will be described. Subsequently, detailed toxicity characteristics of each subgroup will be listed. Finally, military as well as civilian potential of such agents will be discussed.

Articles from scientific databases.

Garantující pracoviště:	Katedra chemie, Přírodovědecká fakulta
Vedoucí práce:	Mgr. Eugenie Nepovimová, Ph.D.
Datum zadání závěrečné práce:	27.6.2018

Declaration

I hereby declare that I have written this Thesis on my own and that I have duly referenced all the sources which I had used.

In Hradec Králové, July 2020 Michaela Dohnalová

Acknowledgement

I would like to express many thanks to my supervisor, Mgr. Eugenie Nepovimová, PhD., for her help, advices, kindness and last but not least correction of my English grammar. Thereafter, I would also like to thank to the Institutional support of the Faculty of Science, University of Hradec Králové.

Annotation

Current Bachelor Thesis focuses on non-lethal chemical weapons and their misuse. In addition to their general characteristics as a group of chemical weapons, history of their use and the Convention on the Prohibition of Chemical Weapons in relation to such group of chemicals are also described. However, the main part of the Thesis deals with a detailed description of individual subgroups, which includes their general characteristics, physicochemical properties, description of individual representatives, mechanism of action, clinical picture of intoxication and therapy of poisoning. Finally, discussion aimed on status of these substances in current world is included.

Keywords: non-lethal chemical weapons, riot control agents, incapacitating agents, malodorants, calmatives, vomiting agents

Anotace

Daná bakalářská práce se zaměřuje na neletální chemické zbraně a jejich problematiku. Kromě jejich obecné charakteristiky jako chemických zbraní, je popsána také historie jejich použití a vztah Úmluvy o zákazu chemických zbraní k těmto látkám. Majoritní část práce tvoří podrobný popis jednotlivých skupin neletálních zbraní, což zahrnuje jejich obecnou charakteristiku, fyzikálně-chemické vlastnosti, popis jednotlivých zástupců, mechanismus účinku, klinický obraz intoxikace a terapii otrav. Nakonec je diskutováno postavení těchto zbraní v současném světě.

Klíčová slova: neletální chemické zbraně, dráždivé látky, zneschopňující látky, malodoranty, kalmativa, látky vyvolávající zvracení

Table of Contents

List of abbreviations

5-HT	5-hydroxytryptamine
7-MEOTA	7-methoxytacrine
BAL	British Anti-Lewisite
BZ	3-quinudinyl benzilate
BZD	benzodiazepine
CA	brombenzylcyanid
CN	chloroacetophenone
CR	dibenzo[*b*, *f*][1,4]-oxazepine
CS	2-chlorbeznylidene malononitrile
CGRP	calcitonin gene-related peptide
CW(s)	chemical weapon(s)
CWC	Chemical Weapons Convention
ED_{50}	effective dose
ICA(s)	incapacitating agent(s)
IC_{T50}	incapacitation concentration and time
LC_{T50}	lethal concentration and time
LD_{50}	lethal dose
LSD	*N*, *N*–diethyl lysergamide
NATO	North Atlantic Treaty Organization
OC	oleoresin capsicum
PAVA	pelargonic acid vanillylamide
PCP	phencyclidine
RCA(s)	riot control agent(s)
SOD	Special Operations Division
TRP	transient receptor potential
WWI/II	World War I/II

Introduction

Wide use of chemical weapons (CWs) and their impact within the world history caused prohibition of use of such chemicals. Currently, non-lethal CWs are widely used, in particular, for riot controlling within the demonstrations or in military training. Among non-lethal weapons also belong agents that are more dangerous than others, e.g. Fentanyl, and therefore more attention has to be devoted to their toxicity, mechanism of action, and therapy of poisoning.

The aim of this Bachelor Thesis is to sum up available information on non-lethal chemical weapons since just a few review publications are focused exactly on their issue. Mostly, when non-lethal CWs are discussed, such articles deal mainly with riot control agents (RCAs) and incapacitating agents (ICAs).

Within current Thesis we tried to summarize all the subgroups of non-lethal CWs, characterizing them, and of course, give examples of exact agents that are commonly used, or which have a huge potential to be used. With regard to a big number of representatives, this Thesis focuses only to the most important ones within each subgroup.

The first chapters briefly describe non-lethal CWs as a group of military weapons, Chemical Weapons Convention (CWC), and the history of their usage. Then, single chapters describe each subgroup in detail.

1 Non-lethal chemical weapons

Non-lethal chemical weapons are supposed to have lower toxic effects than other chemical weapons, which induce serious health issues or can even kill. Thus, effects evoked by non-lethal chemical weapons either disappear after the exposure or some time after it, or the intoxication caused by these agents is easier to treat. Such CWs are supposed to incapacitate the victim physically (RCAs, malodorants) or psychically (ICAs, malodorants). Although the main aim of non-lethal chemical weapons is not to cause permanent injury or even to kill, there is always a risk of fatal end. [1], [2] We should always keep in mind the definition of poison stated by Paracelsus [3]: "It is only a dose which makes a thing poison". The same can be also applied for non-lethal CWs. If such substances are used as expected, then their effects are not that toxic. However, if high concentrations are used, especially in enclosed area, the intoxication evoked by these agents can lead to death. For this reason, these CWs are called "less-lethal" instead of "non-lethal". [1], [2]

The official definition of non-lethal weapons by North Atlantic Treaty Organization (NATO) is as follows: "Non-lethal weapons are weapons which are explicitly designed and developed to incapacitate or repel personnel, with a low probability of fatality or permanent injury or to disable equipment, with minimal undesired damage or impact on the environment" [4]. By this policy, non-lethal weapons are presumed to enhance the capability of NATO forces to achieve such objectives:

1. to accomplish military missions and tasks in situations and conditions where the use of lethal force, although not prohibited, may not be necessary or desired;
2. to discourage, delay, prevent or respond to hostile activities;
3. to limit or control escalation;
4. to improve force protection;
5. to repel or temporarily incapacitate personnel;
6. to disable equipment or facilities;
7. to help decrease the post-conflict of reconstruction.

Non-lethal CWs are used not only in the military within some operations or to train soldiers for a possible chemical attack, but they can also be used against

civilians, e.g. to calm demonstrating crowd. Additionally, non-lethal CWs could be also used against terrorists and/or in some countries as a mean of self-defence. [5]

Sometimes, the term non-lethal chemical weapons is confused with the term "incapacitating agents", since their main focus is to incapacitate the person. However in the military meaning, incapacitating agents represent a subgroup of non-lethal CWs. Classification of non-lethal CWs is listed in Table 1. RCAs are usually divided into lachrymators and sternutators. Several literature sources state vomiting agents to be a separate subgroup of RCAs [6], [7]. However, since the representatives of sternutators and vomiting agents are the same, we have decided to merge mentioned subgroups into a single one. Another group of non-lethal CWs are malodorants. The third main group - ICAs could be divided into four subgroups: psychedelics, deliriants, calmatives, and stimulants. Since the latter subgroup has almost no potential to be used as chemical warfare, it has not been included among the objectives of this Thesis.

Table 1. *Classification of non-lethal chemical weapons.*

Main group	**Subgroup**	**Representatives**
riot control agents	lachrymators	agent CS, agent CN
	sternutators/vomiting agents	Adamsite, Clark I, Clark II.
malodorants		Skatol, Cadaverine
incapacitating agents	psychedelics	LSD
	deliriants/anticholinergics	Agent BZ
	calmatives	Fentanyl, Midazolam, PCP, Ketamine
	stimulants	Caffeine, Cocaine, Amphetamines

2 Chemical Weapons Convention

It is widely recognized that CWs cause serious toxic effects on human health or even death. In 1868, an international military commission in St. Petersburg elaborated a declaration stating that chemical weapons are causing useless suffering of people and that their use is against humanity rules. In 1874, it was additionally declared that the war does not give a freedom of choosing tools for enemy's destruction. Based on this declaration, the Convention Respecting the Laws and Customs of War on Land was elaborated in Haag in 1899 – 1907. The so-called Hague Convention prohibited the use of poisons, poisonous weapons and weapons or agents causing useless suffering. Unfortunately, this Convention did not prevent from using CWs within the World War I (WWI). The Geneva Protocol from 1925 prohibited using choking gases, liquids, or similar means in war conflicts, as well as use of bacteriological weapons. The Protocol did not prohibit or limit preparation of chemical or biological weapons. In addition, the term chemical weapon was not exactly defined. [8], [9]

Hague Convention as well as Geneva Protocol did not prohibit chemical weapons sufficiently, which resulted in the Chemical Weapons Convention preparation. CWC is the Convention dealing with prohibition of the development, production, stockpiling and use of chemical weapons and their destruction. It was introduced in Paris on January 13, 1993 after complicated proceeding. CWC entered into force on April 29, 1997 [1], [5], [8]. To this day, 193 countries ratified the Convention [10]. More than 70 000 tons of chemical agents were destroyed, constituting 97.51 % of the whole world's declared amount of chemical weapons. [10]

CWC consists of four main subparts. The first one is complete and irreversible describing destruction of chemical weapons, objects for their preparation, as well as methods of their destruction. The second subpart characterizes the control of non-proliferation. Help and protection are the main aims of the third subpart, which includes not only the help to member states in case of chemical attack, but also training and education. The last, fourth, subpart comprises International Cooperation ensuring meeting and conference organization to share experiences and knowledge and to support the usage of chemistry for peaceful purposes. [8]

CWC also defines chemical weapons as [5] all toxic chemicals and their precursors, except when used for purposes permitted by the Convention in

quantities consistent with such a purpose. The same document defines toxic chemical as [5] any chemical which through its chemical action on life processes can cause death, temporary incapacitation or permanent harm to humans or animals.

CWC does not prohibit using chemicals in industry, agriculture, scientific researches and also usage for protection against toxic chemicals or chemical weapons, for military operations, and to maintain the public order - RCAs (but those cannot be used as the chemical warfare agent). [5]

The definition of RCAs by CWC is any chemical not listed in a schedule which can produce sensory irritation or disabling physical effects rapidly in humans and which disappear within a short time following termination of exposure [5].

The CWC does not define ICAs, but they are included in the definition of "toxic chemical". Since both of these groups are allowed to be investigated, stockpiled and used, there is also an easy way how to abuse these agents by terrorists, or countries which still did not ratify the CWC. In any case, it should be highlighted that several RCAs/ICAs can be more dangerous than the prohibited ones. [11]

Except prohibiting the usage of non-lethal CWs in wars, there is no other restriction connected with it, and that is a reason of the danger.

3 History of non-lethal chemical weapons

The most extensive usage of chemical weapons took place within the World War I, when Germans used chlorine in Ypres on April 22, 1915. Other dangerous agents, e.g. phosgene or mustard gas, were also used in the same time. After the war, people perceived chemical weapons as inhumane and refused their usage, however, they were still deeply investigated, synthetized and stockpiled. [9]

Vomiting agents (Adamsite, Clark I and Clark II) were developed and weaponized at the end of the WWI. Clark I was used in June, 1917 by Germans, while Adamsite was never used within the same conflict. It was used later during the Russian Civil War and Second Indochinese War. [12], [13], [14] Maybe it will sound surprisingly, but within World War II (WWII) chemical weapons have been never used, although more than 400 000 tons of chemical warfare agents were stockpiled. One of possible reasons was unfortunate experience of Adolf Hitler from the WWI when he was affected by a mustard gas. He assumed that his enemies also possess CWs and that in case of chemical conflict they would use it too [1]. After WWII, countries were still developing novel CWs or were making the stocks of them. [9]

Later, non-lethal chemical weapons started to soar in popularity. Although, RCAs were for the first time used within the WWI, they get significantly more attention in years 1960 – 1970, when they started to be used by police to control crowds [15] Agent CS was used also in the Vietnam War (1955 – 1975) by Americans [16]. Another example of RCAs use was attack with tear gas on religious sect Branch Davidian by federal agents in 1993 [7], [17].

Incapacitating agents are well-known for their potential to induce hallucinations. The first agent investigated by the army was LSD-25 [9]. In 1951 in French town Pont-Saint-Esprit, many people were seriously intoxicated by unknown agent [18]. One of the versions was consumption of bread contaminated with ergot alkaloids. This case will be described in detail in Chapter **5**. Total synthesis of LSD-25 is expensive and complicated, therefore, the research continued with other substances. From the military point of view, agent BZ (3-quinuclidinyl benzilate) became the most appropriate agent. After the US army implementation of agent BZ into ammunition, the research searching for agent BZ antidote was launched. Military medical academy of Jan Evangelista Purkyne in Hradec Kralove (currently Faculty of Military Health Sciences, University of Defence) achieved a success in such

field, introducing antidote 7-methoxytacrine (7-MEOTA). Later, with CWC entering into force, the USA destroyed their stockpiles of agent BZ. [9], [19]

Currently, it is allowed to use RCAs by police or special forces against terrorists. An inappropriate use of such agents is known from the terrorist attack on Moscow theatre by Chechen rebels in 2002. Russian special forces used fentanyl, or its analogue, against terrorists with terrible consequences. [20] This event will be described in detail in Chapter **7**.

CWC prohibits usage of chemical weapons in war conflicts, but as it has been mentioned above, this limitation is binding only on countries which ratified this document. It is clear, that terrorists who would like to achieve their goals will not follow it. An example of such abuse were seven letters containing a vomiting agent Adamsite that were sent all around Belgium in June 2003 by Iraqi political refugee. [21] This will be discussed in Chapter 8.

At present, non-lethal chemical weapons are widely used on Greek borders where they are used by police to prevent illegal migrants from entering Greece from Turkey. [22]

4 Riot control agents

4.1 Characteristics

Riot control agents constitute a subgroup of non-lethal chemical weapons, which are highly irritating sensitive receptors in eyes, skin and mucous membranes of respiratory and gastrointestinal tracts. The human body protects itself against such agents by various reflexes (e.g. winking, coughing, tearing or vomiting). [23], [24] These agents are also known as harassing agents, tear gases, incapacitating agents or lacrimators [16]. In military meaning, they cannot be called Incapacitating agents because that is another group of non-lethal CWs with different characteristic properties.

These agents belonged among the first chemical weapons that were used within the World War I. Since that times, a lot has changed. Chemical Weapon Convention in its current wording says, that RCAs cannot be used in wars [5]. However, there are other situations when their use is allowed, e.g. within harassment, temporary incapacitation or dispersion of a crowd. In several countries, they can be also used by people for self-defence. [12]

One could suppose that general characteristics of RCAs and incapacitating agents is the same – to incapacitate, however, their effects are different. There are three basic properties common for all types of RCAs: i) rapid effect (generally seconds to minutes); ii) short duration of action (usually 15 – 30 minutes); and iii) high ratio of safety (significant difference between effective dose - ED_{50}; and lethal dose - LD_{50}). The effect of RCAs is immediate, and it ends quite fast after the exposure. The intensity of the effect depends on the type of the substance, concentration, time of action and way of usage. Extremely high doses can also cause a death. [2], [6], [7]

RCAs are usually divided into two subgroups that differ by the localization of receptors which they affect. The first group is called lacrimators. Such agents affect receptors of sensitive nerves in cornea or conjunctiva. Typical symptom of intoxication is lacrimation. The second group represent sternutators, i.e. substances causing receptor irritation in respiratory mucosa. Among the main signs of intoxication belong sneezing and coughing. Some sources state vomiting agents, that irritate mainly gastrointestinal tract, to be another group of RCAs. However,

representatives of sternutators and vomiting agents are the same and we will describe it in the detail in Chapter 8. [23], [7]

4.2 Physicochemical properties

At room temperature, RCAs are solid crystalline substances with low vapor pressure. They are usually used in the form of a solution or as aerosol sprays but can be dispersed as fine powders or foams. Some are odourless, but e.g. CS agent has a pepper-like odour. [13] Its solubility in water is low, but it can be dissolved in organic solvents. [25]

4.3 Representatives

In the table below (Table 2) are compared values of lethal concentration and time - LCt_{50}; incapacitating concentration and time - ICt_{50} and safety ratio for humans of three riot control agents for better toxicity comparison.

Table 2 *– Estimates of ICt_{50} values and LCt_{50} values for various RCAs* [13]

Agent	**LCt_{50} ($mg/min/m^3$)**	**ICt_{50} (mg/m^3)**	**Safety ratio (LCt_{50}/ICt_{50})**
CS	25 000 – 150 000	5	5 000 – 30 000
CN	8 500-25 000	20-50	425 - 500
CR	>100 000	1	100 000

4.3.1 CS (2-chlorbenzylidene malononitrile)

CS (Fig. 1), an agent with pepper-like odour, was prepared by Corson and Stoughton. Therefore, the name CS stands for an abbreviation of the discoverers. Its prototype was chemical substance called brombenzylcyanid (CA), which is not used anymore due to its low stability and high toxicity. [23]

CS exists in more forms – CS, CS1 and CS2. CS is pure white crystalline powder. In CS1, silica is added to a micro-pulverised CS powder to increase its effectiveness and persistency. CS1 can stay active for 14 days in a closed place and one week in open air. CS1 mixture is used into pepper sprays for self-defence. In CS2 form, CS powder is mixed with silicone-treated silica aerogel, which helps to repel water and prolongs the effect. [24]

There are several evidences confirming effects lasting about six months and even more, which is the full opposite of its characteristic. [24], [26], [27], [28]

If it is applied on skin, it can cause blisters in the places of sweating or where the clothes touch the skin. If an eye comes to a contact with CS, it induces irritation of conjunctiva, which disappears after some time. The probability of any eye harmful impact is much lower with CS than with other agents. [23]

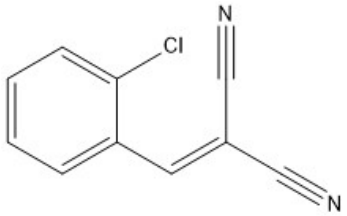

Figure 1 – Agent CS

4.3.2 CN (1-chloroacetophenone)

CN (Fig. 2), crystalline solid substance with pungent odour, was developed after World War I. Agent CN was supposed to replace lacrimators derived from Adamsite, which was the most effective RCA that days. Nowadays, CN is not used anymore by the military forces, but it can appear in the mixtures used by the police. [23]

CN evokes excessive lacrimation, salivation, conjunctivitis, nasal secretion and lethargy. At higher concentration it can damage corneal epithelium. [23]

Clinical effects of CN are similar to effects of CS, but it is more harmful, and it can cause serious side effects. The effective dose of CN can be more toxic than effective dose of CS up to ten times. In the past, several fatal cases caused by too high concentration of CN used in closed places were described. The cause of death was lung oedema, alveolar bleeding and necrosis of mucosal lining. [29], [30] In April in 1981, prisoners were exposed to CN agent by correctional officers, to enforce the order. It was released as an aerosol and decontamination was lasting several days therefore the ocular and dermal effects were worse. Six deaths have been reported. [30]

Apart from irritating effect, toxic chlorine derived from CN could be formed during contact with skin or mucosa. Moreover, due to the humidity of the environment it could be reduced to hydrochloric acid, which can, thereafter, burn the skin. [23]

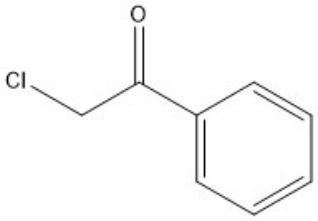

Figure 2 – Agent CN

4.3.3 CR (dibenzo [*b*, *f*] [1,4]-oxazepine)

CR (Fig. 3) is stable, lightly yellow loose substance, which is dispersed in solution as a liquid or aerosol spray. It is a potent sensory irritant with toxicity lower than that observed in CS or CN. [23], [24]

This agent has strong lacrimation effect and causes an immediate and effective irritation of the eyes, nose and skin; however, it does not cause any harmful side effect, such a corneal damage. CR exerts high efficiency, 5-times higher than CS. Due to its high efficiency, lower concentrations to get the requested effect are needed. CR´s efficiency manifests as redness, that usually disappears within 2 hours, and intensive burning feeling, which lasts for about 30 minutes. [7], [23]

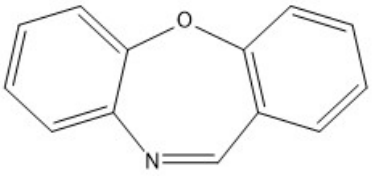

Figure 3 – Agent CR

4.3.4 Oleoresin capsicum

Oleoresin capsicum (OC) is a natural mixture of various substances isolated from many different kinds of pepper, for example, chilli, red or jalapeno. Mostly, OC contains about 70 % of capsaicin (Fig. 4), which belongs to a group of capsacinoids, and is the most effective substance in OC mixture. [24]

OC causes burning of mucosa and skin, makes people cough, belch and evokes troubles with breathing. Due to these effects, it is used as RCA, as an incapacitating agent for dangerous individuals, or in pepper sprays for self-defence, which can contain only OC or a mixture of OC and CS1. [7], [24]

Except using OC as an RCA, it is also used at low concentration in some ointments due to its warming up effect. Currently it is possible to replace natural capsaicin by

synthetically prepared nonivamide, which is more safe, stable and pharmacologically equally active. [23]

Mostly, as a carrier of capsaicin, is used isopropylalcohol. Because of this carrier it is more complicated to determine exactly the toxic effect of capsaicin since isopropylalcohol is toxic as well. [23]

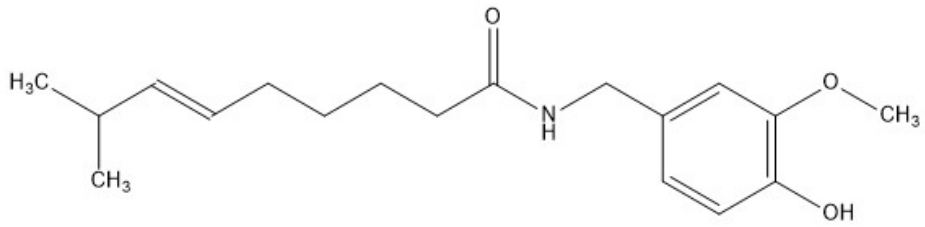

Figure 4 - Capsaicin

4.3.5 PAVA (Pelargonic Acid Vanillylamide)

PAVA (Fig. 5), also knowns as nonivamide, is a synthetic form of capsaicin. Due to its immediate effect on eyes, inflammation of mucosa and of upper respiratory tract, PAVA is also classified as an inflammatory substance. [24]

The eye pain is slighter than pain evoked by natural capsaicin, but it is more severe than pain caused by CS agent. [7], [24]

The onset is immediate, and it has a high rate of effectiveness, however, it disappears 15 – 20 minutes post exposure on the fresh air. Additionally, it was proved that PAVA is ineffective in people who drank some alcohol before the exposure. [7]

There are two forms of PAVA: captor I and captor II. Captor I contains 0.3 % of PAVA with a mixed solvent of ethanol and water in the same ratio. Captor II contains 0.3 % of PAVA in propylene glycol, ethanol and water. [7]

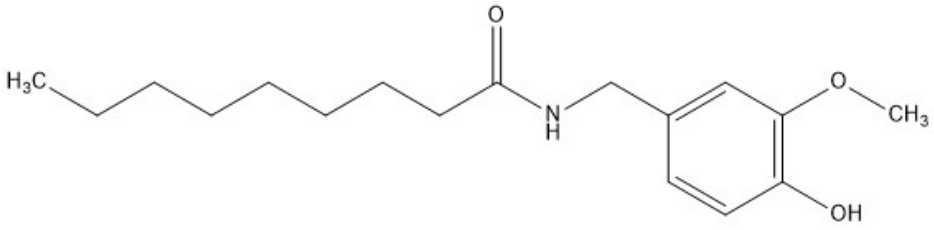

Figure 5 - PAVA

4.4 Mechanism of action

4.4.1 CS, CN, CR

The mechanism is not fully understood, but one of the presumed one is the irritation of sensorics and sensitive receptors in eyes, skin and mucous membranes of respiratory and gastrointestinal tracts. The toxic effect of blisters, irritation and burns on skin can be explained as a reduction of chlorine ions and subsequent production of hydrochloric acid that injures mucosal membrane. A tissue injury can be caused by inactivation of metabolic enzyme systems that react by their thiol and sulfhydryl groups with RCAs. The affected enzymes are, for example, glutamic dehydrogenase or pyruvic decarboxylase. One source claims that lactic dehydrogenase is completely unresponsive [31], another, on the other hand, says that it is highly inhibited by CS. [32]

4.4.2 Capsacinoids

The mechanism of capsacinoids consists in binding to specific vanilloid receptors V1, which are a part of transient receptor potential (TRP) channels. They are labelled as TRPV1 and are found in peripheral and central endings of primary nociceptive neurons. [33]

Vanilloid receptors belong among the ion channels opened by a substance of the capsacinoids type, or by the warm initiating. While channel opening, Ca^{2+} and Na^{+} ions start to influx, depolarizing thus the neuron and releasing neuropeptides from sensory neurons (e.g. substance P, calcitonin gene-related peptide (CGRP) and neurokinin A which are causing the toxic effect typical for capsacinoids. [7]

The sensitivity of vanilloid receptors to capsacinoids is really high, therefore, only low concentrations of capsacinoids are needed. [7]

4.5 Clinical picture of intoxication

The expression Ct is used to indicate its inhalation toxicity and it is defined as “the product of concentration (C) in mg/m^3 multiplied by exposure time (t) in minutes”. There is also used LCt_{50}, for lethal dose, and ICt_{50}, for incapacitating dose to 50 % of the exposed population. [7]

Clinical symptoms RCAs are usually disappearing after 30 minutes, but it can last longer according to dose and time of exposure. The concentration and time of exposure are also influencing exact effects. Higher concentration in shorter time

evokes more harmful effects than lower concentration for longer period of time. Eyes and respiratory tract are the most affected organs. [16]

Effect on **eyes** is typical for lacrimators, which are causing intensive and fast stinging and burning of eyes, together with lacrimation. At high concentrations, they can even reversibly damage the eyes, in particular cornea. [23] Except the symptoms mentioned, also photophobia, blepharospasm, conjunctivitis etc. may occur. Some people can also exert less specific symptoms, such as headache or fever. [16]

The respiratory system is attacked mostly by sternutators. They irritate highly sensitive TRPV1 receptors, which are abundantly present in respiratory mucosa. The first symptoms include reflexes, such as cough, stinging or burning feeling in the nose, sneezing, and struggles with breathing. Increase in concentration of RCA could evoke in the patient severe chest pain. Capsaicin can also affect upper respiratory tract and cause bronchoconstriction and pulmonary oedema. [16], [23]

Skin is getting into a contact with RCAs almost in all cases and, therefore, it would not be surprising that it could be affected a lot. After agent CS exposure, the patient can feel tingling or burning. However, if the exposure takes longer time, it could cause blisters, oedema and superficial burns. The CN agents may induce blister formation, rash and pruritus, but also more severe injuries, such a second degree burns or subcutaneous oedema. [16]

RCAs inhalation can lead to an aftertaste on tongue or induce burning feeling. CS **ingestion** may cause nausea, vomiting, crampy abdominal pain or diarrhoea. On the other hand, capsaicin can cause various toxic effects especially on gastric mucosa, e.g. oedema, epithelial cell damage or mild erythema. [7]

4.6 Therapy of poisoning

Clinical symptoms resulting from RCA exposure usually disappear within one hour. First of all, it is needed to get the patient out of the infested area to minimize the exposure time. In case of **eye** intoxication, it is important to remove the contact lenses. If the agent, that was used was just an irritant compound, it is recommended to use a flush of warm air to get rid of solid particles from the eye. Rinsing an eye with water could make the irritation even worse. If the patient is not sure what type of compound was used, he has to use water or physiological solution for 10 minutes immediately in all cases. To relieve the pain, it is possible to use a local anaesthetic.

Finally, the patient has to be checked by an ophthalmologist to avoid any injury or inflammation of cornea. [23], [7]

If **respiratory** system is affected, aminophylline, for smooth muscle relaxation and relief from bronchial spasms, and/or glucocorticoids for inflammation suppression should be applied. [23]

If **skin** irritation does not disappear within one hour, the patient should use corticosteroid creams. The particles of RCAs can be caught by make-up or false eyelashes; therefore, they should be removed. Furthermore, it is important to take away contaminated clothes. For dermatitis induced by agent CS intoxication, it solution of 6% sodium bicarbonate, 3% sodium carbonate and 1% benzalkonium chloride can be used. The blisters should be cared by tiles with Burow/Jarisch solution for 30 minutes, 3 times per day. [23], [7]

Vomiting and nausea usually disappear without any need for further treatment. [7]

5 Incapacitating agents

5.1 Characteristics

Similarly to RCAs, the purpose of incapacitating agents is to incapacitate, which means (in military meaning) to make the person not able to accomplish his orders or finish his work, activity [12]. There are two main differences between these two groups of chemical warfare agents: i) comparing to short-lasting effect of RCAs, the effect of ICAs lasts for hours or even days after the exposure; ii) the main biological targets of ICAs are placed in the central nervous system, whereas RCAs affect mainly the peripheral one. However, the effect of ICAs is not persistent and is reversible. The last but not least distinctive feature of this group of non-lethal weapons is that the dose causing incapacitation is much lower than the lethal one. Therefore, the cases of serious injuries caused by ICAs in open area are rather unique. [12], [24]

There are criteria for ideal properties of ICA listed below [34], [19]:

1. Effectiveness – the agent must significantly reduce or completely eliminate the enemy's ability to fight;
2. Relative lack of toxicity – if used appropriately, it should not evoke any permanent injury or death;
3. Persistence – effects must be temporary lasting minutes to hours or maximum few days;
4. Logistical feasibility – the agent needs to be stable, potent, and suitable for a munition;
5. Treatability – the effect should be fully or partially reversible, or easily treated by simple medicaments. Even without treatment, the agent should not cause any permanent injury;
6. Predictability – the behaviour caused by this agent must be predictable, it must not endanger civilians or increase the probability of activating weapons of mass destruction by this affected individual;
7. Manageability of casualties – if the incapacitated individual is captured, he should be under control, and deaths or injuries must be prevented;
8. Expense – the cost of production and usage must be affordable.

Classification of ICAs is complicated and there are more ways. *Patočka* [14] divides it by its structure, *NATO Handbook* [35] divides it into two groups –

stimulants and depressants. I decided to choose a classification by *Ketchum and Sidell* [34] and by *U.S. Army Medical Research Institute of Chemical Defense* [36]. They say that ICAs, so-called psychochemical agents, could be divided into four subgroups: deliriants, psychedelics, depressants and stimulants. **Deliriants** are a subgroup of compounds which are causing hallucinations, confusion and disorganized behaviour effects (called delirium) if they are given in a high dose. In lower doses, their effect is rather therapeutic. Just a few of deliriants are good to be used for military purposes, in pharmacology this group of compounds is called anticholinergics [24]. The most common mechanism of action deliriants and anticholinergics is blockade of muscarinic effects of acetylcholine (ACh). The most military significant deliriant is BZ agent [34]. Some publications are also categorizing it as depressant due its interfering with transmission of information across synapses.

The next subgroup is called psychedelics ant it is producing abnormal psychological effect resembling mental illness. The main representative is drug LSD, which was intentionally developed as incapacitating agent. However, due to its unpredictable behaviour its testing was stopped. There are some other psychedelics sharing indole ring similarly to LSD, like psilocybin, ibogaine or harmine, but if we compare them, LSD is a highly potent agent, which causes complete incapacitation after the oral dose of 2.5 μg/kg, while e.g. psilocybin evokes effects like muscle weakness, nausea, visual field changes after an oral dose of 60 μg/kg. [12], [34]

The third subgroup are depressants which are also denoted as calmatives in military. Typical symptoms induced by these drugs are passivity and sleep [34]. As calmatives are an diverse subgroup of agents with different mechanisms and properties, they will be discussed in the next chapter.

The last subgroup is called stimulants. They are speeding up mental and physical processes in the brain [37]. Among stimulants belong, for example, amphetamines, cocaine, caffeine, nicotine, and strychnine with metrazole which are also considered as epileptogenic substances. Stimulants do not have real potential to be used as effective non-lethal chemical weapons because their low dose can be actually evoking more energetic or aggressive behaviour. Stimulants are used in pharmacology more. E.g. Amphetamines are used for decreasing tiredness and improvement of cognitive functions (memory, concentration, attention, etc.) [34]

Incapacitating agents are easy to synthetize or isolate from natural sources. Because of their effects some of these agents are synthesized and used as recreational drugs. Also, it is used in medicine, or by police and special forces in cases with a hostage. [12]

The most military important agents of ICAs are BZ agent and LSD-25 which will be discussed more below.

5.2 Physicochemical properties

Most of incapacitating agents are insoluble or just slightly soluble in water. ICAs are soluble in organic solvents, such as alcohols or oils. Salts of these agents are soluble in water. Vapours of volatile ICAs exert higher density than air so they accumulate in low laying areas. However, most of them are non-volatile, so their vapours do not cumulate so much. Some of ICAs are slowly decomposed by water. The rate of decomposition may increase by making an aqueous solution of these agents more alkaline. [12]

Military exploitable agents can be stored without any stabilizers, since they are stable enough. Since they do not have any odour, or just a little, and the vapor is not irritating eyes, it is hard to recognize its presence. Liquids or solid agents are not even irritating the skin. [12], [38]

5.3 Representatives

5.3.1 Agent BZ (3-quinuclidinyl benzilate)

Agent BZ (Fig. 6) is a synthetic ester of glycolic acid and its anticholinergic action is similar to atropine [25]. It blocks the muscarinic action of acetylcholine at central and peripheral cholinergic synapses. [19] Firstly, it was studied as a therapy against gastrointestinal diseases. Within this study it was also reported that it could evoke hallucinations even in small concentrations and therefore it was turned over to the US Army as a possible incapacitating agent. [7], [14], [34]

It is a highly persistent agent in soil and water and its half-life is three to four weeks in moist air. [13], [38] Without loss of its incapacitating activity, it is stable at least for one or two days at field conditions. [7]

If the exposure to this agent lasts 1 – 2 hours it causes mydriasis, dry mouth and skin, but after 4-hour exposure CNS anticholinergic effects are accompanied by delusion state and hallucinations. Agent BZ also causes troubles with cognitive

functions, such as solving problems, attention and comprehension. Such effects can insist for more days and during this time it is more easy for the patient to get some injury. [19] The person is disorientated, behaves inappropriately, speaks indistinctly and cannot properly follow commands which makes the BZ agent a suitable ICA. [13]

Even BZ can be absorbed by many routes, the chemical attack would probably involve inhalation of aerosol because it can be easily dispersed, or ingestion of contaminated food or water. [38]

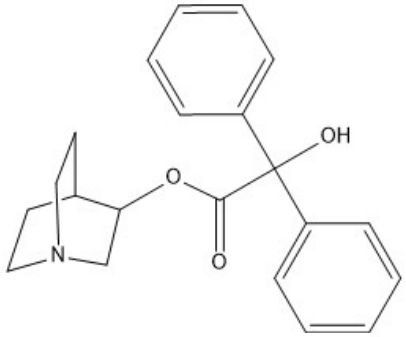

Figure 6 – BZ agent

5.3.2 *N*, *N*-diethyl lysergamide (LSD-25)

LSD-25 (Fig. 7) is one of psychedelics [34], but in some older publications, it can be found as a CNS stimulant.

LSD-25 is odourless, colourless crystalline, soluble in water. In biochemical research it is used as serotonin antagonist and also it is used an illegal drug. [12]

LSD-25 is a polo synthetic compound synthesized from ergot alkaloids, known for a long time already. Its effects can be seen at really low concentration (1-2 μg.kg^{-1} s.c.) and that is why LSD is biologically the most effective compound of this group. The lethal dose is thousand times higher than the biologically active dose. [14]

Effects of LSD-25 are mostly hallucinations, people can see just more bright colours, they can see different shapes of things around them, but they can also see completely unreal things. Person can also have problems to talk, to move, he can laugh without any reason. More will be said in chapter 5.5. [14]

LSD-25 was a potential considered as incapacitating agent with a great use in military, thanks to its low effective dose, high lethal dose and because of its pharmacological/toxicological effects on humans. There was an experiment, when people in important functions, such as commanders, who were intentionally intoxicated with LSD-25 and, thereafter, they were completely incapable to give

orders, make decisions, organize further steps [14]. Also, even trained soldiers became totally unorganized. LSD-25 evokes unpredictable behaviour and even if it does not really induce any serious health problems, the affected person could possibly hurt anybody else, or itself. [34]

On August 16, 1951, 300 residents of French village Pont-Saint-Esprit complained about sudden nausea, vomiting and headache and approximately 100 residents had hallucinations. Some people committed suicide, several experienced self-injurious behaviour and some became insane. Finally, at least 7 people died, 46 had to be detained in asylums and many others could not get a job again. It was claimed that bread from the town's bakery was contaminated by ergot, which caused all those symptoms. After almost 60 years later claims proved that the CIA and the U.S. Army's Special Operations Division (SOD) were responsible for this situation because they tested the effects of hallucinogens. [39]

There are also other analogues of LSD-25, such as LAE-32 (Fig. 8), ALD-52 (Fig. 9), which are causing similar effects, but the dose that evokes such effects should be much higher. [14]

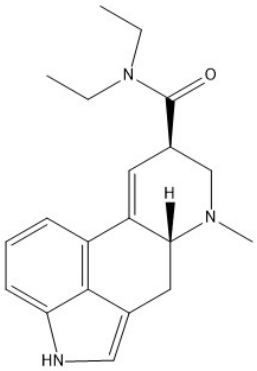

Figure 7 – LSD-25

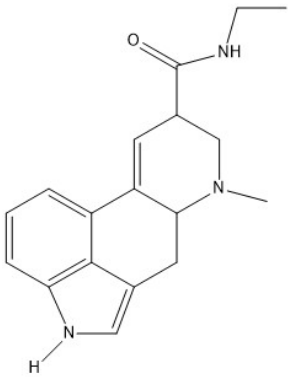

Figure 8 – LAE-32

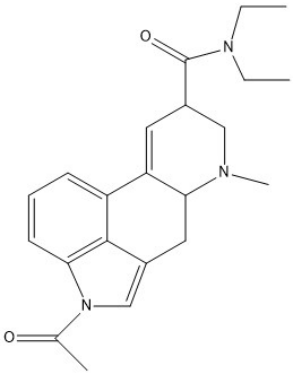

Figure 9 – ALD-52

5.4 Mechanism of action

The mechanism of action of agent BZ consists in blocking the effects of acetylcholine, because it occupies receptors of Ach. There are two types of receptors that are stimulated by ACh, i.e. nicotinic and muscarinic receptors. Agent BZ, similarly as other anticholinergics, act as antagonists of muscarinic receptors, causing respective symptoms on nerve functions in CNS and also in periphery. At higher concentration it can also affect nicotinic receptors. [13], [14]

The effect of LSD-25 on CNS is caused via its structural similarity with neurotransmitter serotonin. [40]

LSD-25 displays affinity to several subtypes of serotonin receptors (5-HT_{1-7}). LSD-25 acts as a partial agonist on 5-HT_{2A}, which is associated with hallucinations. Stimulation of these receptors activates second messengers, which are affecting central and peripheral functions and evoking many changes of central, movement and vegetative functions (mydriasis, non-coordinated movements, tachycardia, salivation). [34], [14]

LSD-25 also interacts with dopaminergic system, especially with dopamine D_1 and D_2 receptors. It is not yet fully understood, how exactly LSD-25 affects dopaminergic system, but probably it releases dopamine, whose increased release is associated with schizophrenia. [40]

5.5 Clinical picture of intoxication

The onset of clinical symptoms induced by agent BZ is slow and can last 2 – 5 days, depending on the dose. There are three phases of agent BZ intoxication. Within the first phase, the patient can suffer from confusion, incoordination or slurred speech, later the effects, such as dryness of skin and mucous membranes appear. [14] Dry skin and mouth are described as “dry as a bone”, the reduction of sweating is inducing that the skin is warm and “hot as a hare” and “red as a beet”. [13], [36] Slightly elevated blood pressure and tachycardia may arise. In the second phase, which is also called deliriant phase, comes mydriasis, stupor and also coma is possible. The main indicator is bizarre acting, or the state of not being able to react on command or conversation, hallucinations, disorientation etc. In the last phase, since the person starts to recover, we can observe normal acting, but it can be interrupted by paranoid attempts to escape and hallucinations. The person is tired and torpid. [13], [14]

The first symptoms of intoxication by LSD-25 appear 20 – 30 minutes after drug administration. They include: feeling of hot and cold, nausea or dry mouth. 30 – 60 Minutes later changes of behaviour and of person’s view on the world around him are coming. The patient does not care about ordinary activities; he sees bizarre shapes and colours of things around. The body becomes so heavy for the person or conversely it can be too light. The most pronounced symptoms arise between 2 – 4 hours after the intoxication and they are associated with fast thoughts. The person

cannot talk correctly, laughs without any reason, has hallucinations. Sometimes the person can go through the stage of euphoria or depression. Movement problems are characterized with non-coordinated moves, twitching of the muscles of the face, or convulsions. Vegetative symptoms, such as tachycardia or higher blood pressure, could accompany the last stages. Four hours after the intoxication, the effects slowly disappear, with a complete recovery 2 - 4 hours later. [14], [34]

5.6 Therapy of poisoning

In the case of persistent mental aberration caused by agent BZ, the antidote physostigmine (Fig. 10) is used in the form of 2 - 3 mg intramuscular injection for alleviation, then continue with injections approximately at 15-60 min intervals [19]. Physostigmine reversibly inhibits acetylcholinesterase, what increases ACh level and thus ACh transposes the BZ from receptors [25]. Another antidote, that can be used, is 7-MEOTA (Fig. 11) with the same mechanism of action as physostigmine. The oral dose for mild intoxication by agent BZ is 100 mg. Intramuscular dosing of 50 mg is more effective for severe poisoning [19]. The research of antidote 7-MEOTA was conducted at the Military medical academy of Jan Evangelista Purkyne in Hradec Kralove (currently Faculty of Military Health Sciences, University of Defence). [9]

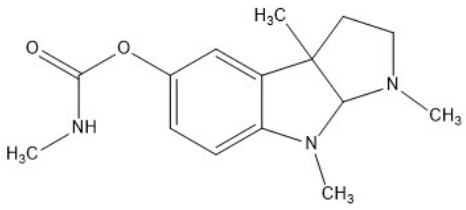

Figure 10 – Physostigmine

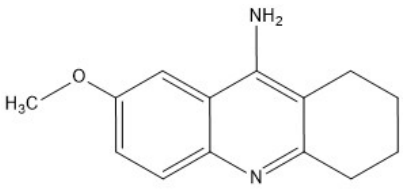

Figure 11 – 7-MEOTA

If there is an acute intoxication by LSD-25, it is important to take care of the person to avoid his abnormal actions to cause any injury of affected person or anyone else. The most effective antidotes are antipsychotics (neuroleptics), which are inhibiting excessive effects of neurotransmitters dopamine and serotonin. The most frequently are used chlorpromazine (Fig. 12) or haloperidol (Fig. 13). From non-typical antipsychotics clozapine (Fig. 14) and risperidone (Fig. 15) are preferred. After LSD-25 poisoning the patient has to visit a psychiatrist. [14]

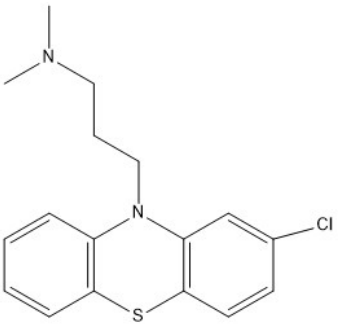

Figure 12 – Chlorpromazine

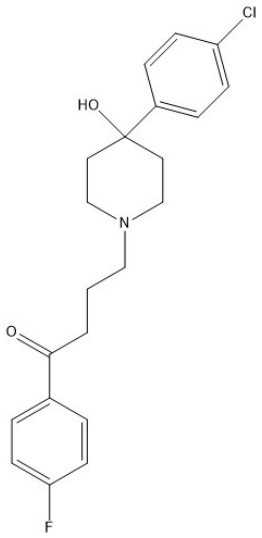

Figure 13 – Haloperidol

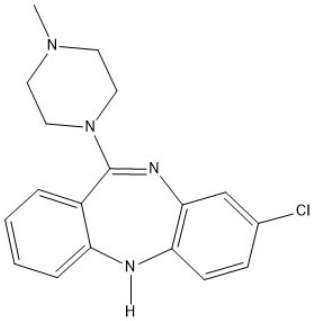

Figure 14 – Clozapine

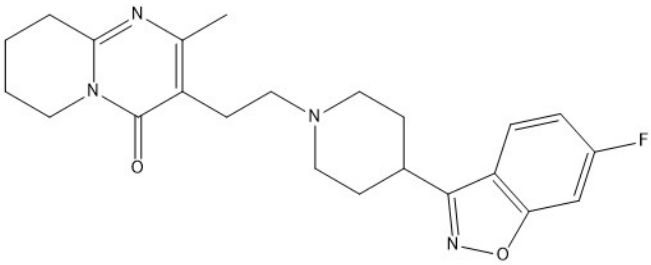

Figure 15 – Risperidone

6 Malodorants

6.1 Characteristics

The next group of non-lethal chemical weapons is a group of chemical compounds, characterized with disgusting odour which is also a reason of another name to this group – stink bombs [1]. They can be in a gas or liquid state. The power of malodorants is not just in incapacitation of one affected person, but also incapacitation of people who will get into the contact with this person later. This is caused by sticking on skin or clothes. Bad odour is still around, and the person cannot get rid of it. People feel very uncomfortable in places with such intense smelly aroma, and it decreases people's performance. [41], [12]

Malodorants could be also classified as RCAs [42], because they are sensoric irritants, in particular irritants of olfactory receptors [24]. Moreover, as it was mentioned above in Chapter 4, RCAs are chemicals causing sensory irritation.

These agents cause physical difficulties as vomiting, nausea or belching, but they can also evoke more serious psychical problems. Bad odour can be evaluated as a danger, which makes the intoxicated person panic and even run away. [12]

It is important to mention, that the odour depends on the concentration of the substance. Skatol, really smelly indole compound causing the smell of excrements, can be also found in a beautiful flower African Cone (*Zantedeschia aethiopica)*, has also a beautiful smell - caused by the same compound Skatol just in a really low concentration. [14]

As other non-lethal CW, even malodorants can cause death by using it in high concentration in enclosed area. [12]

Chemicals with an intense odour are used in many areas, e.g. food industry, pharmacy, as chemical intermediates for insecticides or an odorant to reveal gas leak. They are also used in a military to train soldiers for chemical attack or by police. [12]

6.2 Physicochemical properties

Malodorants are mostly stable, but several of them can be highly sensitive to a light and air. Such agents slowly decompose by water. As an active agent it is in a form of solution, an odour intensifier and liquid carrier. The liquid has high vapor pressure at ambient temperature. [12], [19]

6.3 Representatives

Since it was really difficult to find special agents used as non-lethal CW, I decided to write briefly about some possible agents.

These agents are made of a liquid carrier, odour intensifier and at least one malodorous substance. There is a lot of potentially usable compounds e.g. organic sulphur compounds, organic nitrogen compounds, organic phosphorus compounds and many more. In some cases, using only one malodorous compound is more preferred because the combination of more may cause interaction and then decrease the required effect, or at the other hand it can create more toxic compound. [12], [43]

One of the main malodorants are thiols and sulphides, whose repugnant odour is well known. Volatile thiols as methanethiol are used as odorants to show a gas leak. The intense odour of secret of skunk is mainly caused by 3-methylbutanethiol (Fig. 16) and 2-butene-1-thiol (Fig. 17). [44] The "Skunk" agent, probably made of the same compounds as skunk's secret, is used by Israelic occupations forces against Palestinians and its effects also include skin rash and irritation, abdominal pains and headaches [45]. *Tert*-butyl mercaptan is used in military trainings to simulate a danger of a toxic agent [12].

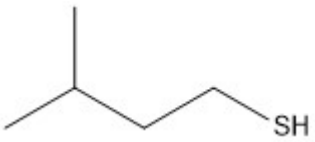

Figure 16 – 3-Methylbutanethiol

Figure 17 – 2-Butene-1-thiol

Skatol, typically 3-methylindole (Fig. 18), but this term can refer also to some other indoles as 4-methylindole or 6-methylindole [43], is a compound which has sweet odour in a low concentration, but it changes into fecal odour with a high concentration [14]. Its low concentration has an ability to intensify the odour [43]. It is causing skin and eye irritation [19].

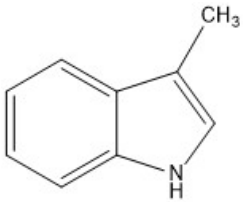

Figure 18 – 3-Methylindole

Putrescine (Fig. 19) and Cadaverine (Fig. 20) form during a bacterial degradation of amino acids. They are responsible for an odour of putrefying fish. [46]

Figure 19 – Putrescine

Figure 20 – Cadaverine

Another substance used at field practice in military is butyryl acid (Fig. 21) with an odour like a rancid butter or vomit, also used as a food additive. [12]

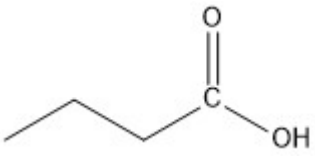

Figure 21 – Butyryl acid

6.4 Mechanism of action

Malodorants are olfactory cells irritants. In a ceiling of a nasal cavity there is a plenty of such cells with cilia, which are submerged in a layer of hydrophilic phlegm. The phlegm is catching odorants that must be in a gaseous form. Hydrophilic substances are dissolved in the phlegm, but lipophilic compounds have to bond to an odorant-binding protein, which is in the phlegm. After dissolving or bonding, particles of odorants are transferring to cilia and its receptors. It creates the excitement to the center of nerve cell and sending the electrical signal to the brain. [46]

There are two main types of nerves. The first is olfactory nerve, also called cranial nerve I, which provides the sense of smell. The second one is trigeminal nerve, so-called cranial nerve V, which provides the sense of irritation. [47]

6.5 Clinical picture of intoxication

Effects of these agents are showed up immediately after exposure. Malodorants have strong, repulsive odour which makes person feel nausea, gagging and vomiting. The effect depends on the concentration. The liquid substance can cause irritation of eyes, skin, mucous membrane or respiratory system. [12], [24]

If it is detected as a dangerous or noxious odour it can also cause a feeling of panic, fear and people may want to elope. If the exposure lasts longer, person can desensitize, and a higher concentration in a closed place can cause death. [12]

6.6 Therapy of poisoning

Effects caused by gaseous odorants are mostly disappearing quickly after getting the person out of the contaminated zone. Eyes must be washed by water or 0.9% saline solution for 15 minutes if there is a worse eye irritation. If there are some open wounds, it is needed to also wash it by water or 0.9% saline solution for 10 minutes. [12]

7 Calmatives

7.1 Characteristics

The name Calmatives is a military designation for chemical psychoactive agents [48] and they are frequently considered to be a part of incapacitating agents [34]. As we can see in the name, such agents are supposed to calm the person. Therefore, they can cause hallucinations but also unconsciousness via their ability to depress the CNS [49]. Agents with this ability are also called depressants. This group also includes many substances, which are used in pharmacy and medicine. However, just a few of them are effective non-lethal chemical weapons. [34]

As possible agents with calming effect were considered morphine and other opioids, but the lethal dose of such compounds is only 10 to 20-fold higher than the incapacitating dose [34]. An example of unsuccessful use of opioids was application of fentanyl derivative by Russian special forces, which showed low therapeutic width [48]. Stronger antipsychotic substances, such as haloperidol, are reducing hyperactivity, but they are causing only little sedation. The other issue is that they cause so-called extrapyramidal symptoms as acute dystonia. [34] Acute dystonia are consistent muscle contractions that lead to abnormal poses of affected parts of the body [50].

As calmatives we could possibly use dissociative anaesthetics, agonists of α_2-adrenergic receptors, benzodiazepines, opioids and muscle relaxing agents [51]. However, as it was mentioned above, not all of them are applicable in the military sector. This chapter will discuss just the most known of them – dissociative anaesthetics, benzodiazepines (BZD) and opioids.

7.2 Physicochemical properties

Since calmatives are a diverse subgroup with many different medicaments, it is hard to summarize their properties. Ramesh C. Gupta in his book [7] states, that there are few main characteristics of calmatives: i) there must be minimal cardiovascular and respiratory side effects; ii) the administration has to be easy – mostly by inhalation, so they are frequently used as vapours and aerosols [51]; iii) rapid onset of effects and ease control of effects; and the last requirement for calmatives are specific antidotes that can be used to antagonize the effects of such non-lethal weapons.

7.3 Representatives

7.3.1 Dissociative anaesthetics - Phencyclidine, Ketamine

Dissociative anaesthetics exert different effects than other anaesthetics [52]. Except calming effect, stupor [11] and pain relief [51], they cause catalepsy, analgesia and reduction of reactions to external stimuli [53]. As an example of dissociative anaesthetics, we can name Phencyclidine (PCP, Fig. 22) and Ketamine (Fig. 23). [11] PCP was introduced to the practise as the first one, but soon it was withdrawn due to initiation of psychotic states [53]. PCP also evokes hallucinations. Ketamine is still used in medicine, but it must be used in a high dose to get anaesthetic effects [54]. At low concentrations it can also evoke hallucinations. [55]

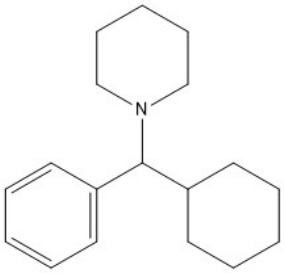

Figure 22 - Phencyclidine

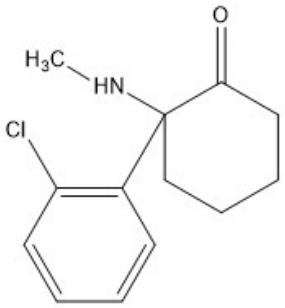

Figure 23 - Ketamine

7.3.2 Benzodiazepines – Midazolam

For their diverse therapeutic effects, BZD are frequently used in medicine [50]. Benzodiazepines, as Midazolam (Fig. 24), calm down and in higher doses they can cause hypnotic effects [51], but also induce languor and sleep [11]. Significant issue of these agents is presence of a high number of side effects and rapid emergence of addiction [56].

If they are used repeatedly for a longer period of time, BZD accumulate in adipose tissue due to slow elimination from the body. [56]

Midazolam, a short-lasting BZD, is used mostly preoperatively as an anxiolytic, sedative and hypnotic agent. Midazolam belongs among the most lipophilic BZDs with rapid absorption and rapid onset of clinical effects. [56]

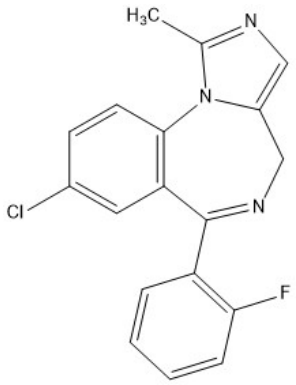

Figure 24 - Midazolam

7.3.3 Opioids – Fentanyl

This subgroup of calmatives includes fentanyl-like compounds which are acting as opiate agonists. Fentanyl (Fig. 25) and its analogues act as synthetic narcotic analgesics and anaesthetics, as tranquilizer in veterinary medicine or as illegal substance by drug addicted persons. Such compounds are highly soluble in lipids and penetrating easily through the blood-brain barrier. Opioids rapidly evoke analgesia, euphoria, miosis and breathing depression. [19]

The best-known case of usage of fentanyl-like compound was a terrorist attack, which happened on October 23, 2002 in Russia, in Moscow theatre Dubrovka. About 50 Chechen terrorists with guns and explosives attached to them, captured about 800 hostages. Terrorists required Russian military forces to leave Chechnya, since such forces stayed here after the Second Chechen War. The situation lasted till October 26, when Russian special forces surrounded the theatre in the morning and pumped the vapor inside. Practically, all people fall down unconscious and that was the time for special forces to go inside and deal with terrorists. Unfortunately, within this very complicated situation, higher concentration of fentanyl analogue was used. More than 100 hostages died, 200 others had to be hospitalized. The number of victims was higher also because the hospitals were not informed about the character of chemical agent used, so they did not know what antidote they should use. [19], [57], [58] The official version was that fentanyl was used. However, several Russian toxicologists claimed, that they found traces of halothane in urine of two hostages [57], [59], [60]. However, prof. van Aken from Germany denied this statement, since halothane is normally used in Russian hospitals, so there is a chance that this

substance could get into the blood and urine of the patients through the respirator. [61]

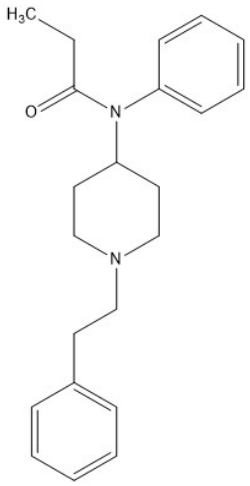

Figure 25 - Fentanyl

7.4 Mechanism of action

Dissociative anaesthetics (PCP, Ketamine) are antagonists of NMDA-receptors. These receptors have many binding sites for various ligands [62], which means that they can exert many different effects. In central nervous system, the protein of NMDA-receptor is formed by non-specific ion channel [14], thus PCP and Ketamine stuck in it [63], and thus block it [14].

Benzodiazepines (Midazolam) bind to a specific site on GABA-receptor, which is associated with chloride channel. BZDs stimulate opening of this channel, what increases permeation of chlorine ions into cytoplasm and dampens the CNS. [51], [56]

Fentanyl and its analogues act as opiate receptor agonists, exerting high affinity to μ-receptor subtype [51]. This type of opiate receptor is coupled with G-protein.

7.5 Clinical picture of intoxication

Each above-mentioned subgroup causes different effects; however, we can generalize them partially. Calmatives have dampening effect. They immobilize and soothe the person. They also induce stupor, drowsiness or sleep. They can evoke sedative-hypnotic state, reduce pain and attention, or increase the pain threshold. [51] The onset of the effect is rapid, occurring a few minutes after exposure. Thereafter, it lasts hours or even days. [48]

PCP causes hallucinations, which can turn into aggressive behaviour. The intoxicated person can provoke fights and be impulsive [64]. Ketamine intoxication is very similar to clinical manifestation of schizophrenia [65]. Moreover, it stimulates heart activity [66].

Benzodiazepines exert hypnotic, sedative, amnestic, anxiolytic, myorelaxant and anticonvulsive effects. [56]

Opiates overdose is usually associated with hypoxia and mild hypotension. Severe intoxication can cause acute lung injury, pulmonary oedema, cardiac dysrhythmia, shock, coma and also death. In particular, Fentanyl may induce respiratory depression, muscle rigidity, spasms, and seizures. [67]

7.6 Therapy of poisoning

In case of PCP intoxication, the cramps must be dampened by benzodiazepines till complete calming down. Doses of 10 mg of Diazepam (Fig. 26) are used every 3-4 hours. [14]

Flumazenil (Fig. 27) is used against intoxication by benzodiazepine overdose. It binds to GABA receptor with higher affinity than benzodiazepines. The dose of flumazenil applied is usually 0.3 mg. [68]

For the treatment of toxic effects evoked by Fentanyl, antidotes Naloxone (Fig. 28), Naltrexone or Nalmefene are used. [19]

Naloxone should be administered intravenously in the dose of 0.4 - 2 mg. The dose of this antidote can be even higher - 10 mg. If the patient does not react on 10 mg dose, he probably suffers from respiratory depression. [19], [69]

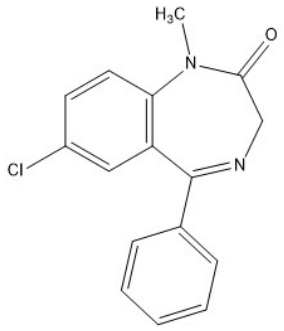

Figure 26 - Diazepam

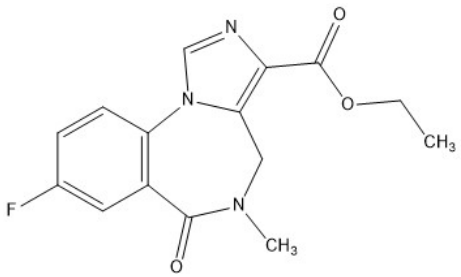

Figure 27 - Flumazenil

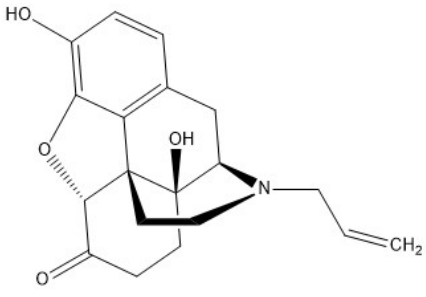

Figure 28 - Naloxone

8 Vomiting agents

8.1 Characteristics

Vomiting and nausea agents are a subpart of irritating agents, that are not toxic enough to be used in war, but they are toxic enough to be banned for use against civilians as riot control agents. Vomiting agents may be used by law enforcement or for special military operations. [12], [13] Most of these agents include arsenic in their structure which is the reason of serious health risk by its decomposition products and reason, why it was banned in 1930 as RCA. [13]

These agents are usually applied as aerosols or smokes and thus the main way of their absorption is respiratory system. Also skin, eye and digestive irritation may occur. [70] The vomiting effect can be used for forcing a soldier to remove his mask, and then, he is usually attacked by the other, more dangerous agent, such as nerve agent. [38]

Vomiting agents exert the same mechanism of action as RCAs, but there are a few differences in their properties: i) the effect occurs several minutes later; ii) higher toxicity; iii) prolonged systemic effects – nausea, headache, vomiting, abdominal cramps which last for several hours. [13]

Regarding the history of vomiting agents, the first records come from the end of the World War I, when it was weaponized as Smoke Candles consisting of a tin canister with a screw lid. An igniting device was under the lid. Adamsite or agent Clark I were put inside the canister. [71]

The most important agents are Adamsite, Clark I and Clark I, which are discussed below.

8.2 Physicochemical properties

The majority of these substances are solid and stable at room temperature. As aerosols they are not too persistent and they are insoluble in water. In water they slowly decompose and form harmful decomposition products, such as HCl, HCN and also arsenic compounds. Some agents are odourless, several of them have garlic or bitter almonds odour. The irritation of eyes, respiratory tract and skin is caused by concentrations much lower than the lethal ones. [12], [14], [72]

8.3 Representatives

8.3.1 Adamsite (Diphenylaminochlorarsine)

Adamsite (Fig. 29), with a code name DM, is a yellow crystalline solid, insoluble in water and almost insoluble in organic solvents with drab odour. Sneezing appears soon after the first contact with Adamsite. At higher concentration, the patient starts to feel nausea, vomits and has a headache. [13] When heated to decomposition, Adamsite forms toxic chloride and arsenic smokes [73]. It is volatile and thus it contaminates the terrain just for 0.5 – 1 hour. Adamsite persists on surfaces or clothing. [38] It is used in a form of mines, hand grenades or aerial bombs. [14]

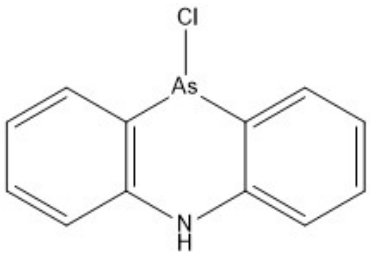

Figure 29 - Adamsite

The name Adamsite comes from the name of the US chemist Robert Adams, who synthetized this substance in 1918 at the end of World War I., however, it was never used that days. *Ellison* [12] claims that the first usage of this agent was within the Russian Civil War by British as a mixture of Adamsite and Clark I., on the other hand *Patočka* in his book [14] states that this compound was used for the first time in the Second Indochinese War.

In June 2003, in Brussel, letters with Adamsite were sent to the US, British and Saudi Embassies; Belgium's Prime Minister Guy Verhofstadt; the Court of Brussels; Belgian ministry; the Oostende airport, and the Antwerp port authority. Two postal workers and five policemen exerted symptoms of skin and eye irritation and difficulties with breathing after exposure to the letters. Three other people from the Oostende airport were hospitalized. Iraqi political refugee was suspected and the house search by antiterrorism investigators revealed a plastic bag with Adamsite powder. [74]

8.3.2 Clark I (Diphenylchlorarsine)

Clark I (Fig. 30), also known as DA agent, is colourless crystalline substance with fruity odour. It is insoluble in water and soluble in organic solvents. It is highly volatile chemical. Clark I contaminates the terrain for just 5 – 10 minutes. [14]

The first usage of Clark I in June 1917 by Germans in Nieuport was also the first usage of vomiting agents in war. It penetrates through the gas masks, and thus the soldiers were forced to take off their masks because of nausea and vomiting. Thereafter, they were exposed to more toxic chemicals – chocking agents, chlorine and phosgene. [14], [71]

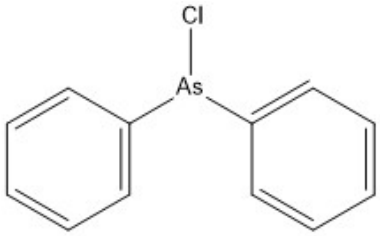

Figure 30 – Clark I

8.3.3 Clark II (Diphenylcyanoarsine)

Another name for Clark II (Fig. 31) is DC agent. Similarly to Clark I, Clark II is colourless crystalline compound, but it smells like garlic or bitter almonds. DC agent is also soluble in organic solvents, poorly in water. It is not as volatile as Clark I. It contaminates the terrain for 10 – 30 minutes. It is more toxic than DA agent. [14], [75]

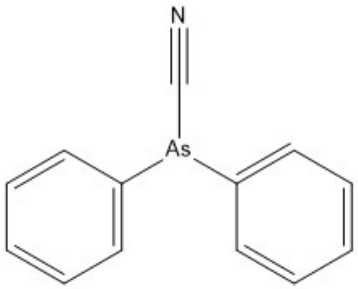

Figure 31 – Clark II

8.4 Mechanism of action

The mechanism of action of irritants in general is irritation of sensoric and sensitive receptors. Vomiting agents, in particular, irritate mainly the mucose membrane of respiratory and gastrointestinal systems. Moreover, vomiting agents

act as inhibitors of enzymes containing -SH group, especially in pyruvate dehydrogenase complex. [14], [71], [72]

8.5 Clinical picture of intoxication

Vomiting agents penetrate by all routes of administration. The onset of the effect is gradual. The first symptoms may occur 30 seconds after the exposure to few minutes depending on the dose. Comparing to RCAs, the effect of vomiting agents lasts longer. It can insist for several hours or even a few days. [12], [14], [71]

Dermatitis may appear on unprotected skin. Eye irritation may manifest as tearing, but the main toxic effect remains on respiratory system that leads to uncontrolled sneezing and coughing for a few minutes. Thereafter, pain in nose and throat, stuffiness, nausea, vomiting, abdominal cramps and diarrhoea appear. Finally, headache and depression may occur. [12], [13], [14], [76], [77]

If severe intoxication occurs, signs of intoxication by arsenic may complicate the health state of the victim, e.g. renal and liver malfunction [14]. Serious complications or death can be caused if such agents are used in a closed space [12].

8.6 Therapy of poisoning

There are no specific antidotes. Firstly, the victim must be taken out of the contaminated area and decontaminated. The skin can be washed with e.g. detergent and water or chloramine. In case of acute conjunctivitis, the alkaline eye ointment should be used. The treatment is more supportive, focused on reduction of irritant and systemic effects. Pain may be reduced by analgesics. If the victim is suffering from scare or anxiety, sedatives are used. [14], [38], [71] In case of severe intoxication by arsenic it is appropriate to use so-called British Anti-Lewisite (BAL) (Fig. 32). [78]

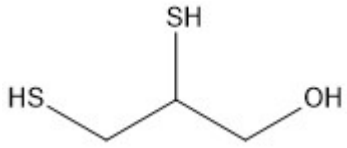

Figure 32 – BAL

9 Discussion

The main aim of non-lethal CWs is to incapacitate the victim, but not to kill him. Unfortunately, in history several cases of fatal end, when such agents were used, are known. When non-lethal weapons are used, strict rules must be followed, e.g. dosage, open space, the way of usage and also health condition of targeted persons have to be taken into account.

Such agents were first weaponized in WWI, later used in Vietnam War, but in the 90´s, when CWC came into force, they were prohibited for the aim of the war. Non-lethal CWs became an important part of defensive systems all over the world. Some of them are more dangerous than others, therefore, the right usage and dosage must be controlled. Due to this fact all possible non-lethal agents have to be tested to know how they can be used with the highest effectiveness and at the same time to avoid unmeant injuries or deaths, as it happened in Moscow's Theatre.

Some people might object that the best way how to avoid the danger of unwanted deaths is not to use non-lethal CWs at all, but we disagree. The reason is simple: if terrorists want to achieve their goals, they will do anything they want, they will not ask for a permission to use them, they will not hesitate to use any weapon, including non-lethal CWs and chemical weapons in general. This is an exact reason why we need to study these agents and find the ways how to antagonize their harmful effect on affected people.

If we admit the disadvantages of non-lethal CWs, i.e. causing serious injuries or even deaths; we also need to admit advantages, i.e. easier way of how to deal with aggressive rioters, how to keep an order, how to fight against terrorists, how to practice chemical attacks in military, and for self-defence. On the other hand, research and synthesis of bigger amounts of these agents can make them more accessible to terrorist's groups and thus it can also be a potential danger.

When applying strict rules in research and usage of non-lethal CWs, they exert significant potential. I doubt, whether it is a good idea to investigate more novel agents, since they can evoke unexpected situations or injuries more likely than the agents which were discovered many years ago and which toxicological profile is known in detail. On contrary, currently it is very simple to find any information about non-lethal chemical weapons.

Conclusion

Currently, there are many agents with high potency to fulfil the definition of non-lethal chemical weapons, but they still need to be investigated in detail. It is important to do everything possible to prevent any unwanted injury or death caused by these agents.

However, in our opinion non-lethal CWs are useful, and should be included in arsenals, of course in concordance to CWCs, which must be fully respected and adhered.

The most used non-lethal CWs are RCAs, vomiting agents and BZ agent as a representative of ICAs. The youngest subgroup – Calmatives comprises many interesting agents with high incapacitating potential, but such agents have not been used much yet, since they are not examined enough.

The aim of this Bachelor Thesis was to elaborate work focused on non-lethal CWs, to characterize them, divide into subgroups and describe them including exact representatives, their mechanism of action, clinical picture of intoxication and treatment of poisoning. We believe, that all goals have been achieved successfully.

References

[1] PITSCHMANN, V. Overall View of Chemical and Biochemical Weapons. *Toxins*. **2014**, Vol. 6, no. 6, p. 1761–1784.

[2] NANCE, P. M. Non-Lethal Weapons, Chemical. In: *Encyclopedia of Toxicology (Third Edition)*. Oxford: Academic Press, **2014**. p. 258-259. ISBN 978-0-12-386455-0.

[3] BORZELLECA, J. F. Paracelsus: Herald of Modern Toxicology. *Toxicological Sciences*. *Oxford Academic*, **2000**, Vol. 53, no. 1, p. 2–4.

[4] NATO, NATO Policy on non-lethal weapons. In: NATO Press Statements [online]. **1999** [Accessed 2020-03-11]. Available from: https://www.nato.int/docu/pr/1999/p991013e.htm

[5] STÁTNÍ ÚŘAD PRO JADERNOU BEZPEČNOST [online]. **1997** [Accessed 2020-03-10]. Available from: https://www.sujb.cz/zakaz-chemickych-zbrani/umluva-o-zakazu-vyvoje-vyroby-hromadeni-zasob-a-pouziti-chemickych-zbrani-a-jejich-zniceni/

[6] OLAJOS, E. J. a H. SALEM. Riot control agents: pharmacology, toxicology, biochemistry and chemistry. *Journal of Applied Toxicology*. **2001**, Vol. 21, no. 5, p. 355–391.

[7] GUPTA, R. C. *Handbook of Toxicology of Chemical Warfare Agents*. Academic Press, **2015**. ISBN 978-0-12-800494-4.

[8] KŘÍŽKOVÁ, J. a T. VITVAROVÁ. 20 let úmluvy o zákazu chemických zbraní. *Chemické listy*. **2017**, Vol. 111, no. 4, p. 285–289.

[9] BAJGAR, J. Bojové otravné látky zneužitelné v civilním sektoru. In C. Klement, *Mimoriadne udalosti vo verejnom zdravotníctve*. Banská Bystrica: PRO, **2011**, p. 52. ISBN: 978-80-89057-29-0.

[10] ORGANISATION FOR THE PROHIBITION OF CHEMICAL WEAPONS, *OPCW: Organisation for the Prohibition of Chemical Weapons* [online]. [Accessed 2020-03-10]. Available from: https://www.opcw.org/

[11] STŘEDA, L. and PATOČKA, J. Incapacitating chemicals – Risk to the purpose and objectives of the Chemical Weapons Convention? *Kontakt*. 1 March **2014**. Vol. 16, no. 1, p. e57–e63.

[12] ELLISON, D. H. *Handbook of Chemical and Biological Warfare Agents*. CRC Press, **2007**. ISBN 978-1-4200-0329-1.

[13] JABBOUR, R., SALEM, H., BALLANTYNE, B. and KATZ, S. A. Arsenical Vomiting Agents. In: *Encyclopedia of Toxicology (Third Edition)*. Oxford: Academic Press, **2014**. p. 302–307. ISBN 978-0-12-386455-0.

[14] PATOČKA, J. *Vojenská toxikologie*. Grada Publishing a.s., **2004.** ISBN 978-80-247-0608-5.

[15] DAVISON, N. *"Non-Lethal" Weapons*. Palgrave Macmillan UK, **2009**. Global Issues. ISBN 978-0-230-22106-2.

[16] SCHEP, L. J., R. J. SLAUGHTER and D. I. MCBRIDE. Riot control agents: the tear gases CN, CS and OC—a medical review. *BMJ Military Health*. *British Medical Journal Publishing Group*, **2015**, Vol. 161, no. 2, p. 94–99.

[17] BROWNE, M. W. DEATH IN WACO: The Tear Gas; Chemical Isn't Meant to Cause Fire - The New York Times. [online]. [no date]. [Accessed 2020-03-10]. Available

from: https://www.nytimes.com/1993/04/20/us/death-in-waco-the-tear-gas-chemical-isn-t-meant-to-cause-fire.html

[18] ANON. *Pont-Saint-Esprit poisoning: Did the CIA spread LSD? | History News Network* [online] **2010**. [Accessed 10 March 2020]. Available from:

https://historynewsnetwork.org/article/130589

[19] LUKEY, B. J., ROMANO, J. A. and SALEM, H. *Chemical Warfare Agents: Chemistry, Pharmacology, Toxicology, and Therapeutics, Second Edition*. CRC Press, **2007**. ISBN 978-1-4200-4662-5.

[20] WAX, P. M., BECKER, Ch. E. and CURRY, S. C. Unexpected "gas" casualties in Moscow: a medical toxicology perspective. *Annals of Emergency Medicine*. May **2003**. Vol. 41, no. 5, p. 700–705.

[21] BYRNES, J. *Advances in Sensing with Security Applications*. Springer Science & Business Media, **2006**. ISBN 978-1-4020-4295-9.

[22] ANON. Greek border police use tear gas, stun grenades to keep migrants out. *Daily Sabah* [online] [Accessed 2020-03-10]. Available from: https://www.dailysabah.com/politics/eu-affairs/greek-border-police-use-tear-gas-stun-grenades-to-keep-migrants-out

[23] KARASOVÁ, J. Žďárová and J. ŽĎÁRA. Neletální chemické zbraně – dráždivé látky, jejich účinek na lidský organismus a léčba symptomů. *Chemické listy*. **2018**, Vol. 112, no. 6, p. 359–365.

[24] CROWLEY, M. *Chemical Control: Regulation of Incapacitating Chemical Agent Weapons, Riot Control Agents and their Means of Delivery.* Springer, **2016**. ISBN 978-1-137-46714-0.

[25] BLAIN, P. G. Human Incapacitants. In: *Clinical Neurotoxicology: Syndromes, Substances, Environments*. Elsevier Health Sciences, **2009**. p. 660-673 ISBN 978-0-323-05260-3.

[26] HU, H and D. CHRISTIANI. Reactive airways dysfunction after exposure to tear gas. Reactive airways dysfunction after exposure to tear gas. *London: Lancet*, **1992**, Vol. 339, no. 8808, p. 1535.

[27] HU, H. et al. Tear gas--harassing agent or toxic chemical weapon? *JAMA*. **1989**, Vol. 262, no. 5, p. 660–663.

[28] KARAGAMA, Y. G., J. R. NEWTON and C. J. R. NEWBEGIN. Short-term and long-term physical effects of exposure to CS spray. *Journal of the Royal Society of Medicine*. **2003**, Vol. 96, no. 4, p. 172–174.

[29] STEIN, A. A. and W. E. KIRWAN. Chloracetophenone (tear gas) poisoning: a clinico-pathologic report. *Journal of Forensic Sciences*. **1964**, Vol. 9, no. 3, p. 374–382.

[30] THORBURN, K. M. Injuries after Use of the Lacrimatory Agent Chloroacetophenone in a Confined Space. *Archives of Environmental Health: An International Journal. Routledge*, **1982**, Vol. 37, no. 3, p. 182–186.

[31] MACKWORTH, J. F. The inhibition of thiol enzymes by lachrymators. *Biochemical Journal*. 1948, Vol. 42, no. 1, p. 82–90.

[32] CUCINELL, S. A. et al. Biochemical interactions and metabolic fate of riot control agents. *Federation Proceedings*. **1971**, Vol. 30, no. 1, p. 86–91.

[33] UCHYTILOVÁ, E. and J. PALEČEK. Úloha TRP1 receptorů v neurálních mechanismech pooperační bolesti. *Anesteziologie a intenzivní medicína* [online]. **2009**, Vol. 20, no. 5, p. 276 [Accessed 2020-02-05]

[34] KETCHUM, J. S. and H. SALEM. Incapacitating agents. In: *Medical Aspects of Chemical Warfare*. Government Printing Office, **2008**. p.287-305. ISBN 978-0-16-081532-4

[35] DEFENSE TECHNICAL INFORMATION CENTER, (DTIC). Incapacitating agents. In: NATO Handbook on the Medical Aspects of NBC Defensive Operations AMedP-6(B) [online]. *Homeland Security Digital Library.* **1996** [Accessed 2020-02-

10]. Available from: https://fas.org/nuke/guide/usa/doctrine/dod/fm8-9/3ch6.htm

[36] U.S. ARMY MEDICAL RESEARCH INSTITUTE OF CHEMICAL DEFENSE. Incapacitating Agents. In: *Homeland Security Digital Library* [online]. **2001** [Accessed 2020-02-10]. Available from: https://www.hsdl.org/?abstract&did=1094

[37] ANON., List of CNS stimulants + Uses & Side Effects. In: *Drugs.com* [online]. **2018** [Accessed 2020-02-10]. Available from: https://www.drugs.com/drug-class/cns-stimulants.html

[38] GREAVES, I. and P. HUNT. *Responding to Terrorism*. Elsevier, **2010**. ISBN 978-0-08-045043-8.

[39] BERGEN-CICO, D. K. *War and Drugs: The Role of Military Conflict in the Development of Substance Abuse*. Routledge, **2015**. ISBN 978-1-317-24939-9.

[40] PASSIE, T. et al. The pharmacology of lysergic acid diethylamide: a review. *CNS neuroscience & therapeutics.* **2008**, Vol. 14, no. 4, p. 295–314.

[41] STŘEDA, L. and KOBLIHA, Z. *"Neletální" chemické zbraně - zbraně pro 21. století?: Léky jako zbraň*. [First edition]. Brno: Tribun EU, **2015**. ISBN 978-80-263-0975-8.

[42] OMEGA FOUNDATION, CROWD CONTROL TECHNOLOGIES, and THE SUNSHINE PROJECT. Non-Lethal Weapons Research in the US: Calmatives and Malodorants. *Backgrounder Series #8 July.* **2001**

[43] PINNEY, V. R. Malodorant compositions, related non-lethal weapon systems, and methods of their use [online]. US PATENT 6,242,489. **2002** [Accessed 2020-02-17]. Available from: https://patents.google.com/patent/US6352032/en

[44] MCMURRY, J. *Organická chemie*. Praha: VŠCHT. **2007**. ISBN 978-80-7080-637-1.

[45] SALEM, H. Sources of Indoor Air Pollutants in the Occupied Palestinian Territories, Including Skunk Liquid, Household Cleaning Products, and Others - *Journal of Environmental Pollution and Control*. **2019**, Vol. 2, p. 1–15.

[46] MAĎA, P. and FONTANA, J. Chuťový a čichový systém. In: *Funkce buněk a lidského těla* [online]. [no date] [Accessed 2020-03-20]. Available from: http://fblt.cz/skripta/xiii-smysly/3-chutovy-a-cichovy-system/

[47] SHUSTERMAN, D. Review of the upper airway, including olfaction, as mediator of symptoms. *Environ Health Perspect*. **2002**; Vol. 110, Suppl 4, p. 649-653.

[48] SUTHERLAND, R. *Chemical and Biochemical Non-lethal Weapons: Political and Technical Aspects*. SIPRI. **2008**. ISBN 978-91-85114-59-7

[49] GROSS, M. L. Medicalized WEAPONS & Modern WAR. *Hastings Center Report*. **2010**, Vol. 40, no. 1, p. 34–43.

[50] ŠTEFÁNEK, J. Benzodiazepiny. In: WikiSkripta [online]. [Accessed 2020-03-20]. Available from: https://www.wikiskripta.eu/w/Benzodiazepiny

[51] PETROVÁ, I. Kalmativa - chemické zbraně pro 21 století? In: *Toxicology* [online], **2007**. [Accessed 2020-03-20]. Available from: http://toxicology.cz/modules.php?name=News&file=print&sid=72

[52] HESS, L., SCHREIBEROVA, J. and FUSEK, J. Pharmacological Non-Lethal Weapons. *Proceedings of the 3rd European Symposium on ´Non-Lethal´ Weapons.* **2005**, V23.

[53] MUIR K. W., LEES K. R. Clinical experience with excitatory amino acid antagonist drugs. *Stroke*. **1995**. Vol. 26, no. 3, p. 503-513.

[54] PAI, A. and M. HEINING. Ketamine. Continuing Education in Anaesthesia Critical Care & Pain. *Oxford Academic*, **2007**, Vol. 7, no. 2, p. 59–63.

[55] ORHURHU, V. J. et al. Ketamine Toxicity. In: *StatPearls* [online]. **2020** [Accessed 2020-03-11]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK541087/

[56] GRIFFIN, Ch. E. et al. Benzodiazepine Pharmacology and Central Nervous System–Mediated Effects. *The Ochsner Journal*. 2013, Vol. 13, no. 2, p. 214–223.

[57] HISTORY.COM EDITORS. Hostage crisis in Moscow theater. In: *HISTORY* [online] **2009** [Accessed 2020-03-20]. Available from: https://www.history.com/this-day-in-history/hostage-crisis-in-moscow-theater

[58] SCHIERMEIER, Q. Hostage deaths put gas weapons in spotlight. *Nature*. **2002**, Vol. 420, no. 6911, p. 7.

[59] DEJMEK, L. Extrémně účinná narkotická analgetika - nový typ „imobilizačních“ BCHL? Část 1. *Vojenské zdravotnické listy*. **2010**, Vol. 73, no. 1, p. 27-36.

[60] HIGHFIELD, R. Test shows gas was „common narcotic" - In: *The Telegraph* [online]. **2002** [Accessed 2020-03-20]. Available

from: https://www.telegraph.co.uk/news/worldnews/europe/russia/1411616/Test-shows-gas-was-common-narcotic.html

[61] ANON. Vier Tage danach: Kreml lüftet Gas-Geheimnis. In: *n-tv.de* [online]. **2002** [Accessed 2020-03-20]. Available from: https://www.n-tv.de/politik/Kreml-lueftet-Gas-Geheimnis-article119739.html

[62] LIU, Y. and ZHANG, J. Recent Development in NMDA Receptors. In: Chinese Medical Journal. **2000**, Vol. 113, p. 948-956

[63] KEMP, J. A. and R. M. MCKERNAN. NMDA receptor pathways as drug targets. Nature Neuroscience. *United Kingdom: Nature Publishing Group*, **2002**, Vol. 5, no. Suppl, p. 1039–1042.

[64] DAVIS, K. PCP (Phencyclidine): Facts, effects and health risks. In: *Medical News Today* [online]. **2017** [Accessed 2020-03-20]. Available from: https://www.medicalnewstoday.com/articles/305328

[65] LAHTI, A. C. et al. Effects of Ketamine in Normal and Schizophrenic Volunteers. Neuropsychopharmacology. *Nature Publishing Group*, **2001**, Vol. 25, no. 4, p. 455–467.

[66] SULEIMAN, Z. A., Kolawole I. K. and Bolaji B. O. Evaluation of The Cardiovascular Stimulation Effects After Induction of Anaesthesia With Ketamine. *Journal of the West African College of Surgeons*. **2012**, Vol. 2, no. 1, p. 38–52.

[67] MONTOYA, I. D. and D. J. MCCANN. Drugs of abuse: management of intoxication and antidotes. In: LUCH, A. Molecular, Clinical and Environmental Toxicology. *EXS*. **2010**, Vol. 100, p. 519–541.

[68] ŠTEFÁNEK, J. Flumazenil. In: *Medicína, nemoci, studium na 1. LF UK* [online]. [no date] [Accessed 2020-03-20]. Available from: https://www.stefajir.cz/flumazenil

[69] SMITH, S. W. Drugs and pharmaceuticals: management of intoxication and antidotes. In: LUCH, A. Molecular, Clinical and Environmental Toxicology. *EXS*. **2010**, Vol. 100, p. 397-460

[70] HOLSTEGE, Ch. P. et al. Unusual But Potential Agents of Terrorists. *Emergency Medicine Clinics*. **2007**, Vol. 25, no. 2, p. 549–566.

[71] ALBRIGHT, R. D. *Cleanup of Chemical and Explosive Munitions*. Elsevier, **2012**. ISBN 978-1-4377-3477-5.

[71] DEFENSE TECHNICAL INFORMATION CENTER, (DTIC). Riot Control Agents. In: NATO Handbook on the Medical Aspects of NBC Defensive Operations AMedP-

6(B) [online]. *Homeland Security Digital Library.* **1996** [Accessed 2020-02-10]. Available from: https://fas.org/nuke/guide/usa/doctrine/dod/fm8-9/3ch7.htm

[72] LEWIS, R. J. *Sax's Dangerous Properties of Industrial Materials*. John Wiley & Sons, Incorporated, **2012**. ISBN 978-1-118-29290-7.

[73] OFFICE OF THE COORDINATOR FOR COUNTERTERRORISM. Patterns of Global Terrorism. In: *Global Security* [online]. **2004** [Accessed 2020-03-20]. Available from: https://www.globalsecurity.org/security/library/report/2004/pgt_2003/pgt_2003_31685pf.htm

[74] HOENIG, S. L., ed. Vomit Agents. *Compendium of Chemical Warfare Agents*. New York, NY: Springer, **2007**, p. 153–161. ISBN 978-0-387-69260-9.

[75] SCHWENK, M. Chemical warfare agents. Classes and targets. *Toxicology Letters*. **2018**, Vol. 293, p. 253–263.

[76] WARDEN, C. R. Respiratory Agents: Irritant Gases, Riot Control Agents, Incapacitants, and Caustics. *Critical Care Clinics*, **2005**, Vol. 21, no. 4, p. 719–737.

[77] SAWANT, S., H. PARIHAR and H. MEHENDALE. British Anti-Lewisite (BAL). *Encyclopedia of Toxicology (3rd Edition)*. **2013**, p. 360-362. ISBN 978-0-12-386455-0