



# Technical Workshop on Incapacitating Chemical Agents

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# Executive Summary



**Stefan Mogl**

Stefan Mogl is a member of the Swiss National Authority for the CWC and Head of the Chemistry Department at SPIEZ LABORATORY since 2007. The chemistry department includes an OPCW designated laboratory, a Schedule -1 facility, an office for chemical arms control and industry declarations and specialist groups dealing with detection and decontamination of chemical warfare agents and response to chemical terrorism. Stefan Mogl was OPCW Inspector from 1997-2000 and Head of the OPCW laboratory from 2000-2005. Since 2008 he is a member of the OPCW Scientific Advisory Board. He holds degrees in chemistry (Polytechnik Winterthur, 1990) and industrial hygiene (ETH Zürich, 1997) and an MBA (British Open University, 2003).

This technical workshop on Incapacitating Chemical Agents (ICA) follows in line with a number of activities Switzerland has undertaken in the past to address uncertainties pertaining to the status of ICA under the Chemical Weapons Convention (CWC). The workshop was organized by SPIEZ LABORATORY together with VERIFIN, the Finnish Institute for the Implementation for the CWC. The objective of this workshop was to bring together policy and technical experts to clarify some of the underlying technical questions that may influence policy discussion on ICA. With the distribution of this report, the presentations and discussions of the workshop are shared with a wider audience. The purpose of this report is to stimulate debate among interested parties and stakeholders of the CWC and to serve as a factual contribution to such discussions.

What are ICA? – ICA are toxic chemicals that typically act on the Central Nervous System (CNS). They are different from Riot Control Agents (RCA) – whose main target is the peripheral nervous system. There is no need for a scientific definition for ICA because such a defini-

tion would not affect their treatment as toxic chemicals under the CWC.

How could ICA be detected? – The procedures for the analysis of chemicals relevant to the CWC cannot be transferred as such to the analysis and identification of ICA, which are likely to be more drug-like substances. Similarly, the procedures used at toxicology laboratories are not aimed at detecting ICA. The expertise reflected in both fields however may serve as starting point for suitable methods. High resolution mass spectrometry is a promising analytical technique to support the screening of ICA type substances.

ICA (will) typically act on the CNS, but any effect is dose dependent, and any agent – including ICA – will have side effects. Furthermore, there is significant variability in the effects due to individual susceptibility. The understanding of the enormous complexity of cellular biology, molecular biology, biochemistry and physiology of the brain is far from complete. Whilst there has been a large increase in knowledge regarding the existence of neurotransmitters, a detailed understanding of their ac-

tions is limited to a small number of them. Furthermore, over-dosing is a typical occurrence when an agent is used in the field, as is known to happen during field use of RCA. There are just too many variables to ascertain that a use would be 'safe' in all circumstances.

It is the way a substance is used that makes it an ICA and not its intrinsic properties. Which risks and how much risk is acceptable is a crucial question in the safety debate on ICA. Outside of medically controlled circumstances – for field use of an agent – the issue of safety is much more complex than just ensuring a wide therapeutic window. Where is the cut-off point for an «acceptable number» of casualties – and, what does this mean for litigation in relation to such casualties? Who would be responsible for risk assessment over the development, deployment and how and when to use ICAs? It is far from clear that such risk assessment would be performed thoroughly. The development of any sort of weapon intended for law enforcement purposes therefore must happen in a transparent manner under public scrutiny – there is no place for secrecy.

Confrontations of large groups of people that lead to possible violence seem to be on the rise and some saw using ICA for law enforcement purposes as a permitted activity – because of a need for a range of response capabilities between 'persuasion' and 'lethal force'. Whilst RCA are in use for a variety of different scenarios – and the CWC contains a functional definition for RCA – it remained unclear what benefits could be gained from the use of ICA.

Science and technology have not changed fundamentally since entry into force of the CWC, when ICA were also discussed but perceptions in relation to armed conflict versus law enforcement may be different today. In light of new roles taken on by military forces in the form of peacekeeping operations and similar scenarios, where is the borderline between law enforcement and combat use, which legal framework(s) would apply? What would the impact be on the CWC, if ICA were accepted in law

enforcement and possibly incorporated into military structure for 'military operations other than war'? If there is no clear view on what is permitted, then the risk is, that ICAs could be introduced (more) into such scenarios.

The types and quantities aspects of agents as well as delivery systems that might be developed for disseminating such agents are critical to the debate in the context of the CWC – in particular to the prohibition of the development and possession of chemical weapons and the prohibition of any military preparations for their use. Furthermore, if ICA were to be developed, stockpiled and used, proliferation will be unavoidable.

The CWC has been a success story and is not about to collapse on account of the ICA issue. But ICA may well represent a first step onto a slippery slope at the end of which countries may start re-arming with a new generation of chemical weapons, more developed than the ones currently being destroyed.

Despite all the ideas presented on the ICA problem, there is a risk of going round in circles – breaking out is the key challenge. Any future debate must include all key stakeholders, in particular the law enforcement community. Law enforcement organisations in the traditional sense have yet to take a public stance on whether they see a need or justification for ICA.

Progress on CBW arms control and disarmament is notoriously slow. Extensive and active NGO interest and campaigning however have been critical factors in securing action in the past. It therefore is highly desirable to engage these communities in further discussions on ICA on the way ahead. One possible approach might be to see the establishment of a process similar to the Meetings of Experts in the framework of the BWC, where the main aim was to 'promote common understandings'. Most importantly though, the debate needs to broaden out to include other states, who thus far have shown little interest in the issue. We hope therefore that this report will assist future deliberations.

# Introduction



**Dr Beat Schmidt**

Dr Beat Schmidt is an organic chemist by training. He is head of Arms Control at SPIEZ LABORATORY and a member of the National Authority of Switzerland. In this function he provides specialist advice to Swiss delegations during international negotiations and to federal bodies in charge of overseeing the implementation of the Chemical Weapons Convention (CWC) as well as for the Australia Group export control regime. He is the reporting centre for all chemical industry declarations required by the CWC, advises the Swiss chemical industry on CWC issues and is escort team during the OPCW inspections. Before coming to SPIEZ LABORATORY he worked for 15 years in a global custom manufacturing company and held different positions in research and development, process optimization, generics, management functions in evolving business development areas and in new investment projects for highly active compounds to extend the technology platform of the company.

## Introduction

Switzerland remains concerned that ambiguities regarding the interpretation of the Chemical Weapons Convention (CWC) in relation to Incapacitating Chemical Agents (ICA) have the potential to undermine it in the future. The Swiss delegation to the OPCW therefore has addressed the status of such agents on several occasions in the past. During the first Review Conference of the CWC (2003) Switzerland made the following statement: «It is appropriate to reiterate that chemical weapons are totally prohibited, whether they are lethal or non-lethal and whether their precursors or components are listed in the schedules of the Convention or not. For the 2nd Review Conference (2008) Switzerland prepared an official paper postulating nine theses under the title «Riot Control and Incapacitating Agents under the Chemical Weapons Convention».

Much of the past debate on ICA has focused on arms control policy and legal aspects. SPIEZ LABORATORY and VERIFIN, the Finnish Institute for the Verification of the Chemical Weapons Convention at the

university of Helsinki, have come to the understanding that the policy debate may benefit from a clarification of some underlying technical questions. The two institutes therefore organised this workshop and invited experts from academia, industry, policy making and arms control to discuss technical aspects surrounding ICA and the impact these technical aspects may have on policy making. The workshop posed six specific questions: what are ICA, what are their effects, how could they be produced, used, detected, and, how could their abuse be controlled? These questions were introduced by expert speakers and then discussed by all participants under the guidance of experienced chairpersons. All debates were conducted under Chatham House Rule. A summary of each of the discussions as well as abstracts of all the presentations can be found in this report.

## Opening Statements

**Minister Andreas Friedrich**, head of Arms Control and Disarmament at the Federal Department of Foreign Affairs, and head of the Swiss National Author-





*Prof Paula Vanninen, Minister Andreas Friedrich and Stefan Mogl at Opening Ceremony*

ity for the CWC, opened the workshop and emphasised how pleased Switzerland was that so many highly qualified experts had accepted the Swiss invitation. He thanked the organisers and the speakers and chairs that had volunteered to contribute. He explained Switzerland's concerns about the ambiguity in the CWC in relation to ICA and emphasised that ICA were toxic chemicals and their use consequently prohibited under the Convention, except for activities not prohibited [...activities undertaken under the label 'law enforcement' could undermine the objective and purpose of the Convention, namely the prohibition of the use of any toxic chemical as a method of warfare].

He invited all participants to discuss the issue openly with an experts perspective and expressed his hope that this would initiate discussions in other countries [...We shall not, from the Swiss side, present today or tomorrow any work plan or political agenda for future initiatives. But we obviously shall carefully analyse the findings of this Spiez workshop at a later stage. It is only then that we will determine whether and in what direction we should become more active on the diplomatic level, in the light of your discussions. And we assume that your respective governments will do likewise]. Minister Friedrich concluded his speech by thanking participants for their active participation in a process which is aiming at raising awareness and clar-

ifying an important issue linked to the CWC [...Your input will be a valuable contribution to the discussions on further improving international security but also on getting the world completely rid of a whole class of weapons of mass destruction].

**Prof Paula Vanninen**, Director of VERIFIN, and co-organiser of the workshop emphasised in her opening remarks

the long standing research cooperation between VERIFIN and SPIEZ LABORATORY on the «Verification of chemical warfare agents and related chemicals», which as of late has also included incapacitating agents. She recalled that science and technology are progressing at an ever higher pace and that research for new drugs is including substances that take effect in the central nervous system. She stated that this workshop should focus on technical issues because it was important to deliver factual and scientifically sound information through this workshop to decision makers. Prof Vanninen furthermore stressed the political context of the discussion surrounding ICA and that while the meeting was focusing on technical matters there was always the political background of the Chemical Weapons Convention [...many issues which are purely technical might have also some political implications or vice versa]. She expressed her hope that this meeting will help to promote discussion on ICA in advance of the third Review of the CWC [...I hope this meeting serves as landmark on the roadmap to the third Review Conference on issues related to the incapacitating chemical agents] and she emphasised that other workshops should follow [...I also hope, this discussion won't be the only of its kind and the discussions before the next Review Conference will be successful and fruitful].

# What are potential ICA ?

The term 'Incapacitating Chemical Agents' (ICAs) is understood differently by different actors and depends on the context in which it is applied. Furthermore, there is no consensus on whether an actual definition for ICA should be attempted in the context of the set of definitions applicable under the CWC (it should be recalled, however, that incapacitating agents are covered under the definition of 'toxic chemicals' of the CWC and thus qualify as chemical weapons if intended for that purpose). In any case, any possible future emergence of an ICA for law enforcement purposes will be strongly dependent on the development in the fields of drugs for medicinal purposes and on progress achieved in the safety margins of relevant high potency substances. Some of the advances in the life sciences, as well as in the dissemination and application of drugs, contain the potential for dual use. Today's inaction by stakeholders may therefore by default assist the introduction of ICA for law enforcement purposes.\*

Several proposals for a definition of ICA exist today. However, because there is no clear-cut line between (non-lethal) ICA and more lethal chemical warfare agents, a scientifically meaningful definition cannot easily be made. One can describe several toxicological effects that could be used to 'incapacitate', but in principle there is no way to draw a line between ICAs and lethal agents. The Chemical Weapons Convention (CWC) contains a functional definition for riot control agents (RCAs) that separates them from other toxic chemicals and puts them under a different legal regime. Even if there was a clear and scientifically sound definition for ICA, this would not affect their treatment under the CWC, because they are still toxic chemicals. Therefore, whatever will be considered legitimate under the CWC for ICAs will in principle also apply to other toxic chemicals (including lethal agents) – the only barrier remaining that types and quantities must correspond to the allowed purposes.

While it is difficult to define ICA as a specific category of toxic chemicals, they can be differentiated from RCAs. Simply put, RCAs make you run away from the scene, whilst ICA make you drop down. Or, more scientifically, the main target of RCAs is the peripheral nervous system, whilst the incapacitating effect of ICAs typically is caused by an action on the central nervous system (CNS).

There remains (strong) skepticism as to whether an agent could actually be developed for which its negative side effects are deemed 'acceptable', so that duty of care can be met. Despite the better understanding of the CNS, it has yet to lead to better drugs in

terms of higher specificity and lower toxic side effects. Also, if a drug could be identified that leads to incapacitation and is sufficiently safe for use, proper means of dissemination would have to be developed for the types of scenarios for which ICA are being considered. In this context it was recognised, that there is a fundamental difference between the use of an agent or a drug under controlled clinical conditions – one-on-one, anaesthetist and patient – versus the use of such an agent or drug as a weapon in the field (see also summary of section 2, What are potential effects of ICA ?).

The development of any sort of weapon intended for law enforcement purposes must happen in a transparent manner under public scrutiny – there is no place for secrecy. After all, this is about using force in non-consensual circumstances against citizens that may be perfectly within their rights or that may have committed a crime but neither is at this stage a proven fact. The same requirement for transparency applies to the development of ICAs as law enforcement weapons for counter-terrorism or counterinsurgency operations. This in turn may render such weapons ineffective, because the element of surprise would be lost. In relation to law enforcement there remains the question as to whether one can draw a clear-cut line between weapons intended for military use and weapons intended for law enforcement use. How clearly can or could military purposes be distinguished from law enforcement purposes in today's security environment (where often, military units are tasked with policing functions, such as in peacekeeping operations or similar scenarios)?

\* The workshop organiser takes full responsibility for this summary text.

## Chair of this session:



**Dr Ralf Trapp**

Dr Ralf Trapp is an independent consultant on chemical and biological weapons arms control. A chemist and toxicologist by training, he worked with the GDR Academy of Sciences between 1978 and 1990. From 1985 to 1985 he was a researcher at the Stockholm International Peace Research Institute (SIPRI), and from 1991 to 1992 at the «Stiftung Wissenschaft und Politik Ebenhausen» (Germany). He acted as technical adviser to the GDR and subsequently the German delegations to the Conference on Disarmament. Between 1993 and 2006, he worked at the Technical Secretariat of the OPCW in the areas of industry verification, verification policy and review, international cooperation, government relations and political affairs, and strategic planning. He was a main contributor to both CWC Review Conferences and the secretary of the OPCW's Scientific Advisory Board.

*[...One can describe several toxicological effects that could be used to <incapacitate>, but in principle there is no way to draw a line between ICAs and lethal agents...]*

*[...There remains (strong) skepticism as to whether an agent could actually be developed for which its negative side effects are deemed <acceptable>, so that duty of care can be met...]*

## What are potential Incapacitating Chemical Agents ? A general overview



**Dr Alexander Kelle**

Dr Alexander Kelle is a political scientist by training and a Senior Lecturer in Politics and International Relations at the Department of Politics, Languages and International Studies (PoLIS) at the University of Bath, UK. He received his PhD from J.W. Goethe University in Frankfurt am Main in 1996. Before coming to Bath he held positions at Queen's University Belfast, University of Bradford, Stanford University, Goethe University Frankfurt and the Peace Research Institute Frankfurt. His research in general addresses international security cooperation and the foreign and security policies of Western liberal democracies.

The interest in so-called incapacitating chemical agents (ICAs) can be traced back to the offensive military chemical weapons programs of major powers in the mid-20th century. The discourse surrounding these weapons since then reveals a variety of different understandings and approaches relating to the substance matter at hand. Looking at the actors involved in the development of and with an interest in the use of such ICAs, both military and police forces have been utilizing the incapacitating effects of chemical agents. While police forces have traditionally relied on peripherally acting irritants or riot control agents (RCA), such as OC, CN, CR or CS, military interest has focussed on agents such as BZ which affect the central nervous system. This distinction is sometimes blurred by the uneven use of terminology, such as in the 2009 «Guidance on the Use of Incapacitant Spray» of the UK Association of Chief Police Officers. Despite referring to incapacitants in its title, the document only deals with irritants in use with British police forces.

Reviewing policy documents and the academic literature on ICAs one cannot but conclude that one is dealing with a contested concept to which a variety of meanings are attached by different actors and ana-

lysts. On a spectrum of contestation one end is constituted by utilitarian approaches which focus on the utilities ICAs might (or might not) have in operational terms. At the other end of the spectrum normative approaches emphasise legal norms embodied in the Chemical and Biological Weapons Conventions and International Humanitarian Law, but also moral norms underpinning such international legal agreements. An effects based understanding of ICAs regards them as causing «temporary physiological or mental effects, or both, which will render individuals incapable of concerted efforts in the performance of their assigned duties» (US Field Manual 3-11.9, p.1-6). As identified by Ketchum and Salem, «today, scientists seeking new nonlethal incapacitating substances are studying neuropeptides and neuromodulators» (2008, p.412). At the extreme utilitarian end of the spectrum of contested meanings are calls for «an urgent need for rethinking and rewriting the existing laws with respect to the implementation of NLTs [non-lethal technologies, the author] using chemicals» (NATO RTO, 2006, E-4). A contrasting normative approach is clearly expressed in the position paper Switzerland submitted to the Second CWC Review Conference. This starts from the premise that «riot control agents and incapacitating agents

are 'toxic chemicals' as defined by the Convention. Hence, they are by definition 'chemical weapons' unless they are intended for purposes not prohibited under the Convention.» (2008, p.2)

When analysing the historical interest in so-called incapacitating chemical agents, both the cases of BZ and fentanyl show the limitations of efforts to actually develop such an agent that would meet the strict criteria of a utilitarian position favourably disposed towards ICAs. Military interest in BZ led in the early 1960s to the standardisation of the agent. However, it was never fully introduced into the US arsenal due to slow onset of effects, the impossibility of covert dissemination, the unpredictability of effects and a safety margin of approximately 40, which carries a much too high risk of fatalities in the context of armed conflict scenarios. As a result, the US stockpile of BZ was declared obsolete in 1976 and destroyed in the late 1980s. Similarly, fentanyl – an opioid 100 times more potent than morphine – and its derivatives received military interest as ICAs during the period of the Cold War. Used as an anaesthetic in operating theatres it has a rapid onset time of only a few minutes and a short duration of effect. However, as it also produces severe respiratory depression as a side effect, the US and UK military did not consider fentanyl as a viable ICA option (Dando and Furmanski 2007, Pearson 2006). The 2002 Moscow theatre siege suggests that other states hold a different opinion (Wax, Becker and Curry 2003).

As Alan Pearson has summarised, the characteristics of a «good» ICA – from a utilitarian perspective – include high potency, rapid onset of symptoms, defined and short duration, reversible effects, stable in storage and delivery, significant and predictable effect, capable of rapid and often covert dissemination and a high safety margin (2006, 159). So far, not a single of the chemical agents considered for ICA use meets all these criteria. Yet, with the continuing advances in the life sciences some of the obstacles mentioned above, e.g. in relation to fentanyl, might be overcome, thus

creating a safety margin that may be deemed «good enough» by some. The research on 5-HT serotonin receptors and agonists may be a case, where the dual-use character of benignly intended research might lead to renewed interest in ICAs with fewer side effects, such as fentanyl-based chemical compounds displaying a reduced or even eliminated respiratory depression. Such developments can be expected to put additional pressure on the normative restraints against the development and use of toxic chemicals as ICAs.

When considering these restraints as contained in the CWC, i.e. Article 2.9(d) on law enforcement, there is again a range of views identifiable among practitioners and scholars. Closest to the normative end of the spectrum is the position taken by Ambassador von Wagner who, based on his experience negotiating the CWC, regards the scope of law enforcement as being limited to riot control and capital punishment. Chayes and Messelson in turn allow for «actions taken within the scope of a nation's 'jurisdiction to enforce' its national law» and actions under UN authority, as long as these do not constitute a method of warfare. While they allow for only riot control agents to be used in this context, Fiddler is more lenient in this regard (and thus farther away from a restrictive normative interpretation), as he interprets CWC Article II.1 (a) as allowing for agents other than RCA to be used. Much closer to the utilitarian end of the spectrum still is the opinion of the US Navy Judge Advocate General who in 1997 declared the limits of «law enforcement» as «not clear and will be determined by the practice of states parties.»

In summary, the meaning of «incapacitating chemical agents» in general and of «law enforcement» more specifically is contested. Utilitarian proponents of ICA emphasize the additional tactical and strategic options that ICA could provide. Normative sceptics caution against or oppose ICA by reference to arms control law, but also international humanitarian law (British Medical Association 2007). Civilian research and development in medicine and the life sciences with

dual-use character may aid in increasing safety margins of potential ICA and thus increase the pressure to develop and deploy such kinds of weapons in the future. Therefore, inaction with respect to clarifying the normative boundaries of the prohibition to use toxic chemicals is likely to play into the hands of utilitarian proponents of ICA.

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## What are potential ICAs ? Advances



**Prof Dr Malcolm Dando**

Professor Dr Malcolm Dando trained originally as a biologist (B.Sc. / Ph.D. at St Andrews University). After Post-Doctoral research at the University of Michigan and the University of Oregon he returned to the UK and held Fellowships in Operational Research, funded by the Ministry of Defence, at the University of Sussex. He moved to the University of Bradford in 1979 and has focused his research on arms control and disarmament since then. For the past twenty years he has studied the impact of advances in science and technology on the prohibition of chemical and biological weapons. Most recently he has been involved in work on the lack of awareness and education of life scientists of the Chemical and Biological Weapons Conventions and of their responsibilities under these Conventions (see [www.dual-usebioethics.net](http://www.dual-usebioethics.net)).

The subject of this meeting clearly has relevance for the 2013 Third Review Conference of the Chemical Weapons Convention, but, given the overlap in the area of toxins, it should also have been relevant for the December 2011 Seventh Review Conference of the Biological and Toxin Weapons Convention. This presentation begins with a slight overlap with Kelle's opening presentation as I want to add more about past and present ICAs to provide a basis for my review of three possible avenues for the development of future ICAs.

In order to produce an effective biological or chemical weapon it is necessary to be able to produce and deliver sufficient quantities of viable agent to achieve the desired effect on the target population. In one of his last publications the US bioweaponer Bill Patrick argued cogently that the US had achieved this capability for a number of agents before President Nixon closed the offensive biological weapons programme. Included in these agents was Staphylococcal Enterotoxin B which could produce debilitating sickness for unprotected victims over a very large area. This should remind us that there are many different possible forms of incapacitation and many different purposes to which incapacitation can be put.

Over the last two decades there have been enormous scientific and technological developments which raise the question of what impact this has had on the potential for new forms of ICAs. Again it is necessary to acknowledge the complexity of this issue because improvements in the means of longer range delivery of RCAs (as described in the studies made by my colleague Michael Crowley) could have implications for future delivery capabilities for ICAs. But the main issue here concerns new agents and the paradigm case is the use of fentanyl-type agents to break the Moscow theatre siege. Essentially, ICAs differ from RCAs because they target the central nervous system directly. What Moscow showed was the difficulty of controlling the dose in different areas of the target space, control of effect of any dose for different persons, and the side effects on respiration when attempting to sedate. So, if we set aside the 'duty of care' to victims of the agent, the question really is whether an agent can be found that will act on a specific sub-type of brain receptor in an isolated circuit to produce a specific effect.

That is what the Penn State researchers were seeking in their 2000 study when they identified benzodiazepines and alpha2 adrenergics (diazepam and

dexmedetomidine) as «appropriate for immediate consideration» as non-lethal incapacitants. Essentially, their idea seems to have been to use medically developed sedative-hypnotic drugs for incapacitation in the field: What we might see as a classic example of attempted 'dual-use' of civil science. However, it needs to be understood that the underlying brain circuits for sedation, sleep, awareness, and alertness are very complex, interrelated, and still only partially understood.

Yet we know that awareness and sleep result from the reciprocal inhibition of sleep-active and wake-active sets of neurons in the brain and that it is possible to influence that interaction with chemical agents. Dexmedetomidine, for example, acts on wake-active noradrenaline-producing neurons. These are naturally self-inhibited by the produced noradrenaline acting on alpha2A adrenergic receptors of the neurons. Dexmedetomidine affects these receptors in the same way and thus indirectly releases sleep-active neurons from inhibition. But dexmedetomidine does not act selectively only on these receptors in this circuit. So medical use has to be carried out with great care and the agent is used as an adjunct to a primary drug – as is mirrored in the efforts to develop a non-lethal agent based on medetomidine by Hess and colleagues.

Similarly, the actions of benzodiazepines are easily understood. Sleep-active neurons produce GABA which acts via GABAA receptors to inhibit wake-active neurons during sleep. Diazepam acts allosterically on GABAA receptors to enhance the effect of the natural transmitter. Whilst great progress has been made in elucidating the nature and functions of GABAA receptors, selective activation of GABAA subtypes is not yet possible and rapid onset, short duration sedation is achieved medically instead by the use of benzodiazepines-type agents that are rapidly metabolised to inactive forms in the body.

Yet it has to be acknowledged that in a period of rapid scientific and technological advance surprises are possible. For example, the discovery of orexin neuropeptides and neuroreceptors in the late 1990s has revolutionised our understanding of narcolepsy. The loss of orexin neurons clearly results in major disruption of alertness because these neurons are normally active during wakefulness and have excitatory effects via orexin receptors on post-synaptic neurons. Indeed

specific antagonists to the OXR2 receptors are being sought with some success in order to deal with problems of insomnia. So perhaps this will eventually lead to the development of specific agents with specific impact on a receptor in an isolated circuit to produce only an incapacitating effect.

In conclusion: an ideal ICA is not yet available, but it might perhaps be in the future. Whilst I do not think the Chemical Weapons Convention was intended to allow the use of such centrally-acting agents others certainly do. But I do not think we should let such ICAs be developed because it seems to me that if we go down that road there is no end in sight. The ongoing advances in neuroscience will open up more and more possibilities for manipulation of the brain for hostile as well as medical purposes. Developing new ICAs for short term tactical purposes, in my opinion, risks destruction of the norm of non-use of chemical agents for hostile purposes that has, over the last 100 years, been embedded in international agreements that we should make every effort to retain.





# What are potential effects of ICA ?

The effects of a chemical agent are always dose dependent (for incapacitants: no effect below a certain dose, incapacitating above that dose, lethal above an even higher dose). Furthermore, any agent – also ICA – will have side effects. If an agent is used in the field, over-dosing is a typical occurrence, as is known to happen during field use of RCA. A second issue relates to the predictability of the toxic effects caused by ICA. The understanding of the enormous complexity of cellular biology, molecular biology, biochemistry and physiology of the brain is far from complete. Whilst there has been a large increase in knowledge regarding the existence of neurotransmitters, a detailed understanding of their actions is limited to a small number of them.\*

A range of effects should be expected from a drug acting on the CNS considering the complexities of the CNS, the pharmacokinetics of an ICA and the metabolic processes that may affect the toxicological properties of the chemical. Important for the intensity of effects is not the agent concentration achieved in the blood stream but the concentration of the drug at its target site. The agent has to enter a person's body (by inhalation, transdermal, orally), enter the blood stream, pass the blood brain barrier to become active in the CNS, and then, reach the target receptor site at the right concentration to cause the intended incapacitating effect(s). Significant variability in the effects of an agent are to be expected depending on the route of administration but also due to individual susceptibility.

It is not possible to achieve an «even» distribution for the dissemination of an agent under field conditions. Consequently, no accurate prediction can be made about the dose a person will receive under such conditions. The safety margin for the agent, therefore, must be extended to a degree where an accurate prediction of the dose is not required.

Many factors affect the response at the level of the individual, including sex, age, medical predisposition, current health status, etc. Furthermore, the use of an ICA would be non-consensual – this has regulatory consequences but as it is known from therapeutic drugs, this may affect or even change the symptomatology. A further factor to be considered would be the effects of the «carrier substance», if the active substance, the ICA, was distributed (i.e. in an aerosolised solvent) with the help of another substance. In conclu-

sion, the problems posed for any possible ICA are potentially high inter-personal variability, the complexity of the chemical actions of the agent in the body, a high variability of the actual dose under field conditions and the potential variability of an individual's response depending on particular circumstances of usage and the current predisposition of the individual (unknown to the user of the ICA). Regarding the use of RCA for law enforcement purposes, there was uncertainty about what kinds of guidelines were available, if any, as to permissible concentrations as well as to types of uses.

\* The workshop organiser takes full responsibility for this summary text.

## Chair of this session:



**Dr Ralf Trapp**

Dr Ralf Trapp is an independent consultant on chemical and biological weapons arms control. A chemist and toxicologist by training, he worked with the GDR Academy of Sciences between 1978 and 1990. From 1985 to 1985 he was a researcher at the Stockholm International Peace Research Institute (SIPRI), and from 1991 to 1992 at the «Stiftung Wissenschaft und Politik Ebenhausen» (Germany). He acted as technical adviser to the GDR and subsequently the German delegations to the Conference on Disarmament. Between 1993 and 2006, he worked at the Technical Secretariat of the OPCW in the areas of industry verification, verification policy and review, international cooperation, government relations and political affairs, and strategic planning. He was a main contributor to both CWC Review Conferences and the secretary of the OPCW's Scientific Advisory Board.

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## Effects of Incapacitating Chemical Agents



**Prof Dr Robert Wennig**

Prof Dr Robert Wennig born 1942, studied chemistry in Luxembourg and Strasbourg where he obtained his PhD in 1970, was head of the Toxicology Department at the Laboratoire National de Santé until December 2009 in Luxembourg. In 1986 he received his Forensic Toxicologist certification from the German society of forensic toxicology GTFCh. His academic career started as teaching assistant in 1965 at Strasbourg and Luxembourg in 1971, followed by a professorship in 1980 at Luxembourg University. He was in charge of GTFCh continuous education over many years and supervised post-graduate students at Strasbourg, Nancy and Metz. His research topics were focused on pesticides, drugs-of-abuse-bioavailability and biotransformation, chronic toxicity biomarkers, and wild mushrooms.

Incapacitating agents can be classified as irritant agents such as vomiting agents, tear gases or sternutators and psychoactive agents with the last being subdivided according to Peters 1991 classification in psychostimulants, which increase CNS activity; psychedelics or delirants, which disturb CNS activity; psycho-sedatives which slow down CNS activity; and antidepressants which slow down CNS activity after an excitation phase. The most likely exposure routes to be considered are by ingestion of drinks or food, by inhalation of aerosols or gases or by skin exposures.

### Effects of psychoactive agents

To understand the activity of psychoactive agents a short overview of the human nervous system covering both the central nervous system (CNS) and the peripheral nervous system (PNS) is essential:

- CNS consists of the brain and the spinal cord. Brain represents 2 % of body weight, but needs 20 % of available energy. The brain consists of an
- PNS consists of the voluntary sensory-somatic nervous system relating sensory (input) and motor (output) information to the CNS which in turn

estimated 100 billion excitable nerve cells, the basic functional units of the nervous system, called neurons which mutually interact by electrochemical signalling, and an estimated 1000 billion non-excitable glial cells which are responsible for isolation, nutrition, structural assistance, repair of neurons and constituting a part of the blood brain barrier. Brain functions include cognitive functions, motor functions, emotions, and autonomic functions with mutual interactions. These are extremely complex with 4 major interconnecting systems: 1, afferent sensory system; 2, efferent motor system with the pyramidal system regulating deliberate motor activity and the extrapyramidal system governing the indirect and unconscious fine motor skills; 3, cognitive system; and 4, the limbic system including the reward system, with all related to endocrine and immune function.

handles coordination with the environment and involuntary autonomic (vegetative) nervous system, with the latter divided into a sympathetic nervous system regulating mostly excitatory effects, the so-called fight or flight response; and parasympathetic nervous system dealing mostly with effects opposed to sympathetic effects, the so-called rest and digest response.

### Neurophysiology

Communication between neurons or with other cells occurs by electrical nerve impulses travelling down an axon to junctions called synapses. These impulses trigger the release of neurotransmitters into what is called the synaptic cleft, inducing a depolarization or a hyperpolarization at post-synaptic membranes enabling the action potential to continue in the post synaptic cell. Neurotransmitters are cleared rapidly from the synaptic cleft. Neurotransmitter concentrations in synapses depend on pre-synaptic release, degradation by enzymes, re-uptake transport, storage, receptor activation or blocking.

The negative resting neuron voltage is due to an excess of organic anions in the axon. Variation of membrane potential is linked to changes in the intracellular and extracellular ion concentrations. Understanding of the enormous complexity of cellular biology, molecular biology, biochemistry, and physiology of the brain is far from complete.

Main neurotransmitters are: acetylcholine (ACh), catecholamines such as dopamine, and noradrenaline, serotonin (5-HT), glutamate,  $\gamma$ -aminobutyric acid (GABA), and peptide neurotransmitters notably endorphins, dynorphins, and enkephalins.

Functional neuronal pathways in the CNS with mutual intermodulations include the following: the cholinergic pathways, dopaminergic pathways, noradrenergic pathways, serotonergic pathways, GABA-ergic pathways (the major inhibitory system), opioid pathways, endocannabinoid pathways, and glutamatergic pathways (the major excitatory system).

### Molecular basis of neuropharmacology

Pharmaco-toxicological activity of psychoactive agents happens at the molecular level in the brain by

interaction with specific targets, mostly proteins, where the agents compete with endogenous ligands notably hormones, modulators, neurotransmitters, second messengers, etc at membrane protein binding sites of receptors, transporters, enzymes, either as agonists or as antagonists.

### Toxidromes

Toxic effects of psychoactive agents can be studied by considering the intoxication syndromes or toxidromes, such as the adrenergic/noradrenergic toxidrome, serotonergic toxidrome, anticholinergic toxidrome, hallucinogenic toxidrome, narcotic toxidrome, hypno-sedative toxidrome, pyramidal toxidrome and extrapyramidal toxidrome. Take the anticholinergic toxidrome for example which is induced by tropane alkaloids, or BZ Agent 15. These chemicals are classified in pharmacology as anticholinergics and act mostly as muscarinic antagonists or parasympatholytics. The following intoxication symptoms are just some of the effects caused by these agents:

- CNS effects: euphoria or sedation, anxiety, amnesia, delirium with disorientation, violent behaviour, and hallucinations, extrapyramidal reactions, rarely convulsions, cardio-respiratory arrest, and coma;
- PNS effects: xerostomia, bilateral mydriasis, flushing, hyperthermia, dry skin, sinus tachycardia, hypertension, myoclonus, sometimes rhabdomyolysis, GIT-atonía, and urinary retention;
- Duration of action is about 2 to 30h or longer in case of BZ Agent 15 (the most probable incapacitating agent to be used);
- Mechanism of action: Agents act as reversibly binding muscarinic ACh receptor antagonists and have little effects on nicotinic receptors or other receptors.

### Drug Discovery

In the past drugs were discovered either as the active ingredient of traditional remedies or by fortuitous discovery. Nowadays, with specific knowledge of diseases, control at the molecular level, enables specific systems to be targeted. Identification of potential candi-

dates includes studying the target site: predictions about which drug(s) fit(s) into active sites, followed by synthesis, physical-chemical characterization (notably drug absorption), therapeutic efficacy; and high-throughput screening with large chemicals libraries to test both selectivity and ability to modify the target; cross-screening to avoid toxicity in unrelated targets, is performed prior to clinical trials of selected molecules. The above procedures are very costly for each molecule. Drug development follows with candidates with some degree of activity to a pharmacophore, being further reviewed by structure-activity relationships to find a lead. The best selected lead will be proposed for drug development; the others considered as “backup”. Pre-clinical studies in vitro, in silico, and in vivo experiments are used to obtain preliminary data to assist pharmaceutical companies to decide on further development of a new drug.

Clinical trials are procedures to assess the safety, efficacy and information about adverse drug reactions of new or old drugs for a new indication, and require the approval of health authorities and ethics committees. The trials start with healthy volunteers and patients in pilot studies, followed by (1) uncontrolled observational or interventional cohort studies and case-control studies, and (2) controlled, randomized, double blind and placebo-controlled trials which invariably provide the best evidence of both efficacy and side effects. Clinical trial design must be documented in clinical trial protocols and in the investigator’s brochure. Trial subjects included must sign an “informed consent” form and must receive the best available treatment according to the 1972 declaration of Helsinki guidelines. The first-in-human trials (phase 0) involve administration of single subtherapeutic doses, to a few subjects to gather preliminary data on pharmacodynamics and pharmacokinetics.

Clinical trials are classified into 4 separate phases which usually take place over many years:

- Phase I trials involve 20 to 100 healthy volunteers and are designed to assess safety, and dose range-finding. This starts with a fraction of the toxic dose (known from animal tests) and looking at food effects via a cross-over study. Also under investigation are the tolerability, pharmacokinetics and pharmacodynamics of the drug, with most work done in an inpatient clinic to observe subjects over several drug half-lives.
- Phase II trials are studies with 20-300 volunteers designed to assess clinical efficiency and safety.
- Phase III trials are randomized, controlled, multi-center trials with 200-3,000 patients to obtain a definitive assessment in comparison with current ‘gold standard’ treatment. At this stage drugs may already be marketed with the condition that if any adverse effects are reported, the drug may be immediately recalled. Successful phase I, II, and III trials are written up as a comprehensive document which is sent for review by appropriate regulatory authorities before any drug receives approval for use in the general population.
- Phase IV trials aka post-marketing surveillance trials and aka pharmacovigilance involve the safety surveillance designed to detect any rare or long-term adverse effects.
- Phase V is comparative effectiveness and community-based research to introduce a new treatment into widespread public health practice.

Drug licensing procedures in Europe have changed: Until 1995, only national health authorities were allowed to license new drugs in Europe. In 1995 the European Medicines Evaluation Agency EMA based in London, took over this task for new drugs. EMA co-ordinates drug licence applications within the European Union assisted by 3 committees with experts from each Member State 1. Committee for Proprietary Medicinal Products (CPMP) for human use. 2. Committee for Veterinary Medicinal Products. 3. Committee for Orphan Medicinal Products for rare Diseases (<5/10,000 People) with special incentives for the pharmaceutical industry which cannot make much profit from these drugs.

## Factors likely to affect the response to incapacitating chemical agents



**Prof Dr Alastair Hay**

Prof Dr Alastair Hay is Professor of Environmental Toxicology at the University of Leeds. He has a BSc in Chemistry (1969) and a PhD in Biochemistry (1973) both from London University. Most of his research is on the effects of drugs and other chemicals on health and he has published many papers and articles in both the scientific and medical press over the years. Professor Hay has also worked on issues relating to chemical and biological warfare (CBW) for some 30 years. Much of his work has dealt with the need for workable, international treaties which prevent the use of warfare with chemical or biological agents. Professor Hay has been involved in field work in Iraq and Bosnia to either establish or refute the use of chemical warfare agents, and more recently to identify chemical irritants used to disperse demonstrators in the West Bank.

In this talk incapacitating chemical agents will be regarded as those agents which affect the central nervous system thereby preventing an individual from functioning. Although riot control agents will also incapacitate individuals through their irritant effects on eyes, nose, throat, respiratory tract and skin, the apprehension these agents cause is secondary to the irritation and they are not treated as incapacitants here; however, it is useful to review what we know about them.

In the last few years it has become clear that many irritant chemicals act on pain receptors (nociceptors) on nerve cells. Receptors on peripheral nerve cells respond to mechanical, thermal and chemical stimuli when the stimulus reaches a noxious range and messages relaying this are sent to the brain. Specific receptors detect heat, one of which responds to the capsaicin (or vanilloid) family of chemicals. Capsaicin is the active ingredient in hot chilli peppers. The receptor is known as transient receptor potential vanilloid 1 (TRPV1). The receptors act as gateways or channels to the nerve cell allowing movement of messenger chemical ions such as calcium or potassium to relay the information.

Specific receptors also exist to detect cooling agents such as menthol, the so called TRPM8 receptor. Riot control agents such as CS, CN and CR operate through the Transient Receptor Potential Ankyrin 1 (TRPA1) channel of which they are potent activators. Passage of calcium ions through the channel is made possible by the chemicals attachment to thiol groups (SH) on proteins which are a part of the channel. The influx of calcium ions into the nerve cell is associated with intense pain. Experimental animals in whom the gene for TRPA1 is non functional have a much more muted response to the riot control agents as do animals treated with specific antagonists which prevent the normal response of the channel to irritant chemicals.

Malodourants have been suggested as possible incapacitating chemicals, not through their ability to affect cognitive processes but simply through an individuals response to an intolerable smell. Some of the chemicals present in the spray of skunks (*Mephitis mephitis* and *Spilogale gracilis* to name but two species) have very unpleasant smells. Much of the smell is attributable to two chemicals (E)-2-buten-1-thiol and 3-methyl-1-butanethiol. Corresponding thioace-

tate derivatives of these chemicals such as 3-methyl-1-butanethioacetate are also present in the spray but far less odouriferous; on contact with water however the thioacetate is converted back into the more potent thiol. Odours are prevented by treating the affected area with oxidizing agents like hydrogen peroxide or baking soda (sodium bicarbonate) which change the thiol grouping on the chemical into a sulphonic acid.

Earlier terminology of chemicals with a thiol grouping referred to them as mercaptans. Individuals are able to detect the presence of these chemicals at levels in the air of about 0.2 parts per billion (ppb). For those working with the chemicals permissible occupational exposure limits are usually set at levels around 500 ppb. An occupational exposure limit is one at which a healthy individual can be exposed for 8 hours a day, 5 days a week, for 40 years without experiencing any ill health. Fatal concentrations in humans are unknown but it is known that levels of 770,000 ppb for 30 minutes are fatal for dogs and 4,020,000 ppb for 4 hours are fatal for experimental rats. Thus there is a factor of about 1000 between what individuals are able to work at and the level which is fatal, at least to experimental animals.

Many chemicals are metabolised by enzymes in the body irrespective of whether they are natural components such as the fatty acids in membranes, or hormones, vitamins, ingested drugs or inhaled chemicals. The metabolism may be either to convert the chemicals into a more active form or part of their denaturation. Initial metabolism is by a set of enzymes known as the cytochrome P450 family. There are many of these enzymes grouped in families according to the substances they metabolise. The activity of individual enzymes will vary between people because of genetic differences (known as polymorphisms). Generally, we might assume a 3-4 fold difference in processing activity between healthy people and about a 10 fold variation if we include the young, the old and the infirm.

The variation in activity of the cytochrome P450 (CYP) enzymes is often established in a limited number of individuals at any one time. Larger populations may indicate greater variation as was the case when we measured the rate of disappearance of caffeine in some 1500 healthy pregnant women as part of a study to look at the effect of caffeine on birthweight. The spe-

cific enzyme which metabolises caffeine is called CYP1A2. In our group of women we observed that the variation in caffeine metabolism was about 20 fold. This shows that if a large enough population is studied variation may be greater than is generally assumed.

When considering dermal absorption of vapours or liquids there will be considerable variation in uptake across the skin depending on skin type, the age of the individual (with skin thickness and elasticity decreasing with age) and whether there are any cuts or other conditions such as psoriasis which reduce the barrier properties. Clothing, temperature and humidity all affect uptake of vapours and clothing certainly will affect liquid uptake as it will initially reduce skin contact but after wetting of fabric may prolong it.

The solubility of agents can be altered too enabling their incorporation into water-based solutions by the simple expedient of altering the acidity of the solution. The drug midazolam, used to treat seizures in children and adults can have its solubility increased some 7 fold by altering the acidity (the pH) of a solution to that approximating vinegar. This solution is then added to tiny capsules called cyclodextrins which have a water favouring exterior and a cavity which is more fat like. These capsules can then be used to introduce midazolam through the nose.

Exposure of individuals to vapours or aerosols is dependent of where that person is in relation to the release. If downwind, the concentration of a one-off delivery will alter by the cube of the distance travelled as the substance becomes more diluted in clean air. Even very short distances from the point of release can mean exposure varying by factors of 10 or 100. Thus calculating potential exposures in any large space to ensure incapacitation only, say, will be a very imprecise art, and particularly difficult if this is done outdoors.

Other variables to be considered in response to chemicals or drugs are the sex of the individual, an individual's ethnicity and any habits. There is a very variable response to the antipsychotic drug Olanzapine between individuals. In one study of some 500 patients some of whom had Alzheimer's disease and the others schizophrenia the rate at which the drug was cleared from people was assessed. There was approximately a 10-fold variation in clearance between people with ethnicity accounting for modest differences in



the rate, males clearing the drug approximately 1.5 times faster than women and smokers clearing twice as fast as non-smokers.

Research on hallucinogens has increased markedly in the last decades given the increased therapeutic value which these agents are now considered to possess. Yet despite many years of high quality research the mode of action of these substances is still far from clear. Receptors in the brain for the neurotransmitter serotonin are considered to be the route through which hallucinogens work. Currently pharmacologists recognise 7 different serotonin receptors and 14 different subtypes. Hallucinations are considered to act through stimulation of the receptor and the release of another neurotransmitter, glutamate. Both the phenethylamine and tryptamine family of hallucinogens are thought to act through a subset of the serotonin receptors and primarily through one called  $HT_{2A}$ . The binding of certain hallucinogens to this receptor ( a prelude to supposed hallucinogenic activity ) is marked, yet other chemicals which are not considered to have any hallucinogenic activity such as the chemical Lisuride also bind avidly to the  $HT_{2A}$ . In short, it is far from clear what the mechanism of action of hallucinogens is.

The dose determines the effect of any chemical. Dosage is crucial for the desired response to a drug, there being a level at which the drug is ineffective, one where its therapeutic effects are apparent and a higher value where side effects begin to increase and escalate as the dosage rises. The same response happens with all chemicals. When considering incapacitants any prospective user would wish to have an agent which was effective at low concentrations, but for which the lethal concentration (or dosage) was many orders of magnitude greater. This means that the chemical would have a large safety factor, derived by dividing the lethal dose by the incapacitating dose.

In practice some drugs used in clinical settings to anaesthetize individuals do not have large safety factors, but when these drugs are administered there is someone present to closely monitor the response, and particularly the breathing rate of the individual. Away from the clinical setting the effects of exposure to an incapacitating agent are going to be much more variable. Determining the rate of release of agents to ensure only incapacitating doses are delivered will be almost impossible, particularly if people are spread out

over some distance. And then there is the variability in response between people. As this talk has demonstrated that variability is very evident with a wide range of different classes of drugs. The same will be true for any incapacitating agent.

# How can ICA be produced ?

The chemical industry today is applying a wide range of well-established, as well as new technologies and processes at different scales. This includes traditional chemical synthesis but also biologically mediated processes, and among others, microwave assisted chemical synthesis. More recently, micro reactor based technology is used for the synthesis of fine chemicals and pharmaceuticals, including highly active pharmaceutical ingredients. The chemical synthesis of high quality peptides is available today almost world-wide. Peptides, and in particular neuropeptides with a potential for dual use, remain relevant for both regimes, the CWC as well as the biological and toxin weapons convention (BWC).\*

Micro reactors are flow reactors that offer a number of advantages over traditional systems. They are small in size, offer high yield (depending on the reaction), allow work with different types of solvents, offer better and faster control of reaction conditions (reaction time, phase transfer, heat control, pressure etc.), lead to higher safety due to small amounts of reactants and offer relative ease of up-scaling. Depending on the down-stream processing they can be run as continuous or as semi-batch processes.

Micro reactor technology is used today not just as dedicated systems for a single process but also as modular set-up (with different plate reactors) allowing the accommodation of different types of reaction characteristics and physical parameters. Process scale-up is achieved not just by parallel use of multiple micro reactors but also by doubling-up the size of plate reactors. While the handling of solids remains a problem with micro reactors, use of ultrasonic devices may help with clogging of channels in reactor plates. The cost of plate reactors is comparable to commonly used laboratory type equipment. Micro reactor based technology is used by industry today for about 25 different processes, mostly with smaller production scales. However, a few large-scale plants are employing micro reactor technology as well. Micro reactor technology is also being developed for biochemical reactions, or, biologically mediated reactions, involving immobilized enzymes.

Peptides are of interest in the context of ICA because peptide based bioregulators are responsible for

the control of a number of vital physiological functions in the human body (body temperature, blood pressure, sleep etc.). About 90 % of peptide synthesis today is done by chemical synthesis. Production ranges in the tens of kilograms but outputs of several hundred kg per year for a peptide plant are feasible, and high quality peptides in smaller quantities can be synthesised world-wide. Nevertheless, peptides remain high-value products, which is reflected in that they are generally priced by the gram. Production also remains infrastructure dependent, as the production of one kilogram of a particular peptide still requires several tons of solvent. But scaling-up from mid-scale to large-scale is deemed no longer a technological challenge. Challenges remain with regard to formulation and mode of application of peptide products, for example with regard to stability - bioactive peptides degrade easily in aerosol form or when passing through the digestive system.

\* The workshop organiser takes full responsibility for this summary text.

## Chair of this session:



**Dr Alexander Kelle**

Dr Alexander Kelle is a political scientist by training and a Senior Lecturer in Politics and International Relations at the Department of Politics, Languages and International Studies (PoLIS) at the University of Bath, UK. He received his PhD from J.W. Goethe University in Frankfurt am Main in 1996. Before coming to Bath he held positions at Queen's University Belfast, University of Bradford, Stanford University, Goethe University Frankfurt and the Peace Research Institute Frankfurt. His research in general addresses international security cooperation and the foreign and security policies of Western liberal democracies.

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## Continuous Flow / MicroReactor Technology at Lonza



**Dr Dominique Roberge**

Dr Dominique Roberge is a chemical engineer. He made his studies at Laval University (Quebec City, Canada), the Technical University of Berlin (Germany), in Kyoto University (Japan) and finally his PhD in the field of heterogeneous catalysis at the University of Technology in Aachen (Germany). For one year he was Associate Professor at the University of Ottawa. He has been working at LONZA, a custom manufacturing company, since 2001 and he assumed different positions in process development, safety assessment and process optimization. His current task is to elaborate on Microreactor Technology for a broad range of synthesis and to make this technology applicable for industrial scale up.

Organic synthesis – and its application in the fine chemicals and pharmaceutical industries – is a mature discipline, dominated by batch-wise production processes that seemingly trace their roots back to the cauldrons of alchemical times. Today, the alchemist's gold sought in synthetic processes takes the form of active pharmaceutical ingredients (APIs), where the pharmaceutical industry pushes on with its quest for innovative, proprietary drugs. The high value-added nature of such innovative pharmaceutical products, coupled with a profound reluctance to implement post-filing process changes, often relegates manufacturing considerations to a lower priority. Consequently, fine chemicals and pharmaceuticals have become industries of waste. The magnitude of the problem is starkly illustrated by the high environmental «E factor» that characterizes these industries, which is rarely lower than 25 ( $E = \text{kg of waste per kg of product}$ ). These industries remain burdened with stoichiometric technologies that generate large quantities of waste. Low process efficiencies are exacerbated by poor track records in product quality, far exceeding that found in any other manufacturing industry. Lonza started a new initiative with the stated goal to bring pharmaceutical production technologies in line with modern, sustain-

able chemical and engineering practices namely the broader implementation of flow and microreactor technologies.

The key concept behind the utilization of flow is to achieve extreme process intensification. The intensification process enables inherently safer conditions that lead to the development of new processes, so-called «**Flash Chemistry**,» that could otherwise never be performed under batch conditions. In a microreactor it is possible to perform highly energetic reactions, work with unstable intermediates, employ more reactive reagents, and use more active catalysts that enable new, out-of-the-box chemistry. In addition, the workspaces can be designed for high temperature and high pressures reactions; a new domain for a typical chemist. A microreactor will be at the heart of flow processes to control the «Flash Reaction» but will be implemented in parallel with other flow unit operations such as liquid-liquid extraction, distillation and crystallization. The outcome will lead to highly intensified mini-plant approaches that will be the basis of the «**Factory of the Future**.» The ultimate results of the initiative are more sustainable, greener, and economical processes for producing a wide range of pharmaceuticals.

## Awareness: Peptide Production & Challenges – Lonza view



**Dr Matt Giraud**

Dr Giraud studied organic chemistry at the University of Sciences and Technology of Languedoc (Montpellier-France), obtained his PhD in Peptide, and joined Lonza in 2001. He has 15 years of peptide experience in all process development phases linked to API life cycle. Inventor of several patents (product specifics & general methodology). In his current position, in addition to his people management role, Dr Giraud is responsible for the IP peptide portfolio, and is leading the external collaborations with universities & with industrial partners in the peptide area to leverage new innovative ideas.

Peptide chemistry was introduced more than a century ago by Emil Fischer, but only later, structure elucidation of more complex molecules and improvements in synthesis paved the way for peptides as drugs. In 1953, DU VIGNEAUD achieved the synthesis of the first peptide hormone Oxytocin by fragment condensation, which became the first peptide drug.



Peptides, such as neurotoxins, from scorpions, spiders, and predatory marine snails comprise millions of unique, disulfide-rich peptides and countless possibilities for developing life-changing therapies. Researchers first noticed the pharmacological effectiveness of snake venoms in the process of developing an-

tisera. Such investigations in the 1950s resulted in the development of the hypertension drug Captopril (BMS), which served as an archetype for future research into the structural information of peptides (proteins) isolated from snake venom. Prialt® (Airmid) is 1,000 times more powerful than morphine. This specific drug is a synthetic compound identical to a toxin in the venom of the Conus magus snail. Due to the high activity of those molecules, they could be considered as potential Incapacitating Chemical Agents (ICAs). The anti-clotting drug eptifibatide was also developed from snake venom. As a final example, the active ingredient



in Byetta is a synthetic version of a protein produced in the saliva of the Gila monster.

Needless to say, that in general, the complexity for peptides as drugs is on the increasing side to meet the requirements of enhanced efficacy and, at the same time, to minimize side effects. In general, there are certain advantages to look into more complex peptides, especially if they display unique protein-like features. In the eyes of pharmaceutical industries, the improvement of efficacy and the further reduction of side effects represent the most important goals to remain competitive.

In the future, interesting structures significantly smaller than 100 amino acids and easily accessible by synthetic methods may be identified.

We considered that less than 10% of the produced peptide are produced by recombinant approach, leaving a high place for chemistry processes. Due to steady improvements in the chemistry and technology for peptide production, the synthesis of small proteins of up to 100 amino acids is even feasible today and, thus, chemical manufacturing will become of interest for the corresponding drugs to come. Despite the fact that for large scale production a huge infrastructure is required to handle the flow of raw materials and tons of solvents (5 tons of solvent for 1 kg of peptide), and special technologies are required like high pressure reverse phase columns for the final purification, or lyophilizer for the final isolation, on lab scale several commercially automated systems allow straight forward small scale synthesis without special elaborated skills.

Due to the high activity of some peptides (i.e. gosereline, decapeptil, leuprolide, busereline, desloreline, triptorelin, abarelix, degarelix) some Safety, Hygiene and Environmental (SHE) considerations based on Occupational Exposure Limit have to be fulfilled to protect operators as well as the product. Lonza's approach is to apply state of art protection and environment. Our expertise is built on our 10 year track record of work with Highly Active Pharmaceutical Ingredients (HAPIs).

In summary, recent technology developments constitute the basis to gain faster access to interesting structures. The use and production of such now

accessible target should be watched carefully. At which point they could be considered as Incapacitating Chemical Agents (ICAs)?

Steady progress in delivery, and modern formulations involving nano-particles, e.g. to ensure transport to the interior of the cell without damage, promote the application of peptides. In the eyes of pharmaceutical industries, the improvement of efficacy and the further reduction of side effects represent the most important goals to remain competitive. As a consequence, the development of an efficient formulation for peptides is no longer perceived as a significant barrier.



# How can ICA be used ?

The way a substance is used makes it an ICA, not its intrinsic properties. The dose and the context of use of a toxic chemical are therefore as important as the toxicological properties of the agent itself. Which risk, or how much risk is acceptable, is therefore a crucial question in the safety debate on ICA. Science and technology have not fundamentally changed since the negotiations of the CWC, when ICA were also discussed. It seems however, that perceptions in relation to armed conflict versus law enforcement may be different today – where do we draw the line between law enforcement and armed conflict?\*

Any development of a potential ICA has parallels to the development of a therapeutic drug and must balance between desired versus adverse effects, solve the problem of how to exercise dose control responsibility, address drug safety etc. Furthermore, similar regulations should apply to the development of ICA as to the development of pharmaceuticals, including transparency of the process to allow for public scrutiny and hence acceptability. Past experience with RCA shows that – for approval for the use of toxic chemicals on the public – openness is an absolute must. Governments that authorise the use of ICAs for law enforcement purposes must bear all responsibility and ensure safety as well as prepare for emergency measures to address potential complications. Outside of medically-controlled circumstances – for field use of an agent – the issue of safety is much wider than just ensuring a wide therapeutic window. There are a number of medical issues related to the safe administration of the agent, as well as to the management of complications and the availability and administration of potential antidotes. Any use of an ICA is likely to cause casualties (possible fatalities as well as long-term damage should be considered). There is no answer to the question of where the «cut-off» point is for an acceptable number of casualties to still justify the use of an ICA. Casualties as a result of using an ICA will trigger litigation, which may become a deciding factor for law enforcement experts on whether or not to accept ICA based weapons. Because, if the litigation potential for such a new weapon is high, it may outweigh the benefits civilian law enforcement authorities were hoping to gain from the introduction of such weapons. The same may not necessarily hold true, if the main application of such weapons is intended for military forces with law enforcement responsibility (where the threshold for acceptability may be considered lower but at the same

time, legal ramifications for the prohibition of chemical weapons must be considered). Also, if ICA were to be developed, stockpiled and used, proliferation will be unavoidable. In particular if proven effective in incapacitating, ICA based weapons will find their way into the hands of non-state actors, criminals and terrorists. Non-consensual uses of ICA may therefore not be limited to law enforcement but also include poisoning of others as well as criminal activity. Any safety concerns in relation to exercising dose control will receive little attention by such actors. Furthermore, the use of ICA based weapons by or against such actors is one possible way for a law enforcement intervention to slip into a full scale combat operation.

Confrontations of large groups of people that lead to possible violence seem to be on the rise and the need for a full spectrum of possible means to respond in the hands of law enforcement includes non-lethal weapons. RCA are in use for a range of different scenarios but it remains unclear what benefits could be gained by the use of ICA. Any use of an ICA in the future will also strongly be dependent on available delivery means, or, delivery means developed for the specific purpose of an ICA. In light of new roles taken on by military forces in the form of peacekeeping operations and similar scenarios, where is the borderline between law enforcement and combat use? Which legal framework would apply in police operations versus armed conflict, and, what would the impact be on the CWC, if ICA were accepted in law enforcement and possibly incorporated into military structure for «military operations other than war»?

\* The workshop organiser takes full responsibility for this summary text.



## Chair of this session:



**Dr Alexander Kelle**

Dr Alexander Kelle is a political scientist by training and a Senior Lecturer in Politics and International Relations at the Department of Politics, Languages and International Studies (PoLIS) at the University of Bath, UK. He received his PhD from J.W. Goethe University in Frankfurt am Main in 1996. Before coming to Bath he held positions at Queen's University Belfast, University of Bradford, Stanford University, Goethe University Frankfurt and the Peace Research Institute Frankfurt. His research in general addresses international security cooperation and the foreign and security policies of Western liberal democracies.

*[...Any use of an ICA is likely to cause casualties (possible fatalities as well as long-term damage should be considered). There is no answer to the question of where the «cut-off» point is for an acceptable number of casualties to still justify the use of an ICA ...]*

*[...RCA are in use for a range of different scenarios but it remains unclear what benefits could be gained by the use of ICA...]*

## Clinical Toxicology of Central Nervous System (CNS)-active Substances



**Dr Hugo Kupferschmidt**

Dr Hugo Kupferschmidt (\*1958), M.D., MBA-HSG, received his Swiss Federal Diploma of Medicine at the Zurich University Medical School in 1985. He is FMH specialist physician in Internal Medicine and in Clinical Pharmacology and Toxicology (1997), and Eurotox registered toxicologist. Dr Kupferschmidt has been working at the Swiss Toxicological Information Centre (STIC) since 1996 and is medical and managing director of the STIC since 2004. The STIC is serving entire Switzerland as Poisons Information Centre providing medical advice in toxicologic emergencies 7/24. Dr Kupferschmidt is giving clinical consults at the Zurich University Hospital in collaboration with its Department of Clinical Pharmacology and Toxicology. He is Faculty member of the Advanced Hazmat Life Support (AHLS) Course and serves as AHLS provider and instructor.

CNS symptoms are the most common symptoms encountered in human poisoning dealt with by Poisons Information Centres, because a large variety of substances will have CNS effects in sufficiently high doses. Symptoms include CNS depression from somnolence and dizziness to frank coma, CNS excitation with agitation, confusion, hallucinations, delirium, and seizures. These symptoms can have fatal consequences either via a direct toxic effect, or via complications eventually leading to death. Because the range of substances able to potentially serve as incapacitating agents is very large and not well defined, this presentation will not focus on agents but on the circumstances of exposure.

The agents involved in cases of poisoning dealt with in the Swiss Toxicological Information Centre (STIC, 1998-2008, n=272'490) include pharmaceuticals (36.5%),

household chemicals (24.5%), plants (11.0%), industrial chemicals (6.8%), cosmetics (5.6%), food and beverages (3.6%), illicit and recreational drugs incl. alcohol and tobacco (3.5%), agricultural agents (3.0%), venomous animals (1.7%), mushrooms (1.6%), veterinary drugs (0.3%), and other agents incl. toxic gases and vapors (2.8%). Poisoning with pharmaceuticals does not only account for most cases but also for the

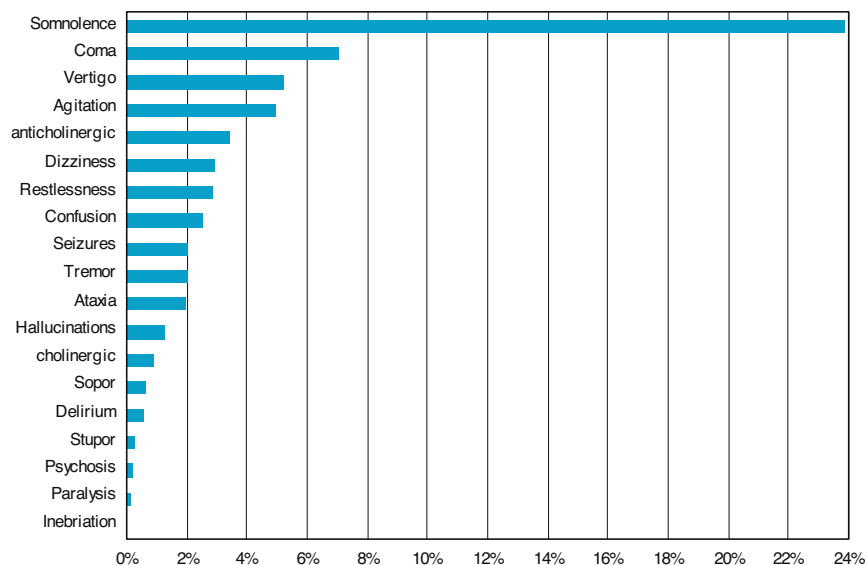


Fig. 1: Symptoms of poisoning cases recorded by the STIC in 2010 (only cases with written medical follow-up)

largest fraction of severe and fatal poisonings. This is particularly true for CNS-active substances (ATC group N). For all these reasons, CNS effects are very common (Fig. 1).

In cases with unclear exposures toxidromes are clinically helpful. Toxidromes are syndromes (clusters of symptoms) caused by different agents which share a mechanism of action thus producing a unique clinical picture of toxicity. Typically, a toxidrome has a uniform treatment which interferes with the particular mechanism of toxicity, allowing rational therapy without knowing exactly the causative agent. Toxidromes frequently seen include the anticholinergic, opioid, sympathomimetic, and toxic alcohol toxidromes.

Poison Centres distinguish two main categories of circumstances of poisoning including accidental poisoning (domestic, occupational, environmental, other) and intentional poisoning, which can be self-poisoning (suicidal, abuse, misuse) or poisoning of others (misuse, criminal, law enforcement). Use of ICA falls under this latter group.

There is a standard approach for the management of acute human poisoning including the effects of incapacitating agents. First (and most important) is the maintenance or reestablishment of vital functions (respiration, circulation, oxygenation), then reduction of substance resorption in order to reduce severity of poisoning (so-called primary decontamination)<sup>1</sup>, the enhancement of elimination with the aim of reducing the duration of toxic effects (secondary decontamination)<sup>2</sup>, and lastly the administration of specific antidotes if available.

From a medical and human rights view, the person or organisation who uses a chemical (a therapeutic drug, but also an incapacitating agent) on other individuals, has the responsibility to firstly obtain the consent of the treated individual, and secondly to minimise harm including optimal application of the chemical (choice of the substance, dose, route of application) and post exposure care for that individual. The choice of substance particularly takes in account its margin of safety (i.e. called therapeutic window in the case of pharmaceuticals), also in the view of the way of administration which has a large unpredictability for incapacitating agents. Therefore, if ever ICA should be allowed under certain circumstances, these circumstances would have to include processes of authorization and transparent declaration by those who use it similar to those with pharmaceuticals. The background of this concept is that every use of a chemical on a human being (including administration of a therapeutic drug) is to be regarded as an offence to individual integrity which can only be done with the informed consent of the affected person.

The discussion in this workshop cannot deal with substances but with the context of their use (i.e. for law enforcement), storage, and formulation (features specific for a use as ICA in the context of the workshop). A substance-focused view can only be used for agents which have no alternative use (as it is the case in warfare agents). For all other substances, not the substances themselves, but how they are used is the problem.

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1 Methods of primary (gastrointestinal) decontamination include induced vomiting (obsolete), gastric lavage, single-dose activated charcoal, and whole bowel irrigation.

2 Enhanced elimination techniques include the administration of multiple-dose activated charcoal, urinary alkalinization, hemodialysis, and hemoperfusion.

## Food for thought on non lethal capabilities



**Dr David Humair**

Dr David Humair studied molecular biology and genetic engineering at the University of Neuchâtel where he got a PhD in Sciences in 2000. From 2000 to 2001 he was responsible for a research project in genetic engineering at the federal agronomic research institute of Changins. From 2001 to 2007, Dr David Humair managed a scientific project for the planning staff of the Swiss armed forces mainly in the area of non lethal weapons. In this function he was active in a NATO working group dealing with the human effects of NLW. Since 2007, David Humair is research program director for armasuisse S+T. In this function he is responsible for coordinating all NLW activities of the Swiss department of Defense. He also acts as a vice chairman of the NATO NAAG Land Capability Group 9 on NLW and is the Swiss representative to the European NLW working group.

Recent world activities exacerbated utterly violent situations where the use of lethal force was neither adequate nor possible without taking the risk of no return escalation. Ranging from massive demonstrations of oppressed people to «normal» football fans confrontations, events requiring crowd control policing showed that new means were needed to assure proportionate public order.

Galloping urbanization, trivialization of violence, centralization of power or heaving demography are actual trends in the environment where the use of force could be required. Centers of gravity, critical to maintaining the rule of law, are nowadays often linked to people or infrastructures that are amalgamated in built-up and crowded areas. Therefore, in order to be able to guarantee the rule of law without trampling basic humanitarian laws, police officers or military personal have to be able to respond «proportionally» to all kind of civil unrest and first and foremost without generating collateral damages by hurting civilians or by damaging infrastructures. And this must be true even in an environment which is increasingly complex and where problems can arise from everywhere at anytime within a broad spectrum of intensity.

Non lethal capabilities (NLC) are already implemented in the majority of police and armed forces around the world. However, due to incomplete approaches in the use of (non lethal) force, major issues have revealed themselves through their implicational history. Most of the time, the problem is that “new tools” are distributed to police officers or soldiers without them having the proper doctrine of use, education, training or even adequate organization and infrastructure to use them properly in a proportional manner. Consequently, during real actions, end result can be no solution and instead exponential problems, going from non-lethal induced injuries or even deaths, for both individual officers or civilians. There are many high profile cases to illustrate such occurrences such as the WTO demonstration around the world and especially in Seattle in 1999, the shooting with FN 303 ammunition of a woman by Swiss police in 2003 or the killing of polish immigrant Robert Dziekanski at Vancouver Airport in 2007.

The media naturally over emphasizes the (minor) misusages and over enthusiastic applications of non lethal force by end users, even if a very small percentage have resulted in deaths. This is indeed a valid

problem in law enforcement engagements, but also increasingly in military operations.

### A complex problem

When non lethal force is employed, we can often observe that a lack of discipline, loose mindset or even dilettantism seem to be present. With lethal weapons law enforcement officers and soldiers are normally always in a correct mindset where «they actually know that using lethal weapons with lethal force can result in casualties». With NLWs, it is not the case. It is almost as if someone was just handing out materials with no serious consequences. It has to be mentioned that very often law enforcement officers or soldiers don't hear any such guidance before being issued NLW's and this must change.

Perhaps the greatest foundational structure for any law enforcement officer or soldier to rely upon is their own Observation, Orientation, Decision, Action cycle (OODA Loop) in the present moment of their reality, within their department/agencies Force Continuum Spectrum. Near reality scenario have to be trained until law enforcement officers and/or soldiers do it unconsciously every day. To train people to become more aware, especially while on the job, and to improve one's OODA Loop, can literally mean the difference between living or dying in difficult situations. Varied experience through training allows end users to also proportionally scale their response and application of non-lethal/lethal weapons along with their usage of non-lethal/lethal force as well.

### No easy solution

In order to increase the efficiency of the use of force along the force continuum spectrum we strongly recommend that the following elements are taken into account:

- Develop a coherent and broadly adopted terminology. Terms such as crowd control, force protection, continuum of force or proportional use of force have to be clearly defined. Technical terms link to procedures and materials also have to be defined. Clarity will aid procedure here.
- Develop a doctrine of use not only for individuals but also for team, squad, platoon and companies. For that, define a doctrine of employment for temporary neutralization means for use by all troops. The idea is to extend the response options available to commanders and to ensure the principle of proportionality in all law enforcement or military operations.
- Define or hone the legal framework. It is important to differentiate between «armed conflict» and «police operations». Police operations are all types of disturbances, violent protests or terrorist acts that do not meet the legal conditions needed to be defined as non-international armed conflicts. This has to be precisely defined. The legal rules are different and have de facto different consequences for non-lethal weapons.
- Develop a concept of communication for non lethal weapons. Critical messages are important to justify the use of non lethal weapons, especially if it turns out that it resulted in casualties.
- Develop and maintain a network of collaboration. Whether in the army, police or private security services, the need and interest in non lethal technologies (in the broadest sense) are widespread, showing that the spectrum of requirements needed to perform a security mission should be as broad as possible.
- Develop realistic and focused training for all levels (soldiers/cops, NCO and officers) both in the military and law enforcement forces. Develop and

set up a concept of tactical training for force protection for all commanders. Define a training concept for defensive crowd control and training for troops/officers engaged in the protection of critical infrastructures. Define the training for special troops like Special Weapons and Tactics, Military Police and Special Forces.

### **Conclusion**

For the development of army and police forces and in order to provide solutions to all commanding levels, it is necessary to invest resources in the area of temporary incapacitation and non lethal weapons, to guarantee scalable proportionality in all operations. This means that military and police forces must have flexible means of coercion in the entire sphere of missions they could be assigned to.

In order that the whole is coherent, it is important that doctrine, training and equipment acquisition are optimally coordinated. The budgets allocated to the theme should be consistent with an environment that may be more deleterious and where the military and police forces will become more active in providing concrete and fair solutions, despite a major uncertainty. Long term operational experience will never substitute for training, nor will training ever equate to operational experience, but a balance has to be established between the two taskings.

To ensure at all times a legitimate response, with the right usage of force and appropriate weapons, will create optimal credibility for armed and police forces. At the end of an encounter or operation, police, soldiers and their respective commands will be reliant upon how well their doctrine and training has conditioned them to successfully resolve the myriad of problems that continue to emerge in today's world. The old adage is more true now than ever «You will not rise to the occasion but you will fall back on how well you were trained».



# How can ICA be detected ?

The procedures for the analysis of chemicals relevant to the CWC cannot be transferred as such to the analysis and identification of ICA, which are likely to be more drug-like substances. Similarly, the procedures used at toxicology laboratories are not aimed at detecting ICA. The expertise reflected in both fields however may serve as starting point for suitable methods.\*

The Organisation for the Prohibition of Chemical Weapons (OPCW) procedures for onsite and offsite analysis are targeted at scheduled chemicals, their precursors and degradation products, generally referred to as chemicals relevant to the CWC. This is a very large group of chemicals (millions theoretically) and they embody a wide range of chemical characteristics. Most of these relevant chemicals contain certain signatures or functional groups for which specific screening approaches have been developed. The identification of these chemicals during OPCW onsite analysis is based on comparison of mass spectral data with reference data libraries, and, during offsite analysis at OPCW designated laboratories identification is additionally confirmed by comparing analysis data (of different analytical techniques) to synthesised reference chemicals.

These procedures are not directly transferrable to detect and identify ICA. No library exists today with analytical data of potential ICA type chemicals and for such chemicals the developed screening approaches are not applicable because (potential) ICA as well as their degradation products may contain different chemical signatures. The analysis of ICA will require a flexible analytical approach that is not primarily list based. Nevertheless, potential ICA should be added to the OPCW's analytical reference library, the OPCW Central Analytical Database (OCAD). In order to allow for the identification of ICA, OPCW designated laboratories and other interested laboratories should cooperate in the development of analytical procedures for ICA and in the creation of a library for ICA type chemicals, which should be integrated into the OCAD.

In case of a field-use of an ICA – potentially triggering an investigation of alleged use – only trace-levels of an ICA type chemical may be present in a sam-

ple, the detection and identification of which would pose a particular analytical challenge – one the OPCW is not in a position to meet today.

Toxicology laboratories are testing for a range of different types of substances including pharmaceuticals, natural toxins and designer drugs. For many of these substances analytical protocols exist today, but not for ICA. Before analytical procedures for ICA can be developed it has to be agreed what ICA actually are. There is no official list of chemicals that could be considered as ICAs. Nevertheless, toxicology laboratories are experienced in forensic analysis and their broad screening approach for target-driven analysis may be suitable for the detection and identification of ICA – considering that many potential ICA may be drug-like chemicals. Screening for ICA appears to be most feasible using a chromatographic separation technique coupled to a high resolution mass spectrometer such as a time-of-flight (TOF) or orbitrap instrument. While other analytical techniques may be suitable as well, this analytical technique offers a new approach for the identification of (unknown) chemicals. It may simplify the identification of a chemical structure in comparison to today's uses of mass spectrometry, where identification is generally based on comparing the fragmentation pattern of a molecule with mass spectral libraries. High resolution mass spectrometry allows determination of the molecular mass of a chemical very accurately. Consequently, the elemental composition (sum formula) of the molecule can be deduced from the molecular weight (without comparing to libraries). Once the elemental composition is known the structure of a substance can be identified more easily using additional analytical techniques.

\* The workshop organiser takes full responsibility for this summary text.



## Chair of this session:



**Prof Dr Paula Vanninen**

Professor Dr Paula Vanninen is director of the Finnish Institute for Verification of the Chemical Weapons Convention, VERIFIN, at the department of Chemistry, Faculty of Science, University of Helsinki. She manages the OPCW designated laboratory and the Finnish National Authority for the CWC implementation. She is in charge of management of various training courses in analysis of Chemical Warfare Agents (CWAs) and in CWC requirements for National Authorities. She is member of the Scientific Advisory Board of the OPCW and the sampling and analysis temporary working group. She is leading the correspondence group on trace analysis.

*[...In case of a field-use of an ICA – potentially triggering an investigation of alleged use – only trace-levels of an ICA type chemical may be present in a sample, the detection and identification of which would pose a particular analytical challenge – one the OPCW is not in a position to meet today...]*

## Do current analysis methods targeting chemical warfare agents cover also incapacitating agents ?



**Martin Söderström**

Martin Söderström has been working at the Finnish Institute for Verification of the Chemical Weapons Convention, VERIFIN, at the department of Chemistry, Faculty of Science, University of Helsinki, for twenty years. Currently, he is coordinator at VERIFIN. He has wide experience in analysis of the CWC-related chemicals using various analytical techniques such as GC, GC-MS, LC-MS and FTIR. Recently, he has been actively involved in the method development and analysis of Chemical Warfare Agents (CWA) in environmental and biomedical samples, old chemical weapons in sediment samples and analysis of Ricin toxin. He also coordinates the analysis done at VERIFIN as the OPCW designated laboratory.

Currently, many laboratories around the world are capable for identification of chemical warfare agents (CWA) from e.g. environmental samples. The Organisation for Prohibition of Chemical Weapons (OPCW) has established a network of so-called designated laboratories. The task of these laboratories is to perform confirmatory analysis of any samples sent to them by the OPCW Laboratory from different OPCW inspections. To obtain designation, a laboratory must establish analysis method, obtain accreditation as well as perform well in the yearly OPCW proficiency tests. Currently, there are twenty-two designated laboratories in sixteen countries.

Typical analysis task for an OPCW proficiency Test has been analysis of samples from a challenge inspection at a so-called single small-scale facility of a chemical plant. The task is normally to analyse and report «any Scheduled chemicals and/or their degradation/reaction products» present in the samples. The Chemical Weapons Convention (CWC) lists the possible target chemical in three Schedules. Schedule 1 contains the most toxic warfare agents – such as nerve agents, mustard gases as well as two toxins: saxitoxin and Ricin. It should be remembered that riot control chemicals, such as tear gases, are not included in the Schedules. In addition to the Scheduled chemicals, the CWC clearly forbids the use of any toxic chemical as a means of warfare. This so-called «general purpose

criterion» means that in some cases the task of the designated laboratories could be to search for any possible toxic chemical present in the samples.

The inspection types listed in the CWC are routine and challenge inspections as well as inspections of alleged use. The goals of these are quite different. In the routine inspections, the analysis would be related to confirmation of presence of Scheduled chemicals or absence of Schedule 1 chemicals. On the other hand, in the alleged use cases the target chemicals could be Scheduled chemicals, riot control agents or any other toxic chemicals. The proficiency tests cover only the Scheduled chemicals.

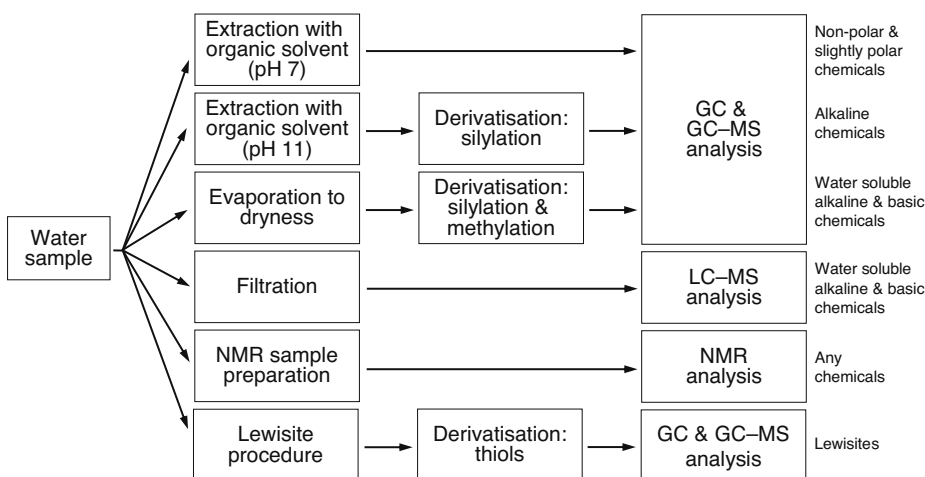
The analysis of CWA starts typically by screening analysis with different methods. Many of these methods rely on the presence of phosphorus, nitrogen and/or sulphur atoms found in most of the CWA chemicals. Reliable screening makes it much easier to detect CWC-related chemicals in low concentrations or in relatively high chemical background.

The identification is normally based on either reference chemicals or reference spectra of CWA. The top-end laboratories are able to synthesise reference chemicals during the analysis. The OPCW has also been developing a reference spectrum database OCAD

(OPCW Central Analytical Database), which includes data for over 4000 CWC-related chemicals. This database allows quick and reliable identification of these chemicals also without the use of reference chemicals.

The analysis process able to detect any CWA is based on first applying a suitable sample preparation to separate different chemicals in various fractions and then examination of the fraction using a suitable analysis method. Such an analysis tree is presented below. The applicability of this process will be the key issue in evaluation and development of analysis methods for ICA.

The incapacitating chemical agents (ICA) differ from CWA in several important ways. The ICAs are clearly a less homogeneous group of chemicals than



CWAs. Actually, there is no clear internationally recognised definition of the ICA. Based on publicly available information, the ICA are generally larger molecules, which has effect on the suitability of some analytical techniques – such as gas chromatography (GC) – which rely on the volatility of the analyte. Additionally, there seems to be less heteroatoms in the ICAs than in CWAs, which greatly limits the application of similar general purpose screening methods used in CWA analysis. Still, many ICA chemicals contain nitrogen and some – especially the malodorants – contain sulphur. ICAs are also chemically different from CWAs as they typically have large hydrocarbon moieties – also aromatic – and polar groups such as hydroxyl groups. This affects the suitability of the used extraction methods for the analysis of ICA.

Before tackling the actual analysis process, a target ICA list should be available. This would be required

for assessing the available methodology and reference data.

Based on available information on possible ICAs, three groups of chemicals were selected for evaluation: riot control agents (e.g. tear gases, capsaicin and Clark I), CNS stimulants/depressants (e.g. amphetamine, diazepam and naloxone) and malodorants (e.g. skatole, ethyl sulphide and isovaleric acid). These chemicals fit – at least partly – to the analysis tree above. The drug-like chemicals seem to be covered less by analysis methods used for CWAs, but fortunately methods for these chemicals exist in several laboratories. The largest problem in establishing analysis methods for ICAs will be how to collect and fit together all available information. It would be beneficial to build a general analysis tree – like for CWA analysis –

instead of putting together a collection of separate methods from different sources. This, however, would require a considerable amount of work.

Before a good analysis method for ICAs can be developed, a set of possible ICA usage and

analysis scenarios should be put together (e.g. drug testing-type analysis, analysis of sprayed ICA or criminal activity related scenarios). Different scenarios would mean different types of samples (e.g. biomedical, environmental and food stuff) and different concentration levels. All these factors will affect the analysis procedures.

The current methodology used for analysis of CWAs could be a suitable starting point for development of a wide-scope ICA analysis method. The whole process would require gathering of information on analysis methods, collection of reference data and possibly of synthesis of some reference chemicals. Also, the methods should be tested with the selected chemicals and sample matrices to ensure that the procedures work.

## How can ICA be detected in a forensic toxicology laboratory ?



**Prof Dr Ilkka Ojanperä**

Prof Dr Ilkka A. Ojanperä was born 18.12.1957 in Espoo, Finland. He received his PhD in organic chemistry from the University of Helsinki (1992) and subsequently became docent of pharmaceutical chemistry and forensic toxicology. Since 1993 he has held the position of Laboratory Director at Hjelt Institute, Department of Forensic Medicine, University of Helsinki. Since April 2011, he is the acting Professor of Forensic Toxicology at University of Helsinki. Ojanperä is a Member of the Editorial board of International Journal of Legal Medicine and a Permanent expert (toxicology) to the National Supervisory Authority for Welfare and Health in Finland.

Forensic toxicology laboratories are prepared for detecting and quantifying a wide range of toxicologically relevant compounds in body fluids and tissues. The main areas of forensic toxicology are post-mortem toxicology related to cause-of-death investigation, driving under the influence, drug facilitated crime, child welfare, and drug testing at workplace and other instances. In Finland, the drugs considered as the most important findings in fatal poisonings in 2010 were codeine (opioid analgesic), amitriptyline (antidepressant), buprenorphine (opioid analgesic), tramadol (opioid analgesic), doxepin (antidepressant), zopiclone (hypnotic), levomepromazine (antipsychotic), quetiapine (antipsychotic), venlafaxine (antidepressant), propranolol (beta-blocker), methadone (opioid analgesic), oxycodone (opioid analgesic), temazepam (hypnotic, benzodiazepine), alprazolam (anxiolytic, benzodiazepine), metformin (antidiabetic), mirtazapine (antidepressant), citalopram (antidepressant), insulin (antidiabetic), pregabalin (antiepileptic), amphetamine (stimulant, sympathomimetic), olanzapine (antipsychotic), clozapine (antipsychotic), morphine (opioid analgesic), paracetamol (analgesic), fentanyl (opioid analgesic), paroxetine (antidepressant), and digoxin (cardiac glycoside). It is evident that drugs acting on the central nervous

system, especially opioids, are the most important findings in fatal poisonings. Our comprehensive analysis procedure with use of gas (GC) and liquid chromatography (LC) and mass spectrometry (MS) detects approximately 300 substances annually, plus metabolites. In our laboratory, 7100 post-mortem and 2600 clinical cases were investigated in 2010.

The substances encountered in forensic toxicology practice are predominantly alcohols, medicinal drugs and drugs of abuse. However, Wikipedia lists the following examples of ICA: BZ (anticholinergic), DMHP (cannabinoid), EA-3167 (anticholinergic), carfentanil (opioid) and 3-methylfentanyl (opioid); and the following examples of riot control agents: capsaicins in irritating pepper spray, and CS, CN and CR in «tear gas» aerosols. The Baselt's standard handbook, «Disposition of Toxic Drugs and Chemicals in Man, 9<sup>th</sup> edition» (1), covers 1240 substances with toxicological and analytical data but only includes 3-methylfentanyl from the list above. Another standard handbook, «Clarke's Analysis of Drugs and Poisons, 4<sup>th</sup> edition» (2), covers 2111 substances with analytical and toxicological data but only includes the CN and CR gases.

In principle, ICA can be detected within forensic toxicological investigation either by target analysis, by multitarget analysis or within comprehensive screening analysis. An example of a target analysis is the determination of 3-methylfentanyl by LC-MS/MS using multiple reaction monitoring (MRM). This very potent opioid caused hundreds of deaths mainly among Estonian Russian speaking drug addicts, and the lethal concentration in blood was found to be only at the low microgram per litre level (3). An example of a multitarget analysis is the determination of opioids by LC-MS/MS using MRM (4). This method allowed simultaneous determination of morphine, naloxone, naltrexone, oxycodone, 6-monoacetylmorphine, ethylmorphine, norfentanyl, tramadol, heroin, pethidine, remifentanyl, pentazocine, norbuprenorphine, fentanyl, p-fluorofentanyl, alpha-methylfentanyl, trans-3-methylfentanyl, cis-3-methylfentanyl, buprenorphine, sufentanyl, normethadone, dextropropoxyphene and methadone in blood at sufficiently low concentrations. The method has proved to be feasible for instance in revealing malpractice by opioids in hospitals.

In comprehensive screening analysis, two techniques are superior today: GC-MS with electronic spectrum libraries and LC coupled with time-of-flight MS (LC-TOFMS) with accurate mass databases. GC-MS libraries are commercially available containing hundreds of thousands of electron ionization spectra. Especially the Wiley/NIST library contains all of the above mentioned incapacitating and riot control agents, except for EA-3167. LC-TOFMS is a technique that enables accurate molecular mass measurement with moderate or high resolution. The fundamental advantage of accurate mass has been stated as follows: «If the mass of an ion from a chemical compound is determined with sufficient accuracy, the elemental composition of that compound could be deduced». Mass accuracy is the

difference  $\Delta M$  between the theoretical value of the mass of an ion and the mass measured using a mass spectrometer. Mass accuracy in ppm is expressed as  $\Delta M/M \times 10^6$ . The better the mass accuracy, the fewer potential elemental formulae exist. For instance methamphetamine ( $MH^+C_{10}H_{16}N = 150.1$ ) and cathinone ( $MH^+C_9H_{12}NO = 150.1$ ) cannot be differentiated by nominal mass using ordinary techniques, but their exact mass difference is as high as  $DM = 36.4$  mDa or 224 ppm. Numerical comparison of theoretical and measured isotopic patterns is an additional identification tool for accurate mass determination. Resolving power is defined as the capacity to separate ions of adjacent  $m/z$ , and resolution is the measure of the separation of the two mass spectral peaks. High resolution is necessary to separate adjacent mass peaks, and its importance is pronounced in samples with heavy background noise due to complicated matrix (5). Accurate mass measurement by LC-TOFMS allows tentative identification even without the availability of reference standards, and reanalysis of stored acquisition data for new target compounds is also feasible.

To conclude, most ICA are not familiar to forensic toxicology laboratories, and these laboratories do not either possess reference standards for specific ICA. Moreover, information on ICA in standard analytical toxicology handbooks is scarce. Consequently, routine analytical toxicology laboratory methods are not aimed for detecting ICA. However, many ICA are drugs or drug-like molecules, and instrumentation of forensic toxicology laboratories is generally suitable for detecting ICA. Screening for ICA appears to be feasible by LC-TOFMS using accurate mass databases and/or by GC-MS with electronic libraries. Forensic toxicology laboratories should be more aware of the existence of ICA.

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# How to control abuse ?

Why are ICA an issue, and why now? Is there a need for a new definition of ICAs if the CWC is considered clear enough on the definition of toxic chemicals? What options exist other than lethal force to deal with some law enforcement problems, when ICAs are considered singularly inappropriate? In any case, what risk assessments would be required before the development and deployment of any such agents? What are the reasons for the continuing interests in such materials and how might the ICA issue best be tackled in the context of the CWC? Would it be prudent to do so in the near future? Is the OPCW route appropriate, and if no, what other mechanism or under whose aegis could the issue be further developed? Could the process practiced at the BWC based on expert meetings be suitable?\*

The CWC has been a success story and is not about to collapse on account of the ICA issue. It contains a clear definition of toxic chemicals – which includes ICAs – as well as a clear definition of RCA. But ICA may well represent a first step onto a slippery slope at the end of which countries may start re-arming with a new generation of chemical weapons, more developed than the ones currently being destroyed. ICAs are toxic chemicals, some are more potent than Nerve Agents – in that less of the substance will be required to cause the anticipated effect – and these effects could be irreversible. The proper question therefore, is whether such materials should even be considered for law enforcement purposes. The term ‘ICA’ is a sugar coating to help make the concept – of using once again the toxic properties of chemicals as weapons – somehow more acceptable.

Some saw ICA uses for law enforcement as a permitted activity – there was a need too for a range of response capabilities between ‘persuasion’ and ‘lethal force’. However, the types and quantities aspects of agents as well as delivery systems that might be developed and used are critical to the debate in the context of the CWC – in particular to the prohibition of the development and possession of chemical weapons and the prohibition of any military preparations for their use. Transparency measures for law enforcement capabilities might be one approach to help provide reassurance over intentions. A problem is that in the last decades more conflicts are taking the form of civil wars, extensive lawlessness and insurrections – circumstances that involve the use of military forces. If

there is no clear view on what is permitted, then the risk is, that ICAs could be introduced (more) into such scenarios and become standard issues for military units (at which point their use in combat – which is illegal under the CWC – could no longer be prevented).

Even in a clear-cut law enforcement environment, the question remains: who would be responsible for risk assessment over the development, deployment and how and when to use ICAs? It is far from evident that such risk assessment would be performed thoroughly. There are too many variables – such as unpredictable effects across a large exposed population where the dose for an individual cannot be controlled or predicted with reasonable certainty – that it would be hard to ascertain that use would be ‘safe’ in all circumstances. The result could be permanent injuries and fatalities, all of which could lead to law suits for compensation. There are risks too for the CWC, including the risk of proliferation. Development and deployment of ICAs could lead to their acquisition by non-state actors and terrorists. Identification and control of effective delivery systems are another dimension to address in this debate. It is not clear that states are ready to address this issue. There is furthermore the risk of creeping legitimisation – inertia and a lack of will at the state level to deal with the problems and challenges presented by ICAs seems evident.

How does an unacceptable weapon become an acceptable one and what are the consequences if that happens? There can be push factors from advances in science and technology and pull factors from armed

forces. Experience in the 20th century with the development of chemical warfare shows that interest has ebbed and flowed. Perhaps, we are seeing another round of this with the emergence of ICAs – the legal framework is however fundamentally different today, with almost universality of the CWC – or maybe we are witnessing something different – this remains a key question to address.

Progress on CBW arms control and disarmament is notoriously slow – the CWC took years to develop and agree and adaptation of its implementation processes to advances in science and technology remains hesitant at best. Other areas related to warfare and conflict have seen dramatic progress over a few years, such as with regard to the prohibitions of anti personnel land mines (APLM), cluster munitions and laser weapons. The same urgency could be imparted in tackling the ICA problem. Extensive and active NGO interest and campaigning however have been critical factors in securing action – certainly for the Ottawa and Oslo Conventions. An important factor for the prohibition of laser weapons was that some states did not want to see their own troops coming home blinded – a similar approach could apply for ICAs with concerns over armed forces personnel returning with permanent mental or other disabilities caused by exposure to ICAs.

The argument for ICAs to tackle law and order challenges in certain scenarios has been put forward not by police forces and other law enforcement agencies, but mainly by military organisations involved in low-intensity conflict, including certain policing-like missions. Law enforcement organisations in the traditional sense have yet to take a public stance on whether they see a need or justification for ICAs. It therefore is highly desirable to engage these communities in further discussions on ICAs on the way ahead. The debate needs to broaden out to include other states, who thus far have shown little interest in the issue. Also, for some states, there may be limited expertise available for the complex interactions between the national security, legal, scientific and technological as well as diplomatic aspects of this problem. The same applies to experts and scientists, where the level of awareness and interest is low or non-existent. Conversely, based on the experience gained with negotiations on other types of weapons listed above (APLM etc.), one could be surprised by the speed the issue might gain from

including other stakeholders. The key elements of the ICA debate should therefore be formulated in clear and simple terms. One or more CWC States Parties should perhaps show leadership on this issue and take the debate forward more intensely (extensively) with a clear purpose – it will not progress on its own. Bringing a specific proposal to the OPCW might be one way of doing so.

One possible approach might be to see the establishment of a process similar to the Meeting of Experts in the framework of the BWC, where the main aim was to ‘promote common understandings’. This could be an open-ended way to tackle the ICA problem in the context of the CWC and disarmament law, human rights law, international humanitarian law (IHL) and the law of armed conflict. Such a process might be able to develop elements of a decision for introduction to the OPCW – possibly for later discussion by the policy making organs. It may however be challenging to initiate such a process in the OPCW context. Its purpose would have to be clarified and mandated, which may become politicised and delay progress. The OPCW Scientific Advisory Board may also have a part to play in furthering discussions, understandings and making progress, but probably not in a leading role. An NGO led process could offer an alternative – comparable to the role played by Pugwash during the BTWC and CWC negotiations. As there is still a marked reluctance in the OPCW context to engage civil society in discussions on such sensitive matters, Geneva may be a better location to hold such talks.

Despite all the ideas presented on the ICA problem, there is a risk of going round in circles – breaking out is the key challenge – we have to start somewhere.

\* The workshop organiser takes full responsibility for this summary text.

## Chair of this session:



**Dr John R. Walker**

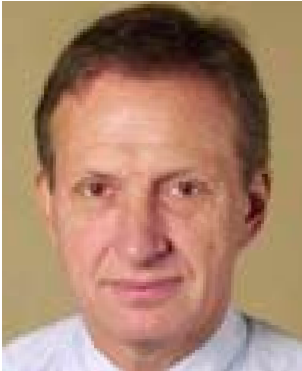
Dr Walker has worked in the Foreign and Commonwealth Office's Arms Control and Disarmament Research Unit (ACDRU) since March 1985. He focuses on Chemical Weapons Convention (CWC), Biological and Toxin Weapons Convention (BTWC) Comprehensive Nuclear Test Ban Treaty (CTBT) issues and arms control verification more generally. He is the last UK official still in post who was involved in the original CWC negotiations. He was an ex-officio member of the UK's National Authority Advisory Committee. He has been a member of UK delegations at BTWC and CWC Review Conferences, the BTWC Ad Hoc Group, CWC Preparatory Commission Expert Groups and CTBTO Preparatory Commission Working Group B meetings on on-site inspection issues.

*[...The term <ICA> is a sugar coating to help make the concept – of using once again the toxic properties of chemicals as weapons – somehow more acceptable...]*

*[...A problem is that in the last decades more conflicts are taking the form of civil wars, extensive lawlessness and insurrections – circumstances that involve the use of military forces. If there is no clear view on what is permitted, then the risk is, that ICAs could be introduced (more) into such scenarios and become standard issues for military units...]*



## «Incapacitating chemical agents»



**Dr Robin M. Coupland**

Dr Robin Coupland is a medical adviser in the International Committee of the Red Cross (ICRC). He joined the ICRC in 1987 and worked as a field surgeon in Thailand, Cambodia, Pakistan, Afghanistan, Yemen, Angola, Somalia, Kenya and Sudan. He has developed a health-oriented approach to a variety of issues relating to the design and use of weapons. A graduate of the Cambridge University School of Clinical Medicine, UK, he trained as a surgeon at the Norfolk and Norwich Hospital and University College Hospital, London. He became a Fellow of the Royal College of Surgeons in 1985. He is the holder of a Graduate Diploma in International Law from the University of Melbourne in Australia. His current work has two tracks: first, the feasibility of an ICRC operational response in the event of use of nuclear, radiological, biological or chemical weapons; second, improving security of health care in armed conflicts.

### Introduction

This presentation raises ten key questions to illustrate some of the ICRC's main concerns about so called «incapacitating chemical agents». The aim is to help clarify some of the key issues under discussion at the workshop, to provide a «reality check» on some of the claims made about these weapons, and to draw attention to the key questions policy makers need to address before considering the development or use of «incapacitating chemical agents».

The phrase «incapacitating chemical agents» is placed in quotation marks intentionally to highlight that this «category» of toxic chemicals does not exist. «Incapacitating chemical agents» are not defined under the Chemical Weapons Convention (CWC), nor is there any other internationally agreed definition. The CWC defines riot control agents (RCAs) but all other toxic chemicals used as weapons, whether having lethal or incapacitating effects, are grouped together.

#### **Q1 Is this not about «tactical anaesthesia»?**

An accurate description of the use of «incapaci-

tating chemical agents» would be «tactical anaesthesia». <sup>1</sup> Essentially, this involves the employment of commonly used pharmaceutical drugs for anaesthesia in a tactical situation. As «tactical anaesthesia» by definition is carried out without the consent of those given the drug(s), and without the continuous medical care provided in a clinical setting, it amounts to poisoning people. This assessment would be the same regardless of which element of anaesthesia is induced (the three elements being hypnosis/sedation, analgesia, and muscle relaxation.)

#### **Q2 In relation to this workshop, what are we talking about?**

There has often been confusion about what we are discussing when we refer to «incapacitating chemical agents». Clearly these are not RCAs, which are defined as a separate category of toxic chemicals under the CWC, distinct from all other toxic chemicals. A useful and simple distinction to make between RCAs and «incapacitating chemical agents» is that the former make people disperse and run away whereas the latter make people fall down and lose consciousness.

Discussions of «incapacitating chemical agents» often describe them as another separate category of toxic chemicals. However, this assumes incorrectly that it is possible to distinguish them from other non-RCA toxic chemicals used as weapons, including traditional chemical warfare agents (The quotation marks around the phrase also emphasise this lack of distinction). «Incapacitating chemical agents» are, in normal parlance, chemical weapons.

### **Q3 In relation to this workshop, what are we NOT talking about?**

It is clear from technical discussions at this workshop and elsewhere that «incapacitating chemical agents» will not provide a safe «knock-out gas» or «magic dust» capability, although this potential is often used to promote their development. Nor are «incapacitating chemical agents» weapons that can somehow be confined to possession by «good guys» for use solely against «bad guys». If the weapons are developed and used then proliferation is inevitable.

### **Q4 Do / will «incapacitating chemical agents» exist?**

If there is an expectation that «incapacitating chemical agents» will 1) cause immediate incapacitation and 2) result in zero lethality, then the answer to this question is no. It can be expected that any use of «incapacitating chemical agents» will result in significant fatalities and other adverse health effects, as discussed in expert presentations at this workshop and other meetings.

### **Q5 What is the real issue?**

Consideration of questions 1 to 4 raises doubts over why we are even discussing «incapacitating chemical agents». However, the reason is that some States have maintained interest in these weapons and continue to carry out research and development work.

Implicit assumptions apparent in this ongoing interest are:

- that solutions to particular tactical situations lie in new technologies;
- that the medical terminology associated with «incapacitating chemical agents» makes them somehow more acceptable than other chemical weap-

ons;

- that «non-lethality» is an attainable goal; and
- that article II.9(d) of the CWC on «law enforcement and domestic riot control» is the only issue States need to consider in assessing the legality and desirability of «incapacitating chemical agents».

The real issue for the ICRC, however, is whether States should employ poison as a weapon in any context, and the profound implications of doing so for various fields of law including international humanitarian law, international human rights law, the CWC, and the Biological Weapons Convention (BWC).

### **Q6 What would «tactical anaesthesia» involve?**

There are marked differences between the use of drugs for anaesthesia in a clinical setting to facilitate treatment of a patient and the use of the same drugs for «tactical anaesthesia» to incapacitate people. A fundamental difference, often overlooked in discussions of «incapacitating chemical agents», is that the latter involves no consent from the person(s) receiving the drug(s). Furthermore, the users in the case of «tactical anaesthesia» are not anaesthetists and so are not qualified in how to administer these drugs safely.

There are many unanswered, and unanswerable, questions about how this «tactical anaesthesia» would be achieved, including:

- How would the right «dose» of the drug(s) be delivered to each person?
- How would that «dose» be adjusted according to the particular characteristics of each individual (eg size, age, health)?
- How would the «dose» be delivered at the right time?
- How would the user ensure the «dose» of a given drug had the intended effects?
- How would the user identify when the drug(s) has exerted the desired effect?
- How would the necessary, agent-specific, medical care be provided to each individual during the administration of the drug(s) to a group of people?

### **Q7 Who needs to be trained and in what?**

The use of «incapacitating chemical agents» would also raise a range of issues for training, including how it would be possible to train the user:

- to deliver the correct «dose» of the drug(s) to the target person(s)?
- to recognize someone who has been affected by the drug(s)?
- to distinguish between an adversary and a civilian who has been affected?
- to recognize whether an adversary has been incapacitated, and therefore cannot be targeted with other weapons, or whether they are still a threat?
- to distinguish whether someone is surrendering if they are already incapacitated?

Those people affected by «incapacitating chemical agents» would have greatly increased vulnerability to the use of force and general environmental hazards. However, it is not clear how those using «incapacitating chemical agents» would be able to protect the victims while they are in this vulnerable state.

The chances of recovery for those incapacitated may also depend on the availability and correct administration of an appropriate agent-specific antidote. However, for this to be possible those using the «incapacitating chemical agents» would have to «win» the tactical situation first. For example, in a hostage situation all it takes is one armed hostage taker not to be incapacitated to prevent the treatment of everyone else in the immediate vicinity, thereby increasing the risk of serious health effects and/or death.

#### **Q8 Does this involve «medicalisation» of an attack?**

Chemicals proposed as «incapacitating chemical agents» are drugs produced in the civil pharmaceutical industry and used in a clinical setting for anaesthesia. Arguments for their use in a tactical situation amount to providing a medical justification for an attack with chemical weapons.

There are significant ethical issues that arise in the research, development and use of drugs as weapons instead of as treatments. These ethical issues are particularly marked for doctors and other health professionals. Given the need to control the «dose» and provide an agent-specific antidote it seems that medically trained personnel would need to be directly involved in planning, executing, and responding to an attack. This would be at odds with the principle of acting in

the best interests of the «patient», and it raises the question of whether the use of «incapacitating chemical agents» threatens the traditional notion of medical neutrality.

#### **Q9 Are counter-measures easy?**

The answer to this question is yes. Inside a building the windows can be broken to allow escape of the «incapacitating chemical agents» and to reduce the concentrations inside. Gas masks can be used by adversaries to prevent the effects of the agent(s). Antidotes can be carried by adversaries to counteract the effects if no protection is available or if the agent(s) starts to exert its effect before protection can be used.

Any use of specific «incapacitating chemical agents», or declaration by States of the non-RCA chemical agents held for law enforcement, would facilitate the preparation of countermeasures. These factors raise further questions about the claimed tactical utility of «incapacitating chemical agents».

#### **Q10 Why is there so much discussion about agents that don't exist, won't work as advertised, and may not provide the intended tactical advantage?**

The questions raised here, and during this technical workshop, highlight the risks associated with using «incapacitating chemical agents» in a tactical situation («tactical anaesthesia»), particularly the technical and practical realities that rule out their use in a safe manner.

It would follow from the above that the discussion of «incapacitating chemical agents» should be reality-based and interest in these weapons diminish. However, interest is maintained and the discussion continues because some States appear willing to develop and use «incapacitating chemical agents» despite the risks, and others fail to exclude this option in the future.

The bigger picture is more worrying. Some seem not only willing to accept the particular risks of using «incapacitating chemical agents» in a tactical situation, but also the much broader risks associated with the development and use of these weapons. These risks include: the undermining of norms against chemical

and biological weapons including the CWC and BWC regimes; the increased likelihood of the use of «incapacitating chemical agents» and other chemical weapons in armed conflict; the inevitable proliferation of these weapons; and the fact that these weapons programmes provide a pathway for further, and even more disturbing, applications of advances in the life sciences for hostile purposes.

Continued interest, research, and inconclusive dialogue about so called «incapacitating chemical agents» raises the spectre of «creeping legitimization»<sup>2</sup> of chemical weapons with increased likelihood of their future use. Discussions about «incapacitating chemical agents» tend to return to article II.9(d) of the CWC – the provision for «law enforcement including domestic riot control» as a purpose not prohibited under the Convention. However, these discussions have brought no further resolution of the outstanding questions raised in this presentation. Such discussions also ignore key aspects of the issue, including: the prohibitions of the BWC; the constraints of human rights law; the responsibility for safety and proportionate use of force in policing; and the requirement for broader social, ethical and moral debate.

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1 See for example reference to ‘tactical pharmacology’ in: British Medical Association (2007) Drugs as weapons. The concerns and responsibilities of healthcare professionals. Available at: [http://www.bma.org.uk/health\\_promotion\\_ethics/warfare\\_weapons/drugsas-weapons.jsp](http://www.bma.org.uk/health_promotion_ethics/warfare_weapons/drugsas-weapons.jsp)

2 Perry Robinson, J P (2007) Non Lethal Warfare and the Chemical Weapons Convention. Harvard Sussex Program, SPRU – Science & Technology Policy Research, University of Sussex, UK, 24 October 2007. Available at: <http://www.sussex.ac.uk/Units/spru/hsp/Papers/421rev3.pdf>

## How to control abuse ?



**Dr Ralf Trapp**

Dr Ralf Trapp is an independent consultant on chemical and biological weapons arms control. A chemist and toxicologist by training, he worked with the GDR Academy of Sciences between 1978 and 1990. From 1985 to 1985 he was a researcher at the Stockholm International Peace Research Institute (SIPRI), and from 1991 to 1992 at the «Stiftung Wissenschaft und Politik Ebenhausen» (Germany). He acted as technical adviser to the GDR and subsequently the German delegations to the Conference on Disarmament. Between 1993 and 2006, he worked at the Technical Secretariat of the OPCW in the areas of industry verification, verification policy and review, international cooperation, government relations and political affairs, and strategic planning. He was a main contributor to both CWC Review Conferences, and the secretary of the OPCW's Scientific Advisory Board.

As a starting point, when I talk about how the abuse of ICAs can be prevented, my focus is on State activities and programmes. There are of course other dimensions to this question, with regard to non-State actors including criminals and terrorists, but these are not my main concern in this presentation.

### Why this discussion?

Let me first reflect on why we are having this discussion. To do so, it is useful to recall what the legal context is for this debate:

- From an arms control perspective, the legal requirements under the CWC are clear: ICAs are toxic chemicals and thereby qualify as chemical weapons unless intended for purposes not prohibited under the CWC (if used for such legitimate purposes, their types and quantities must be consistent with such purposes; this also implies that such uses may be subject to other types of legislation and regulation).
- The only exception that the CWC makes from this general prohibition is the one for RCAs (which are separately defined and have their own regime under the CWC);
- This exemption from the comprehensive prohibition recognizes that States Parties wanted to retain the RCA option in their law enforcement 'tool kit', as one of the method of enforcing law alternative to the use of lethal force.
- Their use in war ('as a method of warfare'), however, is prohibited.
- From the perspective of law enforcement as usually understood (policing of events, fighting crime) the situation is equally clear:
  - In addition to the precautionary and proportionality principles, human rights law will always apply to law enforcement;
  - Due care and responsibility of the State require restraint not just in the methods used but also in terms of how they are being used in law enforcement;
  - In this context, the use of RCAs is well established and, at the national level, there are accepted protocols for how they are to be used in law enforcement.

- So why are we debating ICAs for law enforcement? Where is the ‘gap’ that they are supposed to fill? Which (if any) are the new requirements that had not been considered by the CWC drafters?
- What is actually being discussed is not traditional law enforcement (police forces have yet to articulate a desire for using ICAs), but:
  - The needs perceived by military forces tasked with policing-like functions, e.g. in the context of maintaining law and order in occupied territories or during peacekeeping missions;
  - Special operations requirements in, for example, counter-insurgency scenarios. Some of these requirements have in the past been articulated as situations when some States Parties of the CWC felt entitled to use RCAs.
- While some of these military tasks may well fall within the scope of law enforcement, others frankly are combat missions and thus subject to the laws and rules of warfare, and of course the CWC. It must be clear that this latter use of ICAs in combat would constitute a breach of the CWC.

At this point, it may be worthwhile to recall a historic debate about the usefulness or not of non-lethal CBW. During the 1960ies, there were arguments in the United States (and probably in other countries) about acquiring a capability to use ‘non-lethal’ biological weapons. The argument was resisted because opponents pointed out that it would be difficult to draw a line between ‘non-lethal’ and ‘lethal’ BW agents – after all, many diseases make sick rather than kill, and in many cases disease can be treated. But if one can’t draw a line between ‘lethal’ and ‘non-lethal’ biological agents, why should others even attempt to stick to ‘non-lethality’? At the time, the fear was that moving down the track of non-lethal biological warfare would eventually lead to acceptance of any kind of BW warfare methods. That was considered undesirable.

The situation under the CWC is not different from that past experience. What applies to ICAs, under the CWC, equally applies to other toxic chemicals. In fact, an example often presented when explaining what the legitimate uses of toxic chemicals for law enforcement purposes are under the CWC, is the use of lethal injections for capital punishment. But does that mean that

the CWC sanctions any kind of use of toxic chemicals for law enforcement purposes?

It should also be recalled that the issue of non-lethal CW and RCAs was not ignored in the CWC negotiations. Proposals to the effect that such agents should be allowed for peacekeeping operations were in fact informally introduced at the end of the negotiations (with respect to RCAs), but failed to get support.

### **Why discuss this issue now?**

The ICA debate has been going on for several years now, prompted initially by the use of a fentanyl derivative to end the Moscow theatre siege. It has so far not led to any generally-agreed conclusion. Some observers remark that nothing much has changed – so why have this discussion now?

A first reason is the pace at which science and technology are advancing in fields that are directly relevant to the ICA issue. Neurosciences, neuropharmacology and -toxicology, research into the role of neuropeptides, neuroreceptors and regulatory circuits are all making rapid progress. This research is unlikely to lead to a ‘good ICA’ but scientific discoveries are impossible to predict with certainty. There will be surprises, and if novel CNS drugs with a large therapeutic index are discovered (or methods found to deliver them with much higher selectivity to the target sites) they may well be perceived as ‘safe’ ICA candidates.

A second reason is that the evolving security context continues to fuel demands and expectations for weapons that are better suited for the new operational environment, with operations being conducted in urban areas and with civilians and combatants mixed up and sometimes impossible to distinguish or separate. Calls for additional, ‘non-lethal’ weapons in the military tool-kit continue, and for some, ICAs may be the answer. There certainly is strong interest in military applications of drugs and other methods that enhance human performance – it is essentially the same science that would lead to drugs that degrade human performance and there may well be arguments that if the one is accepted than why not the other.

These developments are quite different from the usual processes of introducing new types of equipment/weaponry and methods of policing into law en-

forcement. The latter, because it relates to the use of State power vis-à-vis its citizens, is a process that should be open to public scrutiny, and in any event can be subjected to legal challenge. The introduction of ICAs into military structures for what is purported to be law enforcement purposes will likely be a secret affair, to ensure surprise.

This leads to the question of when the acquisition of an ICA capability would become a threat to others. Two questions should be asked in this respect: how certain can States be about the intentions underlying the acquisition of such new weapons by other States, and how much certainty can they have about what this new capability actually is. The latter is particularly pertinent if the weapons appear in military force structures. Furthermore, if pursued in secrecy, threat perceptions related to the acquisition of ICA weapons would likely be aggravated.

A third and final reason for discussing this matter now is this: the ICA issue has come up in the margins of the First CWC Review Conference; it was more prominently discussed at the Second Review Conference – yet without leading to the adoption of a clear understanding or common position of the States Parties on the matter. This continuing uncertainty tends to reinforce ‘pragmatic’ views that the issue should best be left to States practice. With the Third Review Conference soon approaching, and the completion of the destruction of the declared CW stockpiles getting closer, a stronger emphasis will be required by the OPCW on reinforcing preventive measures to ensure that chemical weapons threats will not return in the future, in whichever form. It is in this context that the ICA issue needs to be seen – and where wrong decisions (or no decisions) may turn out to be the first step onto a slippery slope at the end of which (some) States may decide to reacquire a chemical warfare capability, albeit in a different shape. What are the options?

So what can be done to resolve the matter? Should the discussion of technical and legal issues relate to the possible use of ICAs for law enforcement purposes continue? Or can this debate actually be counterproductive? Are there practical steps that could help resolving the issue?

In the context of the CWC, the options range from doing nothing to restating clearly the existing rules and

prohibitions, to finding common understandings for the relationship between ‘law enforcement’ and ‘method of warfare’, to (in the extreme) amending the CWC’s provisions to legitimize ICA use in certain military scenarios. Not taking any action at all bears the risk of the CWC being undermined over time, amending the treaty could easily unravel and destroy it.

In the context of law enforcement, it is first of all important to separate the issues of RCAs and ICAs (which are often intermingled), given the different legal regimes that apply to them. Secondly, it will be important to clearly understand and appreciate the requirements and constraints related to any sort of weapons or policing method that is to be applied for law enforcement purposes (and hence in a non-consensual manner). These relate to safety, due care and diligence. In addition, any acceptance of the use of drugs as means of law enforcement would by necessity require an open and transparent process with public involvement and debate – given the nature of such non-consensual use of a drug and the human-rights dimension thereof. It would help this debate to involve police officers and other law enforcement officials in these discussions, rather than limit the view to scenarios where law enforcement is done as part of a broader mandate which also involves other types of military missions including combat operations.

### **Possible next steps**

The discussions of the technical dimensions of the ICA issue have been more or less exhausted; little can be gained by continuing these discussions. Instead, it appears that more discussion is desirable of the underlying long-term goals and risks associated with the ICA question. This is a discussion of policy rather than technical risks – but it needs to be undertaken in a fully-informed fashion to which this seminar has contributed not a little.

This debate will have to start from the recognition that the CWC involved a conscious decision to forgo a military option (the option to use chemical weapons) given the overall benefits that an international system without the menace of chemical warfare has over any perceived advantages of having resort to such weapons in certain tactical situations. In other words, more debate of the issue is needed, but only if it starts from the conviction that the preservation and protection of the prohibition of chemical weapons is an essential part of it.





## Participants list

Name	Contact Details
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<b>Dr Augustin Baulig</b>	Chemical Scientific Advisor Prime Minister – General Secretariat for National Defense and Security
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<b>Dr Robin Coupland</b>	Medical Adviser International Committee of the Red Cross
<b>Mr Michael Crowley</b>	Project Coordinator Bradford non-lethal weapons research project University of Bradford
<b>Dr Malcolm Dando</b>	Professor of International Security University of Bradford Department of Peace Studies
<b>Dr Neil Davison</b>	Science Advisor International Committee of the Red Cross
<b>Minister Andreas Friedrich</b>	Head of Arms Control and Disarmament Section Federal Department of Foreign Affairs
<b>Dr Matt Giraud</b>	Group Leader R&D Petides Lonza AG
<b>Dr Hugh Gregg</b>	Head OPCW Laboratory Organisation for the Prohibition of Chemical Weapons OPCW Laboratory & Equipment Store
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<b>Mr John Hart</b>	Senior Researcher Stockholm International Peace Research Institute Head of the Chemical and Biological Security Project
<b>Dr Alastair Hay</b>	Professor of Environmental Toxicology University of Leeds LIGHT Institute
<b>Mr Peter Herby</b>	Head of Arms Unit International Committee of the Red Cross
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<b>Dr Alexander Kelle</b>	Senior Lecturer in Politics and IR University of Bath Claverton Down
<b>Mr Ralph Dieter Knauf</b>	Bundeswehr Officer German Bundeswehr
<b>Dr Hugo Kupferschmidt</b>	Director Swiss Toxicological Information Centre
<b>Mr Vladimir Ladanov</b>	First Secretary Russian Mission to the OPCW
<b>Dr Hua Li</b>	Chinese Academy of Military Medical Sciences
<b>Dr Robert Matthews</b>	Head, NBC Arms Control Unit Defence Science and Technology Organisation (DSTO)
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<b>Dr Ralf Trapp</b>	Consultant CBW arms control and disarmament
<b>Dr Paula Vanninen</b>	Director VERIFIN Finnish Institute for Verification of the Chemical Weapons Convention Department of Chemistry
<b>Dr John Walker</b>	Senior Principle Research Officer Foreign and Commonwealth Office Arms Control and Disarmament Research Unit
<b>Dr Robert Wennig</b>	Laboratoire national de santé Division toxicologie

## Technical Workshop on Incapacitating Chemical Agents (ICA) 7–8 September 2011, Spiez, Switzerland

Scope: To further a technical understanding of what ICA are and what potential for abuse they pose today and in the next 5 – 10 years

### 7 September 2011

Tentative Schedule	Block	Topic <sup>1</sup>	Presenters' Names
0830–0900		Workshop Opening	<b>Minister Andreas Friedrich</b> Head of Arms Control and Disarmament Section, Federal Department of Foreign Affairs  <b>Dr Paula Vanninen</b> Director VERIFIN  <b>Stefan Mogl</b> SPIEZ LABORATORY
0900–0945	1	What are potential ICA?	<b>Dr Alexander Kelle</b> University of Bath, UK
0945–1015		Coffee Break	
1015–1100	1	What are potential ICA?	<b>Dr Malcolm Dando</b> University of Bradford, UK
1100–1145	2		<b>Dr em. Robert Wennig</b> University of Luxembourg
1145–1230	2	Effects of ICA	<b>Dr Alastair Hay</b> University of Leeds, UK
1230–1330		Lunch	
1330–1415	3	Development and Scale up: How and by what means can such substances	<b>Dr Dominique Roberge</b> Lonza AG, Visp, Switzerland
1415–1500	3	be produced with a significant yield (kg) today and in 5 – 10 years?	<b>Dr Matt Giraud</b> Lonza AG, Visp, Switzerland
1500–1530		Coffee Break	
1530–1615	4		<b>Dr Hugo Kupferschmidt</b> Swiss Toxicological Information Centre, Switzerland
1615–1700	4	Systems of Use: How are or would ICA be used; How do you distribute / administer them (voluntarily and involuntarily)	<b>Dr David Humair</b> armasuisse, Switzerland
1900–2300		Workshop Dinner	

<sup>1</sup> Format: 2 Expert presentations per topic followed by participants' discussion (ca. 90' total per topic)

## Content

## Chair

Welcome

Introduction to the goals of the Workshop

Administrative information

General Overview to what type of substances could be ICA (including law enforcement)

Dr R.Trapp

Presentations on advances: existing and potential future ICA; what is possible today, what in 5 – 10 years:

What are in «general terms» the places of action in the body; which physiological processes are affected and how; what are the pharmacokinetics (stimulants and depressants, psychedelics and delirant drugs)

Dr R.Trapp

How are highly active pharmaceutical intermediates produced today with modern multi- purpose equipment and micro reactors – outlook to the future.

How are highly active peptides produced from development to scale up – outlook to the future

Dr A. Kelle

What are the most frequent intoxications with CNS-active substances? What kind of antidotes could be used after an ICA mass intoxication? What could be the most critical factors with ICA intoxications?

How are such substances administered in the present? What would be the most suitable delivery systems for potential future situations of use?

Dr A. Kelle

What is technically thinkable today, what in the next 5 – 10 years?

## 8 September 2011

Tentative Schedule	Block	Topic <sup>1</sup>	Presenters' Names
0830–0915	5	<b>Do current analysis methods targeting chemical warfare agents cover also incapacitating agents?</b>	<b>Martin Söderstrom</b> VERIFIN, Finland
0915–0945		<b>Coffee Break</b>	
0945–1030	5	<b>How can ICA be detected</b>	<b>Dr Ilkka Ojanperä</b> Helsinki University, Finland
1030–1200		<b>Group Photo</b> <b>Tour of SPIEZ LABORATORY</b>	
1200–1300		<b>Lunch</b>	
1300–1345	6	<b>How to control abuse?</b>	<b>Dr Robin Coupland</b> International Committee of the Red Cross, Geneva, Switzerland
1345–1415		<b>Coffee Break</b>	
1415–1530	6	<b>How to control abuse?</b>	<b>Dr Ralf Trapp</b> Consultant, CBW arms control and disarmament, France
1530–1600	7	<b>Workshop Closure</b>	

<sup>1</sup> Format: 2 Expert presentations per topic followed by participants' discussion (ca. 90' total per topic)

**Content****Chair**

How to prepare for a potential analysis of ICA: Perspective of the designated laboratory of the OPCW towards the analysis strategy of ICA. How well the current methods are applicable for analysis of ICA after a use, if unknown.

Dr P. Vanninen

How to prepare for a potential forensic analysis of ICA: What forensic analytical strategy might be most promising in identifying the substance(s) after a use, if unknown.

Dr P. Vanninen

Post 1: Biological Safety Lab (20')

Post 2: Chemical Safety Lab (20')

Post 3: Incident Response (20')

What are the concerns about the development and use of «incapacitating chemical agents», and more broadly, the use of drugs as weapons?

Dr J. Walker

When does an ICA capability become a security issue for others; how could the concerns be addressed?

Dr J. Walker



LABOR





DR SPIEZ





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