IUPAC WORKSHOP: Impact of Scientific Developments

BERGEN, NORWAY – 30 JUNE -3 JULY, 2002

Welcome to Bergen and to the IUPAC Workshop. We look forward to a busy three days of lectures and discussions aimed at providing sound scientific guidance to the Organization for Prohibition of Chemical Weapons and the 145 States Parties to the Chemical Weapons Convention. Even with a very full schedule, we hope that you will be able to enjoy the sights and ambience of Bergen.

Summary Schedule

Sunday, June 30

4:00 to 6:00 pm – Registration — All in the Faculty of Law Building
6:00 pm – Opening Session — University of Bergen
Reception — Magnus Lagabotes plass 1

Monday, July 1

9:00 am to 6:00 pm – Workshop sessions, Science Building, University of Bergen, Allegaten 41

Tuesday, July 2

9:00 am to 6:30 pm – Workshop sessions, Science Building

Wednesday, July 3

9:00 am to 5:30 pm – Workshop session, Science Building
7:00 pm – Meet at funicular starting point for Mount Floyen
7:30 pm - Conference Dinner, Floyen Restaurant

Information Desk

An information desk will be set up in the entrance hall of the Science Building. Please direct questions to the student volunteers who will staff this desk. They can help you with computer and copy facilities if needed.

Workshop Program

The complete program of the Workshop is given on the following pages. Plenary sessions – lectures and discussions – will be held in the main lecture room of the Science Building. Breakout sessions for discussions in smaller groups will be held in nearby rooms to be designated.

Social Program

Participants and accompanying persons are cordially invited to attend the short Opening Session on Sunday evening and the reception that will follow.

Participants and accompanying persons are invited to attend the conference dinner on Wednesday evening.

The all-day sightseeing tour "Norway in a Nutshell" is highly recommended. Arrangements can be made individually. However, if there is sufficient interest, guidance can be provided to a group of accompanying persons on Tuesday. Contact the Information Desk.

The feasibility of a group social/sightseeing event is being explored for Monday evening. Details or suggestions for individual activities will be available at the Information Desk.

Meals

Breakfast: Breakfast is included in all hotel room rates.

Lunch: A light lunch [sandwiches, etc.] will be provided for all participants in the Science Building on Monday, Tuesday and Wednesday.

Dinner: Participants will be responsible for obtaining their own dinners except on Wednesday. A number of restaurants are located nearby and in other scenic areas in Bergen. Suggestions can be obtained at hotels and at the Information Desk.

Conference Dinner: The official conference dinner will be held at the Floyen Restaurant, overlooking Bergen. Mount Floyen is reached by funicular. All conferees and accompanying persons are invited. Information on menu choices will be available at the Information Desk.

SPONSORS

This Workshop has been made possible by the generous financial support of the following donors:

John D. and Catherine T. MacArthur Foundation

Ploughshares Fund

U. S. National Academies

International Union of Pure and Applied Chemistry

Ministry of Foreign Affairs of Norway

University of Bergen

Royal Society (London)

International Council of Chemical Associations

Staff support for the Workshop has been supplied by the U. S. National Academies, IUPAC, and the University of Bergen.

IUPAC WORKSHOP: Impact of Scientific Developments on the Chemical Weapons Convention

Sunday Evening, 30 June, 18:00 – Opening of the Workshop

Ted Becker, Chairman

Introductory Remarks: The Role of IUPAC – *Pieter Steyn, President, IUPAC*

Keynote Address – *John Gee, Acting Director-General, OPCW*

Welcoming Remarks – *Leiv Sydnes, University of Bergen*

Welcome Reception for all participants and accompanying persons

Monday Morning, 1 July - *Claude Eon, Chairman*

Background and Context for the Workshop: The First Review Conference

09:00 – Introduction – *Claude Eon, Chairman OPCW Scientific Advisory Board*

09:15 - Background to the CWC and OPCW – *John Gee, OPCW*

10:00 - Verification procedures – *Ron Manley, OPCW, Retired*
Comments – *Horst Reeps, OPCW*

10:50 – Break

11:10 - Responding to Chemical Terrorism: The Role of States Parties – *Ralf Trapp, OPCW*

11:45 - Industry Changes for Enhanced Security – *Marybeth Kelliher, American Chemistry Council*

12:15 - Preliminary Discussion and Wrap-up of the Morning Session

12:30 - Lunch

Monday Afternoon, 1 July – *George Parshall, Chairman*

New Developments in Chemical Synthesis

13:30 – Introduction – *George Parshall, DuPont, Retired*

13:45 - Supported Synthesis and Improved Experimental Design – *Mark Bradley, Southampton University*

14:45 - Chemical Crop Protection Research - Methods and Challenges – *Urs Mueller, Syngenta*

15:20 - Catalysis for Organic Synthesis – *Irina Beletskaya, Russian Academy of Sciences*

16:00 - Break

New methods in Biological Synthesis of Chemical Compounds

16:20 - Biotechnology and Biochemical Weapons Development – *Mark L. Wheelis, University of California, Davis*

17:10 - Advances in Biocatalytic Synthesis – *Kurt Faber, University of Graz*

17:40 - Wrap-up of the Afternoon Session

18:00 - Adjourn

Tuesday Morning, 2 July

New Developments in Processing and Manufacturing – *Detlef Maennig, Chairman*

09:00 - Introduction, *Detlef Maennig, International Council of Chemical Associations*

09:10 - Manufacturing and Processing: An Overview – *George Parshall, DuPont, retired*

09:40 - Chemical Processing Technologies – *M. M. Sharma, University of Mumbai*

10:10 - Advances in Microreactors – *Holger Lowe, University of Mainz*

10:40 - Break

11:00 - Breakout Session #1 and Reports of Discussion on topics discussed above

12:45 - Lunch

Tuesday Afternoon, 2 July

Analytical Techniques – *Tom Inch, Chairman*

14:00 - Introduction – *Tom Inch, OPCW Scientific Advisory Board*

14:05 - Current Conventional Analytical Methods – *Herbert Hill, Washington State University*

14:50 - Parameters for Field-Portable Trace Detection Equipment: Transitioning Analytical Instrumentation from the Lab to Harsh Environments – *Robert Turner, Graseby Dynamics*

15:25 Break

15:45 - NMR-Based Metabonomic Approaches to the Investigation of Toxic Processes – *Jeremy Nicholson, Imperial College*

16:30 - Possible Use of System Analysis and Knowledge-based Tools for Monitoring Advanced Chemical Activities Potentially Challenging the Chemical Weapons Convention – *Ferenc Darvas, ComGenex, Inc.*

17:00 - Breakout Session #2 and Reports of Discussions

18:30 - Adjourn

Wednesday Morning, 3 July – *Boris Myasoedov, Chairman*

Analytical Techniques, Continued

09:00 – Introduction – *Boris Myasoedov, Russian Academy of Sciences*

09:05 - Recent advances in Capillary Chromatography/Electrophoresis with Element and Molecule Specific Detection in Organic Trace Analysis– *Johanna Szpunar, CNRS EP 132*

09:35 - Clean up Methods and Separations – *Maria Luque de Castro, University of Cordoba*

10:10 - Immunoassay/Biological Analytical Techniques – *Richard Venn, Pfizer*

10:40 -Break

11:00 - Biosensors for Quantitation of Neurotoxins of Various Classes, including Chemical War Agents, and Biocatalytic Technologies for their Destruction - *Sergei. Varfolomeyev, Lomonosov Moscow State University*

11:30 - Lab on a Chip – *Takehiko Kitamori, University of Tokyo*

12:00 – Discussion

12:30 - Lunch

Wednesday Afternoon, 3 July -- Issues for the IUPAC Report to OPCW and the First Review Conference

13:30 - Breakout Session #3 and Reports of Discussions

16:00 - Final Discussion, Conclusions and Recommendations – *Alan Hayes, Chairman*

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IUPAC Workshop: Impact of Scientific Developments on the Chemical Weapons Convention— Speaker Abstracts

The Scientific Advisory Board of the OPCW

The IUPAC Workshop and the information and conclusions that will flow from the Workshop to OPCW and the States Parties are intended to complement the continuing important work of the OPCW Scientific Advisory Board [SAB]. The following Overview by Dr. Claude Eon, Chairman of the SAB, provides very useful information for participants in the Workshop.

The Overview describes the formation, composition and functioning of the Board, and it provides a number of examples of specific issues that have been addressed. Sometimes the Board's advice has been accepted; sometimes it has not. However, even on matters where the scientific advice was not accepted, there may be reason to revisit some of the issues during the Workshop, which is being held in the context of the first Review Conference scheduled for 2003. The Review Conference is expected to have great latitude in considering ways to improve the functioning of the Chemical Weapons Convention.

The Scientific Advisory Board of the OPCW: An Overview

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1. FOREWORD

The Scientific Advisory Board was inaugurated on the September the 21st,98. It has since been driven by the willingness to solve problems, not to create new ones and to deliver quickly.

What have we come up with ? Has it been useful? What have we learned? This is the thrust of this paper. While expressing my own opinion, I believe that I also reflect the sensitivity of the Board, though not necessarily uniform on all the issues at stake.

2. THE SAB: WHY, WHO AND HOW?

2.1 Why and Who?

While not always being identifiable during the negotiating phase, it was perceived that: some future scientific and technical developments could potentially impact the Convention and that some issues, not fully resolved, could need to be revisited on the light of the experience gained. This was at the origin the SAB, an idea that was first put forward by the French delegation in 87-88.

The SAB is mandated to render specialized advice in areas of science and technology relevant to the Convention, to the Director-General, the Conference, the Executive Council or the States Parties.

The nomination of the 20 members of SAB (among 108 proposed by 44 states parties) was completed by mid 98. The group represents a very broad range of expertise: university

professors, chemists, analytical chemists , pharmacologists, engineers, military experts….and as it should, it also covers a wide geographical representation[1].

We have been designated for three year. We all have signed a security agreement not to disclose any information we have access at, should that access be necessary. Board Members are expected to be fully independent and not to represent nor to express the view of his/her country.

2.3 How?

The Board cannot address any issues on its own: as a subsidiary body of OPCW, it gets its mandate from, and report to the Director General.

On special issues, the Board can split into smaller groups : Temporary Working Groups (TWG) are then appointed by the DG on advise by the Board.

Placed under the chairmanship of one permanent member of the SAB, these TWG are widely open to specialists, from industry or academia[2]. These TWG report to the Board for further discussion. Once consolidated by SAB, the recommendations are then forwarded to the DG.

All the sessions are private: no Member State representative is allowed to attend, even as an observer. During the sessions, trust, mutual confidence and friendship always prevail. While not unduly revealing State Member's protected information, relevant and informative presentations have been made from OPCW so that the Board could approach the subject with full knowledge of the existing background.

3. QUESTIONS ASKED-SAB ASSESSEMENTS

Broadly speaking, they fall into two main categories: clarification of what is to be declared and verification issues. In addition the Board has also initiated discussions on destruction technologies.

3.1 What is to be declared?

Ambiguities or not fully resolved issues have led to different interpretations among States Members the as regarding some of their commitments. The problem, paramount for obvious reasons, has a real bearing on ensuring compliance as well as in terms of commercial transfers; it is therefore important to try to clarify the issues and to put every body on the same footing.

[1] The members are Dr Will Carpenter (USA) co-chair , Prof Claudio Costa Neto (Brazil), Dr Ashok Kumar Datta (India), Dr Claude Eon (France), Dr Alfred Frey (Switzerland), Prof Shintaro Furusaki (Japan),Dr Thomas Inch (UK), Weimin Li (China), Dr Maria Consuelo Lopez-Zumel (Spain), Prof Gerhard Matz (Germany), Prof Brahim Youcef Meklati (Algeria), Prof Giorgio Modena (Italy), Prof Victor Petrunin (Russia), Prof Erno Pungor (Hungary), Dr Marjatta Rautio (Finland), Prof Burkhard Seeger Stein (Chile), Dr Abbas Shafiee (Iran), Prof Theodros Solomon (Ethiopa), Prof Branko Stanovnik (Slovenia) and Prof Stanislaw Witek (Poland).

Dr Ralf Trapp from the OPCW is the Board Secretary.

[2] So far TWG have been assembled on the following issues: Adamsite: chair Prof. Claudio Costa Neto; Ricin: chair Dr. Thomas Inch; Low concentration mixtures: chair Dr. Will Carpenter; Analytical procedures: chair Dr. Marjatta Rautio; Equipment; chair Prof. Gerhard Matz; Destruction: chair Prof. Giorgio Modena.

3.1.1 Saxitoxin:

For the prevention paralytic shellfish poisonings, Saxitoxin is used and sold in minute quantities in kits for food testing . Also one country, for pharmacological research purpose, imports tiny quantities of Saxitoxin , and re-export it after tritiation. As a Schedule 1 chemical, the strict adherence to the convention imposes severe limitations on producting and selling the kits, in particular its prohibits the exports to non-States Parties, imposes a requirement to notify the OPCW of any transfer between States Parties 30 days in advance and prohibits re-transfers between States Parties.

The decision making authorities, fully aware of the problem, asked the Board to examine any possible drawback of setting a threshold under which these transactions would not have to be reported.

After reviewing all legitimate uses for Saxitoxin , the Board expressed the view that , the above commercial transactions would not put the Convention at risk paving the way for a formal decision by the Executive Council (November 99) that transfers of 5 mg or less shall not be subject to modification.

3.1.2 Adamsite:

Adamsite holdings in bulk or in some kind of dispersing devices exist. They have been reported by some nations either as a riot control agent (RCA) or as old chemical weapons 5OCW) or as chemical wastes[3]. As the obligations for the declaring States differ greatly from one category to the other, the Board was asked if there was reason not to put any one on the same footing.

The Board observed that: Adamsite (DM) has at present no medical, industrial or other legitimate uses, except for research. Also, when DM is used with restraint, and in the open, the occurrence of permanent damage or death is unlikely. However, some fatalities have been reported (presumably as a result of excessive quantities of DM having been disseminated for riot control purpose).

Irrespective to the fact that DM is not listed in the Schedules, the Board recommended that DM should no longer be used as an RCA as it fails to meet today's concerns both for safety and in respect to environmental protection (in particular arsenic contamination).

Should a country maintain the option of retaining DM as an RCA, the holdings should be consistent with such intended use (a few tons at the most and not in weaponised form). Larger quantities of DM held in bulk or weaponised, would have to be regarded as CWA (or OCW/ACW depending on the circumstances and on future decisions on usability guidelines for OPCW). In that logic, DM produced before 1925 would also need to be reported, to possibly become toxic waste after it has been inspected by the OPCW.

The fates of these recommendations are not known at that stage

[3] As Adamsite is not listed per say in the convention, it could not be ruled out that other holdings exists elsewhere that have not been declared at all.

3.1.3 Ricin production:

Ricin is listed as a Schedule 1 chemical. It can be extracted from castor beans after pressing. The SAB was asked to assess the risk of Ricin to be produced and stored covertly from castor oil production plants.With a World wide production of about one million tons of castor beans yearly, any hasty decision on that matter could have very severely impacted a lot of independent farmers and small grinders businesses, particularly in India, China, South East Asia and South America.

The Board passed the following recommendations: Ricin "enters" the arena of declarable activities when it is extracted from the plant material (crude extract). It remains accountable as long as the A-S-S-B bond is not broken, irrespective of the isoform(s) present. That also applies to toxic mutants of ricin.

Hot pressing of castor beans constitutes the economically preferred technological choice, and it also destroys the ricin contained in the seeds. Cold pressing, which continues to be done at the level of individual farmers, usually involves pre-soaking and steaming of the seeds before pressing. Thus, the Board considered it neither worthwhile nor realistic to establish a system for monitoring each and every producer of castor oil[4]; Were castor oil producing facilities to be integrated into larger chemical production complexes with additional capabilities that might give rise to concerns, normal chemical industry reporting procedures, under Article VI, are likely to apply to these sites, unrelated to the presence of a castor oil pressing plant. Such sites are likely to be DOC sites, which are subject to declaration and eventually inspection under the Convention.

A governmental expert meeting (February 2000) agreed with the Board that castor oil plants should not be subject to the Convention's reporting procedures.The DG then recommended that a draft decision on ricin production be submitted for approval to the Conference.

3.1.4 What is the meaning of "production by synthesis" ?:

The questions relates to the production Discrete Organic Chemicals. Should biochemical and biologically mediated processes be included and what then would be the relevant facilities to be inspected?

The Board concluded that from a scientific standpoint, it is no longer possible to make a clear distinction between "chemical" and " biologically mediated" processes. The emphasis should be on the product rather than on the process. The impact of that approach on declarations would be negligible at this stage. Yet it would be prudent to keep the situation under review in the future, as advances in science and technology may lead to an increased number of chemical products being manufactured in sizable quantities using biological systems or principles.

The meeting of governmental experts (February 2000) disagreed with the Board's conclusion that the emphasis should be on the product rather than the process but they did agree

[4] However, given that castor seeds are a potential source for ricin extraction, the Board recommended that the Director-General encourage National Authorities in castor oil producing countries to promote hot pressing and other techniques that destroy ricin so as to minimize the risk of illicit ricin production.

that the issue should be kept under review. The DG suggested that the meaning of "production by synthesis" be included in the agenda of the first Review Conference**.**

3.1.5 Salts of scheduled chemicals:

The Board received a request on whether certain groups of scheduled chemicals, containing amino-groups, implies that the provisions of the convention also applies to the salts of these chemicals, such as hydrochlorides, even if the entry of the Schedules of chemicals make no mention of such salts.

This creates a rather paradoxical situation: should those unmentioned salts be ruled out, Saxitoxin for example, while now being monitored for transshipments exceeding 5 mg , could legally be sold as an hydrochloride salts with no ceiling and no need to be reported[5]. Also, some precursors of CWA (i.e. like the bis(2-chloroethyl) ethylamine for nitrogen mustard), while subject to severe controls and obligations from the manufacturers and users would become totally uncontrolled in their hydrochloric form. When one knows the ease with which one can recover the free base, the problem is obvious.

The Board assessment is: the salts of these chemicals are chemically district from the parent compounds, and have different physical and chemical properties, as well as their own CAS registry numbers. However, the dynamic equilibrium between the base and the salt means that a certain amount of the free base is always present. In industry, a base is often converted to a salt if it is more convenient to handle a compound in that form. Normally, there is no essential difference between the free base and the corresponding salt from the standpoint of the user. The majority of board members concluded there should be no differentiation in relation to the treatment of a free base and the corresponding salts under the Convention[6][7].

Again the governmental experts disagreed with the Board that the salts of all scheduled chemicals should be subject to declaration and verification. The DG proposed more time for reflection and further discussion**.**

3.1.6 Low concentration mixtures of Schedule 2 chemicals:

Because there was no agreement on the concentration thresholds for reporting Schedule 2 containing mixtures, discrepancies have surfaced in the reporting of commercial transactions (i.e. between sellers and buyers); also further tracking the chemicals became inextricable. The difficulty has been overcome by an agreement between OPCW and the Chemical Industry, endorsed by the States Parties, that sets the threshold at 30%.

No decision was taken for the Scheduled 2A chemicals namely, PFIB, Amiton and BZ and the Board was asked to look at that question.

By the time this paper is written, a dedicated TWG has looked at this issues (in August). No formal report had yet been made to the Board as such, not to mention the DG.

[5] No wonder why, shipments of small quantities of saxitoxin are no longer reported as the product is sold as hydrochloric salt , evidently for escaping the burden of reporting , not for violating the convention.

[6] the same principle has long been accepted in relation to the control of narcotic drugs. For example, prohibitions in relation to morphine are of course also applied to morphine sulfate ; in fact, the two names are used interchangeably.

[7] There was a dissenting view that additional data may be needed to substantiate this conclusion

Here is the preliminary assessment, should it be endorsed by the Board. The group was not aware of any production or uses of Amiton that would exceed quantities typical for research purposes. The group concluded that any decision on a concentration limit for mixtures containing that chemical in a low concentration can be based on regulatory considerations only. The group proposed no specific concentration limit.

BZ is an intermediate in the manufacturing of Clidinium Bromide, an active pharmaceutical ingredient with anticholinergic activity at the peripheral nervous system. It is not isolated during the process: under the actual 30% threshold no production of BZ as an intermediate would be declarable. Given the history of BZ as a CWA , the group concluded that if the objective of the regulator was to have the production and consumption of BZ declared and inspected, if exceeding the respective threshold, the concentration level should be set below 1 per cent.

PFIB (perfluoroisobutylen) is a chemical that is formed as an unavoidable byproduct in the production of TFE and HFP, both monomers used for the synthesis of flouro carbon polymers.PFIB itself has no uses, given its toxicity. It is destroyed on the spot either by thermal oxidation or by reacting it with methanol. The three different processes in use for the production of TFE and HFT differ significantly on the concentration of PFIB produced at any one time.

The group stressed that the decision on a concentration limit has to be based on the regulatory purposes, not on scientific considerations per se. If the intention of the regulator is to regulate materials that could be diverted for CW purposes as they are, the concentration limit should be set somewhere above 10 per cent but clearly under 50 per cent. If, however, the intention of regulator is to address the potential of diverting the material in order to recover PFIB for weapons purposes, there should be no concentration limit or it should be set well below 1%.

4.2 Verification issues

The OPCW has developed and maintained a high standard of expertise in analytical chemistry: up to date equipment is a available (yet not so friendly user when it comes to shipping and to be easily deployable on the field). As for the Inspectorate, chemical analysts have staffed it, for one third. While, according to the Convention, the right to take samples is always granted the inspectors, routine inspections have shown that compliance can almost always be asserted without sampling and analysis; information available (from inspectors) suggests that there would have been little benefit from such analysis. On the other end, analysis will ultimately be the last and only recourse to resolve ambiguities or disputes, even more when alleged uses are to be investigated.

This justified that the Board and the dedicated TWG would revisit the purpose, the use and effectiveness of the on going analytical procedures.

The related ongoing study are not yet fully available for presentation but some salient features emerge. Before all, the Board recognized the professionalism and dedication of the OPCW staff involved.

4.2.21 Sample taking and analytical procedures

Sample taking has been the object of ample debates. In particular, one country by national law, would not let the samples leaving its territory for further analysis. The dedicated TWG and the Board have concluded, that on scientific ground, using the local inspected State Party equipment was acceptable for routine inspection, when that option has been spelled out in the facility agreement and made practical recommendations to that end.

Alternatively, as one of the purpose of routine inspection is to confirm the authenticity of the product declared as being produced, simple equipment like a portable Infrared spectrophotometer would appear to be sufficient, at least for chemicals in bulk. It has also been recommended to investigate the usefulness of some kits (civilians and military): would they be adequate in a chemical plant environment?

Should the problem request more sophisticated equipment, the Board made the simple recommendation –almost obvious- that under the clarification provision of the Convention, samples should be taken , appropriately stored and secured till the inspector bring their own equipment (including their mobile mass spectrometer). Analysis would then be carried out on site by OPCW inspectors prior to the conclusion of the inspection.

In that case, recourse to designated laboratories would become almost exclusively limited to the extreme cases: challenge inspection or investigation of alleged uses.

Also: (irrespective of the legal issues as regarding sample taking and being forwarded to accredited labs), experience has shown that more data where needed in the data bank in particular for non schedules chemicals, degradation products and riot control agents. To that "end, prioritization of data needed is underway. The results have not yet been discussed by the State Parties.

4.2.2 Accredited laboratories designation procedure

The 6th official proficiency test, should have it been scored as usual, would have led to an unusual proportion of laboratories not meeting the selecting requirements. Some failed to detect traces of Lewisite (some didn't even look for it which is a serious mistake) but there was a major difficulty with break down products a sparkled chemical[8]. While degradation do occur in real life, here it could be doubted that every one, at the end, got hold of the " same sample".

While some laboratories performed better than others, the Board assessed that, in doubts, laboratories should not be penalized: it would be counterproductive for OPCW as highly competent laboratories could loose their designation.

On a more general ground, the Board expressed the opinion that the proficiency tests had so far put to much emphasis on scoring (like a pass or fail exam) and that too little attention was paid to enhance the common knowledge and on the lessons to be learned. For the Board occasional" failures" should be de-dramatized and be considered as part of a learning process. Indeed, the Board saw more difficult tests as a mean to gradually increasing the OPCW capabilities and made recommendations to that end.

The Conference of the State Parties then considered a draft decision on the criteria for OPCW-designated laboratories to retain their status in the light of the Council's consideration of the issue. The revised criteria would mean that rather than automatically losing their designated

[8] The preparation laboratory used 1.5-bi(2-hydroxyethylthio)pentane (precursor of 1.5-bis(2-chloroethylthio)pentane. For unknown reasons this compounds has oxidized in the samples send to the participating nations, a phenomena that was not seen during aging studies carried out before the test.

status, laboratories that failed a test would be suspended until they were able to pass a test. The Conference was unable to adopt the decision.

4.2.3 Samples of biological origin.

So far the evidences of use of CWA would mainly rely on environmental samples. Still it would also be useful, to analyze samples of biological origin: i.e. blood, urine, flesh. The Board has initiated preliminary discussions on the problem. Should the Board be formally entrusted with the task of making recommendations, Prof. Victor A. Petrunin (Russia) would chair a dedicated TWG.

4.2.4 Equipment issues:

The board considered possible improvements of the equipment used by the OPCW during inspections, mainly in respect to analytical equipment (in relation to the analytical TWG), and the usefulness of simple analytical instrumentation or sensor technology that may be procured as approved equipment in the future. Results have been somewhat disappointing. While a very extensive review of current and future technologies has been completed, the Board, on the basis of its TWG, concluded that no new equipment are expected to appear in the 3-5 years range that would greatly improve the actual situations.

As for the continuous monitoring of destruction, with a view to optimizing the personnel resources required, the assessment is still underway in combination with the TWG on destruction technologies.

4.3 Destruction technologies:

The Convention stipulates that it is the CWA owner's sole responsibility to select and run the destruction facility. The OPCW is not to interfere on those issues; still the Board has recommended that OPCW should become the main depository of information on chemical weapons destruction technologies. To this end, contacts had been established, inter alia, with the IUPAC Committee on CW Destruction Technologies. Prof. Joe Bunnet, the chairman of that committee, as been appointed as a member of the destruction TWG. It is to early, at that stage, to report on this issue.

5. WHAT ARE THE LESSONS LEARNED? WHAT IS THE FUTURE OF THE SAB?

We, the Members of the Board all take great pride of contributing - even modestly – to the States Parties endeavor to get a World free of Chemical weapons. Our assessments, based on scientific grounds, are intended to be translated in practical measures that meet the (perceived) concerns of the OPCW.

Yet the Board cannot be seen as the only "dispenser of truth" and, not surprisingly it is expected that not all of its recommendations would be endorsed by the policy-making authorities as legitimate political and commercial concerns have to be accommodated with. Indeed, most of them have not been endorsed.

Experts from States Parties have reopened some issues–as it is their right-but the Scientific rational of the Board 's recommendations have rarely been challenged. At that stage, it rather looks as if, for some States Parties, any adjustment or slight departure from the existing situation could carry the risk of opening the Pandora's box.

It would be presumptuous for the Board to question the wisdom of the State Parties; still, let's think of what a little latitude, should that be acceptable, could do without endangering the Convention.

Should there be a "legal or practical zero" or at least a willingness to only track quantities that would have some practical (not political) significance, the inspection scheme would be greatly simplified : i.e. the task of demonstrating that there is no trace of any forbidden chemicals would be greatly alleviated. Also, holdings and transfers of minutes amount of Scheduled one chemicals for legitimate purposes, as they have no military significance, would have made the actual transfers of Saxitoxin a non issue in the first place.

Should there be an acceptance, not to witness the destruction of any single shell or other ammunition: a statistical scheme with random presence of inspectors, at very short intervals, could alleviate the man power requirement without any significant prejudice to the assessment of compliance.

Many other examples abound: with all due respect for the drafters of the Convention, and while being fully understanding of the industry's concerns, the salt question and to some extend the one on production by synthesis have somehow turned as a theological debate. Here again, a little flexibility, in interpreting the text in the spirit of the Convention could fix what might be perceived as potential loopholes.

These issues will probably be on the agenda of the first Review Conference to be held in 2002 as well as more general questions, that may require a prior comprehensive analysis,: i.e. are the scientific foundations of the convention still fully valid? Are all relevant area of sciences and technology be taken into account?

On that line, areas that the Board considers to necessitate prior detailed studies could include chemical analysis, equipment and instruments, biosynthesis and other trends in chemical manufacturing, biotechnology, remote sensing, nano-technology (both with respect of synthesis and analysis) bioassays.

Regardless of the final outcomes, it is my hope that the Board, should it be entrusted with any Review Conference related tasks, will be seen as a valuable forum to promote independent, neutral and results oriented debates on some those not fully resolved issues, or new ones.

Verification under the Chemical Weapons Convention: A Reflective Review

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This presentation will provide a review, based on five years operational experience, of some of the key elements of the verification regime of the Chemical Weapons Convention (CWC)

Declarations

A key element of the verification regime of the CWC is the declaration(s) required to be submitted by each State Party to the Convention. With the exception of special situations, such as a "Challenge Inspection", on-site inspections - the other key element of the Convention's verification regime - are restricted to the confirmation of the voracity of these declarations. Their quality and completeness is therefore of considerable importance. This factor was well understood by the drafters of the Convention and the text relating to the declaration requirements is both extensive and detailed. The degree of detail contained in the final text, however, has, in itself, generated problems. The declaration requirements are, in some instances, so complex that their correct interpretation requires a considerable knowledge of the subject and specialised training.

In accordance with the Convention each State Party is required to submit its initial declaration within 30 days of the Convention entering into force for it. The principal declaration requirements are as follows. Each State Party must provide detailed information on any chemical weapons or chemical weapons production facilities that it has on its territory or has had at any time since 1946. It must, to the extent it can, provide information on any chemical weapons that have been abandoned on its territory or that it has abandoned on the territory of another State Party in the period since 1925. Information on how a State Party proposes to destroy any chemical weapons it possesses in accordance with the requirements and timelines set down in the Convention must also be provided. States Parties must also provide a wide range of information in relation to the chemical industries on their territory that produce, and in certain instances process or consume, chemicals contained on the schedules of chemicals annexed to the Convention. Administrative information such as, the name and contact information for its National Authority – the body or person appointed by the State Party to serve as its focal point for the Convention and its designated points of entry for OPCW inspectors must also be provided.

In reality only a few States Parties were able to even come close to meeting this requirement and of these, almost all subsequently submitted amendments to their initial declaration as further information became available. The Technical Secretariat of the OPCW was, therefore, faced with a very large influx of data, of varying quality and completeness. In addition most of the data received from the States Parties was classified as highly confidential. The absence of an approved, secure, computer system meant that until late in the year 2000 all of

this data had to be handled in hardcopy format. And, even though all declaration data is now scanned and stored electronically, its detailed analysis remains difficulty due to the lack of a relational database, capable of operating at the level of security required by States Parties to protect their information.

The situation was further complicated by the fact that five years of operational experience have shown that, despite the best efforts of the drafters of the Convention, a number of the declaration requirements are still open to interpretation. This is a particular problem with respect to declarations made under Article VI of the Convention that deals with activities not prohibited under the Convention, i.e. "chemical industry declarations". Despite many hours of discussion by the Member States, consensus on the precise meaning of a number of these problem areas has yet to be achieved. As a result each State Party continues to place its own interpretation on the declaration requirements in each of these problem areas. This has greatly complicated the OPCW Technical Secretariat's task of assessment and analysis of States Parties declarations and the subsequent planning of inspections. Despite these difficulties, however, a considerable amount of statistical data has been generated and more than a thousand inspections have been completed involving around 50 of the States Parties.

Inspections

OPCW inspectors are full-time employees of the Organisation. They are recruited from Member States, trained and paid by the Organisation. Each inspector has completed a six month training course which provided, *inter alia*, extensive training on the Convention, an introduction to chemical weapons, their production and safe destruction, inspection skills, health and safety issues and the development of multicultural, communication and negotiation skills. They also received further intensive training in their respective specialist areas. The Organisation has approximately 200 inspectors drawn from 68 Member States. Most are either professional chemical engineers or industrial chemists. The remainder, are chemical weapons specialists, analytical chemists or medical personnel. One of the problems currently facing the Organisation is how best to train new inspectors required to fill the vacancies created by the small number of inspectors who leave each year. Repeating the original intensive, six month, training programme for the small numbers of replacement inspectors required each year would be very expensive and, in any case, may not be the optimum way forward. A solution to this question of the training of future inspectors becomes more urgent as each year passes.

The CWC provides for a number of different types of on-site inspection. Chemical weapons production facilities are subject to routine inspections until they have either been destroyed or converted for use for peaceful purposes. Where approval has been granted, by the States Parties, for facilities to be converted they remain subject to inspection for at least 10 years after the conversion has been completed. Facilities at which chemical weapons are stored are subject to routine inspection until such time as all of the chemical weapons stored at the site have been destroyed. OPCW inspectors are also required to maintain a continuous on-site presence at chemical weapons destruction facilities during any period in which chemical weapons are being destroyed.

The inspection regime for facilities declared under Article VI, chemical industry facilities, varies depending on which of the Convention's three schedules the chemicals being produced - in the case of Schedule 2 produced, processed or consumed – appear on. Facilities producing Schedule 1 chemicals, for example, are subjected to inspection at a rate ranging from once to twice per year. For schedule 2 chemicals the inspection frequency is determined by the assessed potential risk posed by the chemicals and the capabilities of the facility, producing, processing or consuming them. Sites for inspection under Schedule 3 are selected on the basis of agreed weighting factors using a specially developed computer programme. A similar process is used to select sites declared as producing discrete organic chemicals including those containing the elements of phosphorus, sulphur and fluorine (OCPFs).

In addition to these routine inspections the Technical Secretariat may also be required to undertake two other types of inspection, an investigation of alleged use or a challenge inspection. The former would occur in situations where a State Party believed that it had either been subjected to an attack by chemical weapons or was under the threat of such an attack. The latter can be instigated at the request of any State Party that believes it has strong evidence that another State Party is undertaking activities that are not in compliance with the Convention. A challenge inspection can be requested at anytime and can involve any location on the territory of the challenged State Party. To date the Technical Secretariat has not been required to undertake either a challenge inspection or an investigation of alleged use.

All inspections are undertaken in accordance with the general rules and guidance set out in the Convention's Verification Annex. In addition the Verification Annex contains specific rules and guidance for particular types of inspection and these must also be applied when the associated type of inspection is being undertaken. In the period since entry into force of the Convention the States Parties have, in the form of Conference decisions, provided additional guidance and further interpretation of some of these rules. The aim of these rules and guidance is to ensure that both the inspected State Party and the inspectors each have a clear understanding of the framework under which the inspection is being carried out and the extent of each sides privileges and responsibilities. In general the rules provide sufficient flexibility to enable both the State Party and the inspection team to reach agreement on a satisfactory means of completing the inspection. The aim is at all times to maintain a balance between the inspection team's need to fulfil its mandate and the State Party's need to protect matters of national security and confidential business information.

Inspectors may only take equipment from the approved inspection equipment list to an inspection site. Inspected States Parties have the right to satisfy themselves, at the designated point of entry to their territory, that the team's inspection equipment is on the approved list and that the equipment complies with the approved technical specifications for the particular item of equipment. The inspection equipment list was drawn up prior to entry into force of the Convention and, therefore, it is perhaps not surprising that, after five years of operational experience, some items have been found to be more useful than others. The drafters of the Convention again foresaw this problem and the text requests the Technical Secretariat to take action to update the approved inspection equipment list as and when necessary. Unfortunately, the text does not provide a procedure or mechanism for achieving this task and to date it has not proved possible to achieve a consensus amongst the Member States on the need to update or

amend the approved inspection equipment list. This is perhaps one of the more serious problems facing the Technical Secretariat as due to this lack of consensus it is unable to take advantage of developments and changes in technology to aid its inspection teams.

The Role of Chemical Analysis

The role of chemical analysis during inspections is worthy of particular mention. During the negotiation of the CWC the use of sampling followed by either on-site or off-site chemical analysis was seen as being an important component of the Convention's verification regime. After five years and more than a thousand inspections the use of sampling and chemical analysis has, however, proved to be the rare exception rather than the norm. In fact only at chemical weapons destruction sites is sampling and analysis used on a routine basis by inspection teams. Clearly one reason for this low requirement for sampling and analysis is that there have been no challenge inspections or investigations of alleged use. Both of these types of inspection would be expected to depend heavily on the use of sampling and analysis. However, it was also anticipated that sampling and analysis would be regularly used during chemical industry inspections. Why has this not happened? The answer is of course complex but a key contributing factor is the fact that the inspection team's principal approved analytical tool is the GC/MS. This equipment poses a number of problems not least of which is that along with the necessary supporting equipment it can weigh in at between one and two tonnes and represent a bulk of several cubic metres. Inspection teams routinely travel on scheduled passenger airlines to the point of entry and often by internal scheduled airlines to the actual inspection site. Transporting this volume of equipment over such routes is not only extremely expensive but also often poses severe logistical problems. This factor alone, however, would not have deterred the inspection teams from taking the analytical equipment.

- A major problem is that the GC/MS is far to effective as an analytical tool and a full spectrum analysis of a sample taken at a chemical industry may also reveal information that is not relevant to the Convention but which has a high commercial value. The chemical industries of the States Parties, therefore, have serious concerns about the routine use of sampling and analysis during inspections of their sites. In their view, sampling and analysis should be a means of last resort and only used where necessary to resolve an anomaly. The problem with this approach is that the inspection teams would have to carry their analytical equipment to all industry inspection but only use it on rare occasions. For the reasons already given this is not a practical option. It follows, therefore, that if we wish to maintain the option for inspection teams to routinely use sampling and analysis during inspections an alternative solution to the problem is going to have to be found.

The Rise of Complex Terrorism, Implications for the Chemical Industry And the U.S. Chemical Industry's Response

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Introduction –

The September 11, 2001 terrorist attacks on the World Trade Center (WTC) and Pentagon, introduced the United States of America (USA) to domestic and complex terrorism. According to terrorism experts, public and private sector targets are indistinguishable to the perpetrators of this evolved form of terrorism. Their objective is to multiply the effect of a modest investment in selecting and attacking a target to create a cascade of consequences. They target a weakness in a system to ideally cause mass casualties, property damage, psychological fear, market upheaval, and the interruption of communication, commerce and government or a combination thereof.

The Implications for Industry -

Globalization continues to influence private and public sector behavior alike while expanding opportunities, particularly for trade in basic industrial commodities such as chemicals. As a globally invested and integrated industry, chemical commerce is extremely reliant on systems for operating, trading, communicating, transporting, and investing. While the terrorist threat warnings remain generic, all systems theoretically present potential opportunities for terrorism to the extent that terrorists consider them vulnerable and sufficiently complex for their purposes. The outstanding question for terrorist experts to answer is whether chemical industry systems represent, or if chemical industry systems are integrated into, a suitable target of future complex terrorism.

Furthermore, the business of chemistry involves materials that can be toxic, hazardous and/or flammable. Chemical industry operations are closely regulated and, in the United States and elsewhere, the government as well as non-governmental organizations (NGOs) the world over publicizes details about chemical industry plants and products on open web-sites. Such details extend to plans for a coordinated industry-government response in the event a possible worst-case environmental, health or safety scenario was to play out. To date, there is clear and credible evidence of terrorists' interest in obtaining and utilizing chemical weapons (CW) but there is neither publicly available evidence of an existing terrorist CW capability nor intelligence identifying industry as a source for such materials and/or capability.

The global chemical industry's counteroffensive against international terrorism began long ago and continues today particularly through the adoption and administration of multilateral measures, including the provisions of the Chemicals Weapons Convention (CWC). In fulfilling the convention's mandate, the Organization for the Prohibition of Chemical Weapons (OPCW) helps prevent CW terrorism. The destruction of existing CW stocks and prevention of any further development, production or stockpiling of CW is both a multilateral commitment and expressed OPCW contribution to the campaign against global terrorism.

The Chemical Industry Response in the United States -

As a strategic national asset and central component of the U.S. critical infrastructure, the chemical industry response to domestic terrorism was significant and swift. The American Chemistry Council's (ACC) Board of Directors immediately moved to require member companies to prioritize, assess, address and thereby meaningfully improve the chemical industry's ability to detect, deter and defend itself against a heretofore foreign threat. In addition, the ACC adopted a new security code to its acclaimed Responsible Care® program that is mandatory for membership and where compliance is subject to third-party verification. ACC also issued guidance on plant site and transportation security that is increasingly serving as the starting point for other manufacturing sectors' security initiatives. Industry continues to draw upon the proven effectiveness of existing programs such as Responsible Care® and to establish new industry-government partnerships in the area of security.

At the same time, ACC's sister associations in the International Council of Chemical Associations (ICCA) also continue to practice Responsible Care® and have reinforced their respective security measures to detect and defend their plants and products against potential terrorism.

Chemical Crop Protection Research: Methods and Challenges

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Introduction

The aim of chemical crop protection is to safeguard crops, to assure and increase the yields of food and feed crops, to improve the quality of harvest goods and to contribute to the efficient and profitable production of crops. Whilst the world population and the calorie intake per capita continue to grow, arable land reserves decrease. Chemical crop protection can contribute to maintain and increase yields per acre. However, chemical crop protection faces opposition in society mainly based on past events and has to prove itself as valuable member of the whole agribusiness. New approaches in biotechnology are beginning to influence and to challenge the chemical crop protection technology.

Chemistry and Chem-Informatics

Similar to medicinal chemistry, today's chemical crop protection research relies on the most modern methods in organic synthesis and employs combinatorial chemistry on solid support and robot supported solution chemistry technology for the production of random and focused chemical libraries. This is illustrated by the lab- and production scale synthesis of fludixonil (1), the enantioselective production of (S)-metolachlor (2), based on homogeneous hydrogenation in presence of a chiral catalyst and the production of (R)–metalaxyl (3). The handling of large numbers of samples is very demanding on IT and logistic. Computational methods have become an integral part of chemistry both for the design of libraries e.g. to help understand diversity /similarity of sets of molecules, and in the calculation and visualisation of the interaction of small inhibitor molecules with large molecules like enzymes leading to rational design of novel inhibitor molecules (4). Natural products play an important role both in finding new leads, which often need intensive chemical optimisation to become suitable candidates for development or as natural products per se. In the latter case production by fermentation is the challenging step since treatment cost per hectare may become a limiting factor. Strobilurins – a new class of fungicides (5) and the development of abamectin (6) illustrate the importance of natural products in chemical crop protection.

Biology – Biochemistry - Genomics

Screening for activity in a weed/disease/pest – crop complex is by nature relatively easy and relies on a long practice of growing plants in the greenhouse, propagating diseases and rearing insects under controlled conditions. In recent years enormous progress has been made in miniaturisation and automation of *in vivo* tests allowing to screen >> 100'000 compounds p.a. with a minimal amount of sample. The search for new key biochemical targets integrating genomics and proteomics has become an integral part in the search for novel pesticides. Since pesticides have to be applied by spraying in a very variable environment, understanding penetration, uptake and translocation of chemicals in the multitude of organisms treated is not

only essential in the search for novel pesticides but also provides the basis for understanding of the ecological behaviour of such pesticides.

Safety and Ecology

Production, distribution and application of large amounts of pesticides in the environments demand an ever-increasing effort in safety evaluations. Exposition in production and application in the field, residues in food and feed, effects on beneficial organisms in the environment, dissipation into surface and ground water, adsorption to different soils are just a part of the extensive risk assessment demanded by the regulatory authorities.

Conclusion

Chemical crop protection plays an important role in modern agriculture guaranteeing yield, efficient production in agriculture and providing save and healthy food and feed. The integration of many different natural science disciplines is key in the search and development of successful and save pesticides.

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Organic Synthesis by Homogeneous Catalysis

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Catalysis by complexes of transition metals allowed to create new simple and efficient routes of carbon-carbon and carbon-element bond formation, to carry out asymmetric reactions with catalytic amount with chiral material (asymmetric catalysis), to obtain new materials, a new generation of pharmaceuticals, natural products, herbicides, new dyestuffs and organic chemicals. Many transition metal complexes (palladium, rhodium, nickel, cobalt, platinum, etc.) in the presence of suitable ligands can be solubilized in organic solvents and serve as a precursor of a homogeneous catalyst. Nevertheless, each process, each reaction requires its own catalyst and the success of the reaction strongly depends upon the nature of the metal and the nature of the ligand. Particular role among all these complexes belongs to palladium complexes.
In this report we shall consider:

1. Pd-catalyzed reactions of carbon-carbon bond formation (cross-coupling reaction, Heck reaction, Sonogashira coupling, Carbonylation);
2. Pd-catalyzed reaction of carbon-element bond formation (C-P, C-N, C-S, C-Se);
3. Pd-catalyzed reactions in water, ionic liquids, microemulsions;
4. Ni- and Pd-catalyzed reaction of element-element bond addition to unsaturated compounds;
5. Conclusion — “green chemistry” and transition metal catalysis.

The Nonproliferation Review/Spring 2002

Biotechnology and Biochemical Weapons

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Biomedical sciences and the pharmaceutical industry are in the midst of a revolution in the science and technology of drug discovery that will significantly complicate the control of chemical and biological weapons (CBW). The 1993 Chemical Weapons Convention(CWC)[2] and the 1972 Biological and Toxin Weapons Convention (BWC)[3] prohibit the development and possession of these weapons, and the 1925 Geneva Protocol prohibits their use.[4] All three treaties are thus threatened by these technological developments. Scientists in fields that are contributing to this revolution must understand these implications of their work. Likewise, arms control experts must recognize that there is a profound revolution underway in biology and that the technical landscape of chemical and biological arms control is rapidly changing.[5] This article seeks to bridge the gap between science and arms control, in order to raise awareness in both fields of the potential ramifications that this scientific and technological revolution may have on CBW proliferation.

New drugs have traditionally been discovered by screening naturally occurring compounds for biological activity in bacterial or viral cultures, tissue cultures, or live animals. Once a compound with biological activity was discovered, it would be chemically modified in various ways in the hopes that one of the variants would have increased activity. Sometimes the spectrum of effectiveness seen with the variants would suggest the critically important chemical features of the molecule (e.g., the ß–lactam ring of the penicillins and cephalosporins), allowing a semi-rational approach to further modification.

For scientists seeking to develop new drugs, the principal bottleneck used to be discovering the initial compounds for screening; however, significant technological advances have now alleviated this problem, and further significant advances are on the horizon. Currently, new compounds are generated in large numbers by combinatorial methods and assayed for potential activity by ultra-high-through-put screening techniques. In the future, genomic and proteomic methods (described in more detail below) will encourage increasing use of computer modeling techniques to identify new drugs. These same scientific developments will also rapidly deepen our understanding of physiological processes in both healthy and diseased states. This understanding will provide the necessary knowledge base for identifying new drug targets and for predicting the consequences of interfering with their normal functioning.

While the drivers of this revolution are to a large extent methodological, the result is a shift in the underlying strategy of drug discovery. Rather than first identifying compounds with biological activity and then determining their mode of action, the new approaches generally rely on identifying likely targets first, then finding compounds that can bind to them and affect their functioning. Drug targets are usually proteins (which are responsible for most of the activities of living organisms) that have binding sites on their surfaces that normally bind specifically to particular compounds (called *ligand*s). Drugs (and many toxins) generally bind in place of the natural ligands and alter the ability of proteins to perform their normal function. Increasingly, the strategy is to identify particular proteins that, because of their function in the body, are likely drug targets, and then to use the techniques described here to find artificial

ligands that bind to them. Thus the process is becoming less empirical and more rational, a trend that will accelerate as our physiological understanding deepens. These trends have significant implications for chemical and biological weapons control, because they are driving a rapid increase in the identification and development of new potential CBW agents. The pace of this technological revolution threatens to outstrip current biological and chemical arms control treaties, and it opens up new pos-sibilities for states and terrorist groups seeking to develop biological and chemical weapons.

This article will review the principal technologies involved in this revolution in the drug discovery process, and point out their relevance to the discovery of new chemical/biological weapons agents.These technologies include: combinatorial chemistry, genomics, microarrays, proteomics, toxicogenomics, and database mining. The relevance of these developments to CBW control under the CWC and the BWC are then discussed, with particular attention to the destabilizing effect of non-lethal weapons development. It concludes with an evaluation of what is needed to prevent a renewed biochemical weapons threat.

THE CBW IMPLICTIONS OF THE PHARMACOLOGICAL REVOLUTION

Combinatorial Chemistry and Ligand Identification

The increasingly widespread use of combinatorial chemistry is one technology driving the pharmacological revolution. Combinatorial chemistry refers to techniques that produce complex sets ("libraries") of related compounds.[6] Typically it involves multiple rounds of reaction between a base compound and other compounds that can react with it, which may in turn provide additional reactive sites. If the process is sequential, batteries of computer controlled microreactors perform each synthesis by adding appropriate reactants and catalysts, and the products then provide starting material for the next round of synthesis. The result of a number of rounds of robotic synthesis and separation is a library of hundreds to thousands of separate, related compounds. Each can then be tested for biological activity against a target—purified protein molecules, tissue cultures, microbial cells, etc. The screening techniques are conducted robotically, allowing extremely high throughput rates.[7]

If the reactions are simultaneous, the result is a mixture of all products, typically thousands to tens of thousands of different compounds. Ligand binding to a target protein can be detected by affinity selection methods: the library is incubated with the target protein, which is then separated from unbound small molecules by micro-scale molecular sieving.[8] Bound ligands are then separated from the protein and identified.

Currently, a single industrial research facility can screen several hundred thousand new compounds per day against several dozen different proteins. In aggregate, the pharmaceutical industry is screening several million new potential ligands per year, and the results are stored in proprietary databases. In the course of toxicity testing of ligands identified in this way, about 50,000 compounds are identified each year that are highly toxic.[9] For the pharmaceutical company, such toxic compounds have little potential as drugs and further development is halted. However, any one of these is a potential lethal chemical weapon (CW) agent.

Genomics and Target Identification

With the complete sequence of the human genome nearly in hand, and with many hundreds of different single-nucleotide polymorphisms (individual sequence variations) identified, a new set of drug development techniques is becoming available to scientists.[10] Genomic sequences allow the identification of many new possible targets for drugs. For instance, many currently effective drugs target either ion channels or membrane receptor proteins. Many new proteins of these types are being identified in genomic sequences, since they have homology to already identified proteins. Others possess features that are easily recognized in deoxyribonucleic acid (DNA) sequences (e.g., transmembrane domains, ATP- or

GTP-binding domains, etc). Once a new target has been identified, the gene can be cloned and the protein produced in quantity for study and for use in screening combinatorial libraries. Thus, as genomic sequences are annotated (assigned a function), the number of potential targets for pharmaceutical development will skyrocket. So too will the potential targets for novel CW agents.

Microarrays and the Measurement of Gene Expression

How genes are expressed into ribonucleic acid (RNA) sequences, and then (usually) proteins, can be important information. The conditions under which genes are expressed at high levels can give hints to their function (important because many genes identified in genomic sequences have unknown functions). Furthermore, comparison of the levels of expression can give an indication of possible therapeutic targets. For instance, genes expressed at high levels in cancer cells but not in normal tissue would be potential targets for anticancer drugs; and microbial genes that are turned on during infection of a host would be potential targets for antimicrobial drugs.

Such differential gene expression is now readily measured using DNA microarrays—glass slides or silicon chips on which thousands of DNA sequences are imprinted. Each spot on the microarray contains millions of identical single-stranded DNA molecules, whose sequence matches that of one of the genes of the organism being tested. A single slide can have tens of thousands of spots, repre-senting each gene of the organism.

These microarrays are exposed to fluorescently-labeled RNA (or a DNA copy of the RNA) from an organism, and then the amount that hybridizes with each gene is measured by determining the amount of fluorescence from each spot. With this method, the cellular levels of expression under a range of conditions can be readily measured, aiding an understanding of the cellular function and importance of each gene, and pointing to the most likely targets of new drug (or weapons agent) design.

Proteomics and Rational Agent Design

Proteomics is the study of the full complement of proteinsof the cell.[11] Unlike the genome, the proteome is intrinsically dynamic: the cellular complement of proteins changes throughout the cell cycle in every cell, is different in different tissues, and can alter in response to environmental changes. Some of these changes can be measured by DNA microarrays, but some of them are the consequence of modification of proteins after synthesis and can only be studied at the protein level.

Much of proteomics is currently concerned with identifying cellular proteins using two-dimensional gels and mass spectrometry, matching them to their genes in genomic sequences, and determining their interactions with other proteins.[12] These efforts will complement genomics in helping to understand pathological states and to identify promising targets for new drug design.

Protein microarrays are under rapid development; a nearly complete microarray of the yeast proteome was recently produced.[13] Comparable human proteome chips are on the horizon, as well as ones for a variety of other organisms of interest. Protein microarrays, combined with combinatorial chemistry, will dramatically broaden the search for new ligand-target combinations with therapeutic (or weapons) applications. They also allow the identification of protein-protein interactions, a critical part of cellular communication systems, and another possible set of drug/weapon targets.

Furthermore, rapid progress is being made in predicting protein three-dimensional structure from genomic sequences.[14] It is now possible to predict the structure of simple proteins with fairly high accuracy, as well as that of more complex proteins when they are homologous to proteins whose structure has been determined experimentally. In the near future it should be possible for most protein structures to be predicted with a high degree of accuracy from their genomic sequences alone. Knowing the structure of the active site allows rational design of ligands with a shape and charge distribution that is precisely complementary to it. This computer modeling approach to drug design promises to complement, and

probably eventually supplant, traditional wet chemistry methods of ligand identification (although of course any design has to then be validated by traditional experimental approaches). The same techniques would allow rational design of new weapon agents.

Toxicogenomics, Database Mining, and the Prediction of Toxicity

Most drug candidates are eliminated in clinical trials due to toxicity problems. Since this constitutes a significant cost to the pharmaceutical companies, there is intense interest in predictive algorithms for toxicity, so that toxic compounds can be eliminated before they enter clinical trials. Of course, exactly the same approach would be useful if the goal were to develop more toxic compounds.

Two approaches have shown significant promise. First, toxicogenomics employs proteomic and microarray techniques to analyze the response of cells to known toxins.[15] If the changes in patterns of gene expression or in the proteome induced by a novel compound are similar to the response to known toxins, the likelihood is that the new compound will prove to be toxic. This allows probable toxins to be screened out at an earlier stage; however, it also allows early identification of potential new biochemical warfare agents.

Second, the analysis (using sophisticated neural network approaches) of databases of drugs and nondrugs allows the selection of a range of descriptors that together can predict whether a compound is likely to be drug-like (pharmacologically active, with low toxicity), or non-drug-like (not pharmacologically active or toxic).[16] Similar algorithms could possibly predict compounds with a variety of other desirable traits for novel biochemical weapons agents, in addition to high toxicity.

THE RATE OF PROGRESS IS VERY HIGH AND ACCELERATING

An immense amount of time and money are being invested into these biomedical fields, and the rate of discovery is very rapid. Furthermore, this is a field in which fundamentally new methodologies are one of the principal drivers. Since new methods open up entire new categories of questions, they act to stimulate the rate of progress significantly.

The intellectual base of the methodologies is supported by an immensely sophisticated and rapidly growing micro-scale instrumentation and computational base. The computer-controlled reaction vessels, ultrahigh throughput screens, robotic microarray printers and readers, time-of-flight mass spectrometers, high speed sequencers, and other devices have been critical to the development of the field. So, too, has the exponential growth of computer speed and memory, as well as the sophistication of software, since all of these laboratory technologies depend on computers for the collection and analysis of data. Indeed, bioinformatics is probably now the rate-limiting technology, as the flood of genomic and proteomic data is overwhelming the capacity to integrate and understand it.

The intellectual momentum of this science is immense and clearly unstoppable. Thus a very large number of new, highly toxic compounds with precisely understood and controllable physiological effects will soon be discovered. Many of these will enter production as drugs or as research reagents. The range of known potential CW agents will thus broaden by a very large factor in a very short period of time, and most of them will be synthesized from precursors that are not currently regulated under the CWC.

THE PROBLEM OF NON-LETHAL AGENTS UNDER THE CWC

The CWC allows states to possess chemical agents and delivery systems designed for riot control and other law enforcement purposes. Non-lethal chemical agents are otherwise illegal: the Convention defines a CW agent as “any chemical, which through its chemical action on life processes can cause death, temporary incapacitation or permanent harm to humans or animals.”

Furthermore, the CWC explicitly prohibits the use of riot control agents “as a method of warfare.” However, at least one State Party (the United States) has interpreted this wording as limiting the

prohibition to interstate armed conflict.[17] This reading leaves open a wide variety of military operations in which such agents could be legally used, including counterterrorism, peacekeeping, monitoring, and the like. Given the potential tactical utility of non-lethal chemical agents in such "military operations other than war," their development, and the development of munitions to deliver them, is being actively pursued. Unless the States Parties to the CWC can reach consensus that the prohibition of riot control agent use covers a much wider range of hostile actions than merely international military conflict, there is certain to be widespread development of this capability.

New "riot control" agents are likely to be of a variety of different kinds.[18] Neuropharmacology is one of the areas in which rapid expansion of knowledge can be confidently predicted. The toll of mental illness, and the growing promise of chemical treatment, makes it certain that a wide range of new psychoactive chemicals will be discovered, as well as chemicals that affect transmission across neuro-muscular and neuro-endocrine synapses. It is likely that in the near future a range of agents will be developed that affect perception, sensation, cognition, emotion, mood, volition, bodily control, or alertness. Given the great potential for such agents to be abused, it would be prudent to delay arming the militaries of the world with them until their long-term implications have been carefully analyzed.

In fact, a categorical distinction between lethal and non-lethal chemical agents is not strictly possible, since "non-lethal"agents may be lethal at high concentration or for specific individuals. More seriously, synergy between two different non-lethal agents may make their combination highly lethal. The molecular techniques I have discussed will soon allow rational strategies to discover such synergistic pairs. Thus the development of multiple non-lethal agents may provide a lethal CW capability, in violation of the intent of the Convention.

Furthermore, allowing states to develop stockpiles of incapacitating chemical agents and munitions for their delivery in combat situations would defeat one of the fundamental purposes of the Convention: to prevent states from entering wars with a stockpile of CW whose use is proscribed, but which might nevertheless be considered under the doctrine of military necessity.

Finally, a legal development program of new riot control agents would provide a nearly impenetrable cover for a covert development program for new lethal agents, thus reducing the capacity of the international community and the Organization of the Prohibition of Chemical Weapons (OPCW) to detect violations of the CWC. For all of these reasons, continued development of non-lethal CW threatens the stability of the regime.

RELEVANCE OF THE BWC

A better case can be made that the BWC prohibits non-lethal biochemical weapons, although it, too, possesses weaknesses. It prohibits the development, production, and stockpiling of biological weapons (BW) agents and delivery devices, as the CWC does for CW, but it lacks the CWC's verification provisions. Furthermore, the scope of its terms "microbial or other biological agents, or toxins whatever their origin or method of production" is ambiguous. However, there appears to be a consensus that "other biological agents" includes all of the biochemical products of the living body that in abnormal doses can be used as toxins, including bioregulators, neurotransmitters, and hormones.[19] Since the final document of the Second Review Conference affirmed that the Convention applied to analogues of toxins as well as to their native form, it would seem that the BWC would apply to all of the biochemical compounds whose discovery I discuss here.[20] Since their activity is a function of their ability to bind specifically to an active site on a protein, they are by definition analogues of the natural ligands and thus covered by the BWC. As toxic chemicals, they are also covered by the CWC. The BWC and the CWC thus overlap quite substantially, and the term "biochemical" weapon agents can be used to describe toxic chemicals in this overlap category.

The BWC prohibits the possession of devices designed to employ biological agents "for hostile purposes or in armed combat." It thus contains a more expansive prohibition than the CWC—hostile

purpose is clearly a broader category than armed conflict, which is, in turn, broader than war. Furthermore, there are no exclusions in the BWC for riot control or for other law enforcement purposes. For these reasons, it would appear that the agents outlined here would be categorically prohibited by the BWC.

States Parties might argue that domestic riot control is necessary to preserve the public peace and thus legal under the BWC general purpose criteria of allowing "protective, prophylactic, or other peaceful purposes." However, an equally strong case could be made that even domestic riot control should be considered a hostile use, given the very general prohibition on hostile purposes beyond armed conflict, and that BW are not to be used even here. The BWC would, like the CWC, benefit from constructive Review Conference consideration of the boundary between permitted and prohibited activities.

CONCLUSION

The emerging biotechnology of drug discovery promises great advances in medicine, biology, psychology, and a host of related sciences. However, the same tools that are revolutionizing drug discovery can be used to discover novel biochemical agents for the purpose of weaponization. Related developments in chemistry and chemical engineering have similar implications.[21]

Most of these novel agents will be synthesized from unlisted precursors and will be nearly invisible to the verification regime of the CWC, although their development, production, and stockpiling will be unambiguously prohibited. Containing proliferation will thus become significantly more difficult, especially in states with mature biotechnology and pharmaceutical industries. Given the rapid dissemination of industrial biotechnology, this will soon include a very large number of States Parties. Effective responses from the Conference of States Parties and the OPCW will be difficult. Certainly a willingness to revise the "Schedules of Chemicals" regulated by the CWC as the need arises will be essential. Vigilance will be necessary, especially during inspections of production facilities that produce discrete organic chemicals. States Parties with the capability may be able to use intelligence and national technical means to detect covert CW programs. This capability, coupled with a willingness to employ challenge inspections, could serve to some extent as a deterrent. In the end, however, the only effective long-term solution is a universal norm against such weapons, which can only be reached via sustained efforts for universality of both Conventions and transparency in chemical and biological defense programs.

Equally threatening is the interest of some States Parties in the development of non-lethal CW in the guise of riot control agents, and their assertion that such development is not prohibited as long as the agents are not intended for use in hostilities between states. This position opens the door to the widespread development, production, and stockpiling of non-lethal chemical agents and munitions designed for their use in military combat. This is clearly contrary to the intentions of the CWC.

If states want to avoid the widespread integration of non-lethal biochemical agents into military arsenals, with all the problems that this will bring, they will need to act decisively to affirm that one or both of the Conventions prohibits all military use of these agents (except perhaps for narrowly specified purposes, such as domestic riot control). Obviously, such an affirmation of the understanding of the meaning of the BWC or the CWC would require consensus; the States Parties that are now engaged in non-lethal weapons development would have to acquiesce in an affirmation that would force them to abandon their efforts.

Even if a consensus were to be reached, it would still be a challenging problem to distinguish the legal development of new riot control agents (if this is allowed under the BWC) from the prohibited development of new non-lethal biochemical weapons. Probably the best curb on the development of a military capability to wage chemical warfare with riot control agents would be to circumscribe legal munitions and delivery devices to those that are already in common use by police forces worldwide.

[1] Thanks to Dr. Lynn Klotz for helpful suggestions. An earlier version of this paper was delivered at the Pugwash Conferences on Science and World Affairs, Workshop on the Implementation of the Chemical and Biological Weapons
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Advances in Biocatalytic Synthesis: Enzyme-Triggered Asymmetric Cascade Reactions

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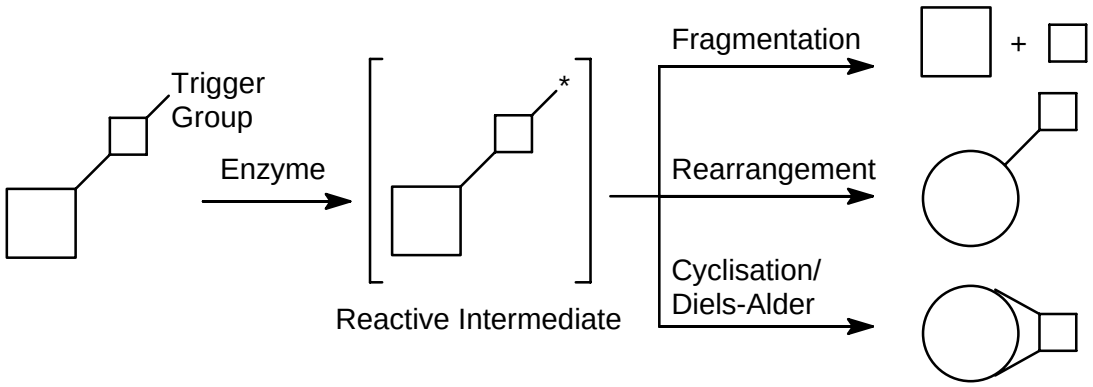
Domino- or cascade-reactions involve the transformation of materials through several non-separable steps, which often proceed via highly reactive intermediates. In case the reaction sequence is triggered by a biocatalyst, the cascade may proceed in a highly chemo- or stereoselective fashion. A survey of enzyme-triggered domino-reactions published to date[1] reveal a common pucture (Scheme 1):

Scheme 1: Principles of enzyme-initiated cascade-reactions.



In a first step, the enzyme modifies a trigger-group within the starting material (e.g. via oxidation, hydrolysis/transesterification) giving access to a reactive intermediate. This, for instance, may bear a liberated negative charge, which can deliver electrons to a π-system or act as a nucleophile. Consequently, the intermediate thus formed immediately undergoes a subsequent domino-reaction, which may consist of a (i) fragmentation, (ii) rearrangement or (iii) a cyclisation/Diels-Alder reaction. These processes show a remarkable advantage: Despite the fact that the cascade is proceeding through a highly unstable intermediate, the final product can often be isolated in good yields, because decomposition of the reactive intermediate is largely avoided since it is transformed in the same instant as it appears and, as a consequence, it does not occur in measurable concentrations.

By making use of the unparalleled specificity of biocatalysts, enzyme-triggered cascade reactions may be turned into highly efficient protocols for the asymmetric synthesis of bioactive materials. Along these guidelines, the following synthetic concept was developed (Scheme 2):

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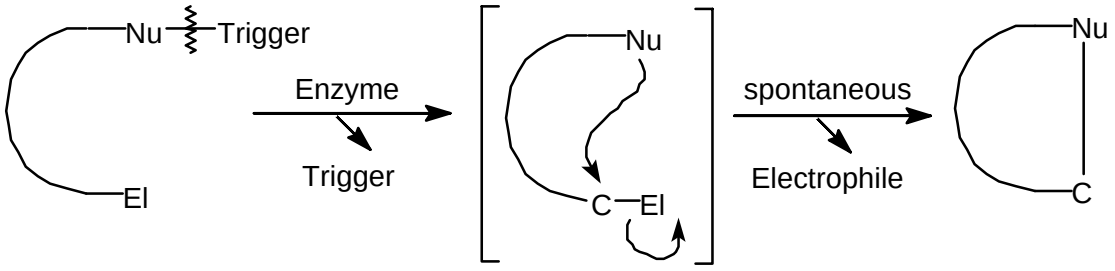
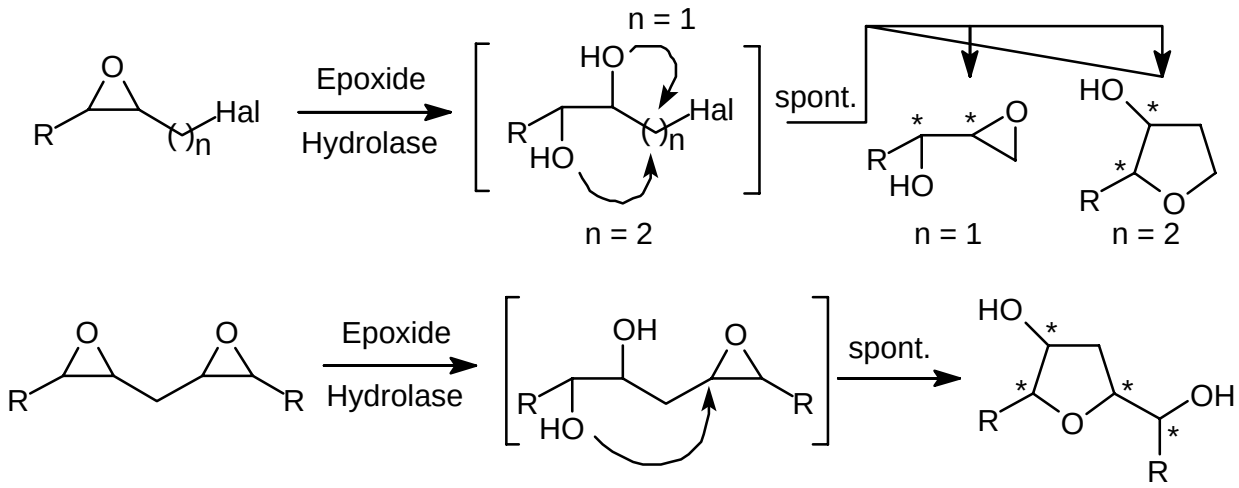
Scheme 2: Principle of enzyme-triggered cyclisation reactions.



From a precursor-substrate (containing an electrophile and a masked nucleophile), the trigger-group is removed by the enzyme thus liberating a reactive intermediate, which spontaneously undergoes cyclisation. In several cases, this pathway was shown to occur in an enantio-convergent fashion, which allows for the transformation of a *rac*-substrate into a single stereoisomeric product in 100% theoretical yield by completely avoiding the occurrence of an 'undesired' stereoisomer[2].

Considering the possibilities of the enzyme-catalysed liberation of a nucleophile (e.g. epoxide › diol, ester › alcohol, ester › carboxylate, carboxamide › amine, thioester › thiol, etc.) the synthetic potential of this hitherto largely unexploited strategy appears to be remarkably wide and will be demonstrated at hand of two examples (Scheme 3):

Scheme 3: Enzyme-triggered cyclisation reactions using epoxide hydrolases.



(i) Asymmetric biohydrolysis of an epoxide furnishes the corresponding *vic*-diol, which attacks an adjacent haloalkyl group to form an oxirane (n = 1) or tetrahydrofuran derivative (n = 2), resp. During this process, up to three chiral centers can be simultaneously controlled [3,4].

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(ii) In case of bis-epoxides, THF-derivatives possessing four chiral centers were obtained in high d.e. and e.e.[5]

Acknowledgements: This work was performed within the Spezialforschungsbereich 'Biokatalyse' and financial support by the Fonds zur Förderung der wissenschaftlichen Forschung (project no. F104) is gratefully acknowledged.

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Trends in Synthesis and Production That Will Affect Implementation of the Chemical Weapons Convention

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Introduction – Many new developments in science and technology will complicate the task of implementing CWC constraints on production of toxic agents for military or terrorist purposes. Many rely on the easy availability of powerful, cost-effective computers and sophisticated software for research and process control. In addition to technological change, the chemical industry is undergoing major changes in the ways that it conducts its business. Some of the business aspects may outweigh technological change in their impact on enforcing the CWC.

Scientific Advances – Major changes have occurred in the way that research is conducted at the interface between chemistry and biology. The availability of powerful computers has stimulated new ways to search for biologically active chemicals such as pharmaceuticals, agrochemicals, and, unfortunately, toxic agents. In addition, greater understanding and control of biological mechanisms has enabled new methods to synthesize organic chemicals using enzymes or whole cell systems.

New search methods – The combination of combinatorial synthesis with high throughput screening and automated analysis of experimental data (bioinformatics) permits scientists to make and test hundreds of chemical compounds per week. Analysis of the enormous amount of data generated in this way depends on specialized programs to detect new forms of biological activity as well as to optimize desired physiological properties. While these methods have been applied primarily to discovery of new drugs and pesticides, they also can impact chemical weapons issues in two ways: (1) New toxic mechanisms may be detected during random screening for other properties; and (2) A rogue nation with moderate scientific infrastructure could screen specifically for new toxic agents.

Biological syntheses – Genetic engineering of microorganisms enables the synthesis of many types of organic chemicals from simple starting materials such as starch. An example of such a process nearing commercial production is the manufacture of 1,3-propanediol (a polymer intermediate) by bioprocessing of glucose. Similar methodologies might be adapted to the biosynthesis of two-carbon bifunctional molecules such as 2-hydroxyethanethiol or 2-aminoethanol useful in the production of blister or nerve agents. These methods may also be adaptable to the efficient production of peptide-based toxins such as ricin.

New toxins – Both empirical screening and surveys of the literature can potentially uncover new toxins that operate through physiological mechanisms different from those involved in traditional chemical warfare agents. New mechanisms can lead to agents that are more difficult to detect and treat. Toxins based on peptides or pseudopeptides based on unnatural amino acids may emerge from screening conducted for peaceful purposes.

Technological advances – Computer automation coupled with new catalytic processes have changed many of the production processes used for manufacture of organic chemicals. Some of these changes could have a major impact on the work of the OPCW by making it more difficult to detect the production of lethal chemicals.

Automated process control – Perhaps the greatest change in the processing and manufacture of chemicals is the use of computers to control the equipment in which chemicals are reacted and purified. Automated control has made production processes safer and more efficient. In many instances, it has reduced the level of skill and experience needed to carry out routine production operations and has made unattended operation feasible. As applied to clandestine production of chemical agents, it has the potential to reduce the number of personnel involved, to make the handling of lethal chemicals safer, and to eliminate emissions that might call attention to illicit production.

Mini/micro reactors - Collections of tiny reactors made by techniques borrowed from the electronics industry can operate continuously and produce significant amounts of lethal chemicals. The production of choking agents such as HCN, methyl isocyanate (MIC), and phosgene has been demonstrated in such reactors. The small size and efficiency of such reactors could facilitate the clandestine manufacture of chemical agents.

New catalysts – Innovative catalytic processes could enable the manufacture of toxic chemicals from new intermediates that are not monitored under current CWC inspection regimes. One example is the production of MIC from readily available N-methylformamide. New heterogeneous catalysts have made the production of phosgene more efficient in that fewer byproducts are emitted. New water-soluble catalysts have facilitated synthesis of a variety of organic chemicals in processes that minimize solvent emissions.

Chemical industry changes – The global chemical industry has undergone dramatic changes in the way that it conducts its business. Some of the changes in business practices may be more important than technological advances in terms of their impact on implementing the CWC.

Globalization – The worldwide chemical industry has experienced may changes in how and where it manufactures chemicals. Economic factors have encouraged the production of many polymers and large-scale chemicals in production facilities large enough to supply the needs of an entire region. So-called world scale production facilities are often built in developed countries where large markets already exist. A recent counter trend is shifting the production of commodity chemicals such as polyolefins and methanol close to sources of raw materials in areas such as the Persian Gulf. On the heels of these world scale plants have followed facilities to make smaller scale specialty chemicals such as agrochemicals.

Dispersal of specialty chemicals production – Many less developed countries have encouraged the domestic production of agrochemicals and pharmaceuticals by imposing high tariffs on imported materials and by relaxing enforcement of patent regulations. Contract manufacture of pharmaceutical intermediates has spread to some developing countries to take

advantage of lower costs for skilled labor. The net result has been to create an industrial base that, without adequate oversight, could carry out surreptitious manufacture of chemical agents.

Dispersal of technicians skilled in production of CW agents – The disavowal of chemical weapons by the countries of the former Soviet Union has had one ironic effect: many of the workers who once produced chemical agents are now underemployed and available for hire. Such individuals could find employment in the development of agent production in the so-called rogue nations. In addition, the skills of other chemical production workers could easily be transferred to illicit manufacture.

Marketing through digital exchanges – Another trend is the increase in sales of chemicals through automated exchanges that bring together buyers and sellers *via* the Internet. An increasing number of chemical intermediates including some materials for making chemical agents are traded in this way. This trend could have either positive or negative effects in controlling the production of potential chemical agents. Without adequate controls, this system could make key intermediates easily available to terror groups. On the other hand, proper oversight of purchases could detect clandestine chemical agent production just as is done currently for detecting narcotics manufacture.

Background Reading

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Strategies of Conducting Reactions on Small Scale: Selectivity Engineering and Process Intensification

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Advances in conducting reactions, new catalysts and reactors have made manufacturing on a small scale very facile and even efficient. Selectivity Engineering and Process Intensification permit minimalisation of the chemical industry.

Use of heterogeneous acidic/ basic catalysts

The availability of a variety of cationic and anionic ion exchange resins, zeolites, heteropoly acids, clays (including pillared clays), hydrotalchites, etc. permit just about any reaction requiring acidic or basic catalyst, such as, alkylation, etherification, aldol condensation, Michael addition, etc. to be carried out in a clean way, avoiding washing of the reaction product. Further the use of cyclodextrins can allow stereo-, regio- and optical selectivity.

Phase Transfer Catalysis (PTC)

A variety of liquid-liquid and liquid-solid reactions have been intensified and made selective by using simple phase transfer catalysts like quats, polyethylene glycol-400, etc. which allow ionic species to be ferried from aqueous phase to organic phase. Thus the problems associated with extremely low solubility of the organic reactants in the aqueous phase can be overcome. In the pesticide and pharmaceutical industries PTC is used extensively and has changed fundamentals of business.

Photochemical reactions

The well known examples of selective side-chain chlorination of toluene, xylenes and substituted derivatives provide the right backdrop. These reactions can be safely conducted on a small scale. Even photo-oxygenations have been conducted.

Ultrasonochemistry (U/S)

Sonic wavelengths in liquids are typically 0.1 to 100 nm, well beyond molecular dimensions. Ultrasonication can speed-up reactions remarkably even in mechanically agitated reactors. Solid-liquid reactions such as Grignard reaction, Barbier reaction, etc. benefit due to creation of 'cleaner' surfaces.

Microwave-assisted reactions

Domestic microwave ovens have been used to carry out a variety of reactions, such as, synthesis of dioxolanes, dithiolanes, oxathiolanes, etc. in a remarkably short time and in an efficient way. Thus 'kitchens' can be adopted to make hazardous chemicals.

Biocatalysis

Biological catalysts allow many important transformations to be carried out under close to ambient conditions, and very high regio-, and stereo-specificity have been realized. Hydrolytic enzymes such as lipases and esterases are widely used. Some examples of difficult conversions are: conversion of benzene to dihydrocatechol; beta nicotinic acid to 6-hydroxy nicotinic acid.

Solid supported reagents

The use of a highly porous support for reagents provides a large effective area for the reactions to be conducted in a facile way, besides making separations of product simpler. Thus metallic nitrates, supported on clays, have been used for nitrations and oxidations.

Membrane Reactors

A range of sophisticated membranes, which can withstand aggressive conditions, are available and thus equilibrium-limited reactions can be conducted with reactions and separations being incorporated in the same system.

Distillation Column Reactors

It is quite feasible to use laboratory distillation columns in a combo-mode and thus make many products in a convenient way.

Electrochemical processes

The ease with which oxidations and/or reductions can be carried out with the practically mass-free 'clean' electrons makes electrochemical processes well suited for such jobs, including paired synthesis. A variety of lab-models are available which can be conveniently adopted to make wanted chemicals.

Adoption of Continuous Reactors

Due to low inventory of reagents, hazardous reactions, such as nitrations, can be conducted in a safe way in continuous reactors and even high pressures, including supercritical conditions, can be adopted. Even 1 cm^3 per second flow rate may result in production of 30 tons per annum of a specified product. The use of static mixers and monolithic catalysts has further improved the utility of such reactors. Continuous reactive chromatography, adopting simulated moving beds (SMB), has further strengthened our tool box to carry out reactions and separations, through adsorption, in an elegant way, particularly for temperature sensitive substances. Laboratory models of SMB can give respectable throughputs.

Concluding Remarks

It is possible to carry out a variety of hazardous reactions in a safe and an efficient way in a so-called small scale set-up without being 'noticed'. Multistep batch processes are amenable to microprocessor-based control systems.

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Advances in Microreactors

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Introduction – Microreactors as a novel concept in chemical technology enable the introduction of new reaction procedures in chemistry, pharmaceutical industry and molecular biology. Miniaturized reaction systems offer many exceptional technical advantages for a large number of applications. The large surface-to-volume ratio of miniaturized fluid components allows for a significantly enhanced process control and heat management. Moreover, the unique possibilities of microchemical systems pave the way to a distributed point-of-use and on-demand production of extremely harmful and toxic substances. On the other side of the coin, miniaturization of complete set-ups for chemical syntheses to a suitcase or even to a shoe-box size opens several possibilities to possibly use them as tools for terrorist attacks and to facilitate the clandestine manufacture of chemical agents.

Microfabrication techniques are common and allow the machining of special materials, e.g., high-alloyed steel, titanium, ceramics or glass. Meanwhile, micromachining techniques are available anywhere in the world. Therefore, these techniques are no longer unique nor proprietary and they cannot prevent construction or distribution of microreaction systems by people with allegiance to a terrorist organization.

Scientific Advances – The use of miniaturized reactors with characteristic dimensions below (and sometimes above) one millimeter attracted great attention in chemical engineering recently. From the early concepts in the late 80'ies to commonly available microreactor devices and semi production-like setups, a world-wide research and development was done not only at universities but also by chemical industry. The development of metal microreactor components such as micro heat exchangers, micromixers and further the integration of these devices into an existing production line for fine chemicals were important milestones.

Microreactors offer many advantages for the performance of heat and mass transfer limited reactions. Large gradients in concentration and temperature are achieved by shrinking the characteristic dimensions of a microreactor down to the micro scale. This is especially advantageous in the case of highly exothermal reactions as well as in the case of mass transport limited processes. Based on these technical advantages new and unusual process regimes becomes technically feasible. For instance, the fluorination of toluene with elemental fluorine was carried out in a microreactor set-up comprising reaction channels and heat exchanger structures in close proximity. Due to the explosive character, this reaction could only be carried out in conventional equipment at -70°C very carefully under lab-scale conditions. By using a specially developed microreactor the reaction mechanism could be changed from a radical chain type (uncontrollable, unselective) to an electrophilic substitution one (safe, selective) even at -10°C.

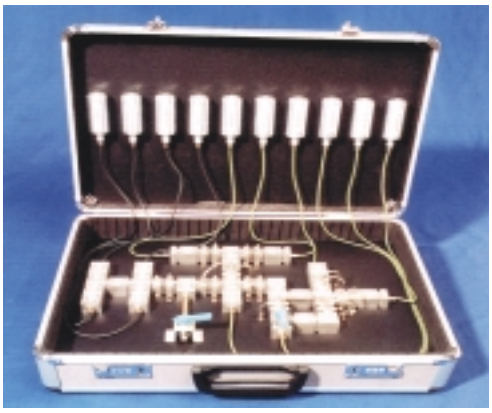
Since a couple of years microreactors were used for small lot production of chemicals. Some examples describe the formation of organometallic compounds. By using matchbox-sized micromixers a tremendous increase of yield and selectivity was observed, even be increasing the reaction temperature from below 0°C up to 50°C.

An important further motivation to use microreactors for chemical processes arises from safety considerations. Very small hold-up of hazardous substance can significantly degrease the expenditure for safety installations. Even working with pure oxygen in the explosive envelope might be possible in a lab-scale environment. In most cases, explosions can be suppressed by using microchannels with a hydraulic diameter below the quenching distance. The microsystem becomes inherently safe, although not necessarily the complete set-up, because it acts itself as flame arrester. Even if an explosion occurs an impact to the environment can be neglected. Reactions under high pressure conditions like hydrogenations with pure hydrogen seem to be possible with minor safety regulations.

Impact on CW – It cannot be denied that microreactors have the potential to be used in military or terrorist applications. They can be fabricated by common technologies, of course only by high skilled personnel at present; but in the future, without any doubt, by a regular workshop. With the knowledge of chemical fundamentals and some advices from the Internet the fabrication of chemicals scheduled 2-3, and in some cases even scheduled 1, by the CWP is no longer restricted to a chemical lab. Of course, there are high risks to handle highly toxic chemicals, but after the 11th September event it cannot be excluded, that terrorists will not discourage a CW attack.
Besides the old warfare CW's chlorine and phosgene, methyl isocyanate becomes more and more important. This widely in chemical industry used substance is volatile and extremely toxic. The pilfering of this substance from a production plant cannot be noticed but the transport is high risky. But it is conceivable to make methyl isocyanate by catalytic dehydrogenation of N-methylformamide, a common and less toxic solvent, by applying a microreactor set-up.

To prevent handling of lethal nerve gases, e.g., sarin, soman or VX so-called binary weapons were developed. In a last step, two primary less toxic compounds were mixed at the point-of-use immediately. The same mechanism can be employed by using high efficient micromixers, which carry out a complete mixing in less than 5 milliseconds at a throughput of a several liters per hour.

A "pocket " chemical plant, as shown in the figure below, cannot be monitored or detected. It has to be pointed out that the shown pocket plant was a 'placebo equipment' serving only for rough graphic nature without any realistic background on chemical engineering issues.



Summary- The situation of "microreactors" , or being better called "micro process engineering" is complex. We found many possibilities for applying microsystems in chemical research and even in chemical production. In the last five years the field has become more and more attractive and a couple of start-up companies and research departments in the chemical industry were founded. The results of the research are promising and some changes in chemical process technology are observable. From our point of view we never expected a possible usage of microreactors for fabrication of CWs or for terrorist attacks which so far has not been reported.

Background Reading

G. W. Parshall, "Scientific and Technical Developments and the CWC" in *The Chemical Weapons Convention – Implementation Challenges and Solutions,* ed. Jonathan B. Tucker, Monterey Institute for International Studies, Monterey, CA, April 2001.

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J. M. Tour, "Do-It-Yourself Chemical Weapons", *Chem. Eng. News,* **2000** (July 10) 42-49.

Current Conventional Analytical Methods for the Detection of Chemical Weapons, their Precursors and Products

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Introduction – In this post September 11 environment where the public is sensitized to the need for analytical methods for the detection and identification of chemical weapons (CWs), the term "tricorder" is often invoked. Coined in the 1960s for the science fiction TV series "Star Trek," a tricorder refers to a small handheld analytical instrument that, in a noninvasive manner, determines the chemical character of biological systems without error. Certainly, it would be desirable to develop a "Tricorder" for chemical weapons. But we are a long way from this fictional goal. Moreover, before we can chart a course to where we want to be, we must know where we are. Before we can develop a sensor which weighs nothing, takes up no volume, uses no energy, responds to all chemical weapons and never produces a false positive or negative report, we must understand the potentials and limitations of current technology. In this presentation, current capabilities to **contact**, **sense**, and **select** chemical weapons (CWs) will be reviewed and critiqued. How do we initiate contact with the weapon or its products? What are the physical and chemical mechanisms we use to sense CWs and their degradation products? And, how do we select a chemical weapon from other compounds in the environment that may mask or simulate its response?

Contacting Mechanisms – Unlike the tricorder, we must, in some way, contact an agent in order to measure it. The most common method used for contacting chemical weapons is to simply collect a sample and transport the sample back to the laboratory for a rigorous analysis, including extraction, clean up, separation, isolation and detection. Matrices for these analyses vary from gas, aqueous and soil samples to those of biological fluids and tissues. While the use of sophisticated **laboratory** analytical instruments in general provide the most accurate data, both expense and time are maximized. To minimize expense and response time, analytical instruments are often carried to the sample. Transportable analytical instruments are, in reality, laboratory instruments that have been "boxed up" and carried to the field to provide real time or near real time data. **Transportable** instruments are often used as remote and fixed sensing devices that provide on site data with minimal loss of integrity. **Portable** instruments are significantly reduced in size from the laboratory or transportable version. In the best cases, they are hand-portable instruments, operating with minimal energy, weight and volume. These instruments can be carried directly to a sample to evaluate the presence of CW related compounds. **Personal** sensors are further reduced in size and power requirements so that individuals can monitor their CW exposure on a routine basis. Current examples of laboratory, transportable, remote, fixed, portable and personal analytical instruments used for the detection of chemical weapons will be described in this presentation.

Sensing Mechanisms – By far, the most common method for sensing the presence of CW related compounds involves the process of gas-phase ionization of the organic species. These ionization mechanisms will be described along with their advantages and disadvantages for the detection of CW related compounds. **Electron impact** and **chemical ionization** are often employed with mass spectrometers. **Matrix assisted laser desorption ionization (MALDI)** is also under investigation as an ion source for mass spectrometry. **Electrospray ionization** is now a common source for converting aqueous samples to gas phase ions for both mass spectrometry and ion mobility spectrometry. **Radioactive** and **corona discharge ionization** are often used with ion mobility spectrometers for gas phase samples. **Photoionization** and **flame ionization** are common detectors used after gas chromatography as well as the **thermionic ionization detector** for the selection of nitrogen and phosphorous containing compounds. Although many CW agents and their related compounds do not have significant chromophors, there are a number of cases in which UV and IR radiation are used for detection both by **adsorption** and **fluorescence**. **Flame photometry** also produces selective light emission for phosphorus and sulfur containing compounds. Some compounds are also electroactive and **electrochemical** methods have been used for their detection. **The surface acoustic wave** response will also be described. Understanding the response efficiencies and mechanisms of these sensing processes is important for defining the limitation and potential for the analytical detectors available tonday.

Selecting Mechanisms – Variation in response efficiency of the sensing device is a primary source of selectivity of the CW compound over interfering compounds. Unfortunately, the sensors cannot provide specific responses and additional selectivity is often required. In addition to the selective response factors, physical separation of species provides most of the selectivity required to reduce effects of false positive and negative responses. Physical parameters used to separate and distinguish chemical species have included volatility, solubility, ion mobility and mass for methods known as gas chromatography, liquid chromatography, ion mobility spectrometry, and mass spectrometry, respectively. Resolution, expense and time are the primary parameters. Gas chromatographs typically provide the best resolution and are often combined with mass spectrometers or ion mobility spectrometers to provide two dimensions of separation. Similarly, liquid chromatography and capillary electrophoresis are interfaced to selective detection methods as well as mass spectrometers to provide enhanced qualitative information.

Advantages of current methods – Advantages of the methods introduced above will be delineated and comparisons of analytical figures of merit made. Requirements of resolution, sensitivity, selectivity, and dynamic response range will be discussed. The power of hyphenated separation/spectrometric techniques for compound verification provides unequivocal analytical data from the laboratory. Reliability and ruggedness of field analytical instruments are also improving. Specific commercial and military field instruments will be described and discussed. Responses of the US military detectors including the automatic chemical agent detector and alarm (ACADA), the improved chemical agent monitor (ICAM), the joint chemical agent detector (JCAD), the joint service lightweight standoff chemical agent detector (JSLSCAD) and the Chemical/Biological mass spectrometer (CBMS) will be described along with other instruments used currently to detect CWs.

Limitations of current methods – Origins of limitations to sensitivity, selectivity, resolution, and linear dynamic range will be discussed as a function of size and energy requirements. Gas chromatographic methods are limited in that they are not easily applicable to polar, non-volatile and high molecular weight samples while liquid chromatographic methods are inherently slow and limited in resolution. Mass spectrometers have high resolving powers but require vacuum systems, which often confine them to laboratory operation. In addition, mass spectrometers are not capable of distinguishing isomers. As the size and power requirements of analytical instruments are decreased, so are the analytical figures of merit. Thus, field instruments are often less sensitive and more prone to false positive and negative responses than are their laboratory counterparts. Specific concerns of the current instruments and methods will be delineated and used to focus the discussion for the workshop.

Future directions – While we may not be on the verge of developing a tricorder, significant advances in analytical methods for the detection of chemical weapons are on the horizon. From pocket size IMS detectors and chip mounted separation devices to powerful hyphenated instruments such as LC/GC-IMS-TOF mass spectrometers, our ability to detect and identify chemical weapons, their precursors and products continues to develop at a rapid and encouraging rate.

Suggested Reading:

1. Chromatography and mass spectrometry of chemical warfare agents, toxins and related compounds: state of the art and future prospects, Ch. E. Kientz, J. Chromatography A, 814(1998) 1-23.

2. Identification of chemicals related to the chemical weapons convention during an interlaboratory proficiency test, E. W. J. Hooijschuur, A. G. Hulst, A. L. de Jong, L. P. DeReuver, S. H. van Krimpen, B. L. M. van Baar, E. R. J. Wils, C. E. Kientz, U. A. Th. Brinkman, Trends in Analytical Chemistry, 21(2), 2002, 116-130.

Transitioning Analytical instrumentation from the Lab to Harsh Environments.

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Introduction

For nearly 20 years my company has been involved with the design and development of instruments employed in the field to detect of traces of chemicals including illicit drugs, explosives and chemical warfare agents. These instruments, mainly based on Ion Mobility Spectrometry (IMS), include the Chemical Agent Monitor (CAM), the Automatic Chemical Agent Alarm (ACADA) and the Volatile Organics Analyser (VOA) which is currently in operation on the Space Station. Sensitivities are generally in the parts per billion level or lower.

In this article I describe some aspects of the process by which technology is taken from the laboratory to use in demanding environments – and some of the particular problems that have been encountered in the manufacture of trace detectors.

Technology readiness

One way of looking at the risks involved in the development of technology into products was developed by NASA in the late 1990s and has subsequently been employed by both the US and UK governments.

In this methodology there are 9 technology readiness levels defined briefly as follows :

1. Basic principles of technology observed and reported.
2 Concept and/or application formulated.
3. Analytical and laboratory studies to validate analytical predictions.
4. Component and/or basic sub-system technology validated in lab environment.
5. Component and/or basic sub-system technology validated in relevant environment.
6. System/sub-system technology model or prototype demonstrated in relevant environment.
7. System technology prototype demo in an operational environment.
8. System technology qualified through test and demonstration.
9. System technology qualified through successful mission operations.

The costs involved in the development of a new product rise exponentially as the program moves through the various stages. Conversely the risks (both technical and in time scale) should fall as the program approaches completion. One of the objectives of the technology readiness approach is to ensure that an appropriate level of technological maturity has been reached before major investment is made. This does not generally mean that all the risks disappear before the end of the project but they do change in nature. Early in the process the scientific risks will predominate. Later stages will gave mainly engineering issues.

It is extremely important to have an accurate specification of the final system, this implies a very clear view of the purpose and modes of use. The specification must be complete but not excessive. For example if the equipment is required to be operational within 5 minutes after long storage then this must be explicitly stated in the specification – it is very difficult to prevent long-term build-up of contamination when trace detectors are stored. On the other hand asking for high measurement accuracy when only qualitative results are really needed can lead to high cost for no purpose.

The costs of development.
The two most recent development programs that we have carried out were both essentially modifications of technology that had already been 'proven' in previous products – corresponding to level 5 in the readiness scale. Each of these programs has cost approximately $3 million and involved teams of about 20 people. The development teams include a mix of disciplines - scientists, mechanical engineers, electronics (analogue and digital) engineers, production engineers, process engineers, software engineers, safety engineers, test engineers and logistics experts in addition to a planner and a project manager. The development time (from level 5 to level 9) is typically 1.5-2 years.

Our development programs involve a considerable amount of time and effort in testing. The tests range from relatively straightforward environmental tests for ruggedness to operational tests in realistic environments. The latter should be carried out as soon as practical and as extensively as possible, we have had some unpleasant shocks as a consequence of a lack of knowledge of the chemical background.

Where does all the money go ?
It is not necessarily the most scientifically challenging areas that take the most resources in the development process. One of the most difficult aspects of the design of portable instrumentation is packaging – how to get all the electronics, pumps, sensors, displays and input/output interfaces in the most compact and ergonomic form. The outside case of the instrument can often be one of the most expensive items both to design and to purchase. The case has to provide electrical screening for both radio-frequency emissions from the instrument and to prevent external fields from affecting its operation. It has to be sealed against the elements and it must be easy to assemble. It has to be as light as possible and yet it must be robust.

Designing for production.
Trained and experienced people can assemble small number of instruments using experience and knowledge to tackle any problems that arise. However this approach becomes less and less viable as the production rate rises and larger numbers of people must be involved. Documentation both of the product and the process becomes vital and considerable effort can be expended in establishing processes that are robust and a design that can be reliably reproduced without specialist knowledge or 'black art'.

Contamination in trace detector manufacture.

For trace detection equipment ensuring adequate cleaning of components used in the sensor assembly becomes a key issue. A significant proportion of the space on our production floor is occupied by washing and baking machinery. Contamination of the air supplies that are used to purge the ovens can stop the production process so these are continuously monitored and a back-up supply is available.

The production process sometimes appears to be a continuous fight against contamination. We have had problems with pollution from traffic and from solvent emitted from the factory next door – though these are well below permitted levels. We have to control the polish on the factory floors and production operator's perfumes and deodorants.

Thoughts on future instrumentation

There is a continual demand for instruments of greater sensitivity. As sensitivity levels are pushed higher more problems are encountered with the chemical background (these problems might be most severe in industrial facilities). More selectivity must go hand in hand with greater sensitivity. Approaches for higher selectivity include the use of a separation stage such as gas chromatography. However this gives penalties in the form of increased complexity, longer analysis times and problems with the provision of inert carrier gas.

Adding chromatography to a detection technique that shows extreme sensitivity towards specific groups of materials can produce a system that combines both selectivity and sensitivity. One example of this is the chemiluminescent method for the detection of explosives. This is an excellent method for explosives that contain nitrogen. However increased use by bombers of explosives based on peroxides makes the method redundant. To make a technique future – proof it must be capable of responding to as wide a range of compounds as possible – which places even more demands on selectivity.

Combining techniques that rely on different principles for their operation is an attractive approach for trace detection. Examples might be combinations of IMS and cavity ring-down spectrometers (CRDS). These techniques are extremely sensitive and sufficiently small to make a combination possible in a portable instrument. Target materials might be more reliably confirmed by detection by multiple techniques. Unfortunately the fact that the methods measure different parameters is not a guarantee that they will together give more discrimination. In fact one might take the opposite view based on the fact that they all respond to the target set of materials.

Conclusion

Designing and manufacturing sensitive portable instrumentation is an expensive and complex activity. Before undertaking such a task it is essential to have a very clear view of the desired objective. At the earliest possible stage the specification should be detailed and its practicality should be determined by testing in a realistic environment.

Recent Advances in Capillary Chromatography/Electrophoresis with Element and Molecule Specific Detection in Organic Trace Analysis

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The detection of trace levels of chemical warfare agents is required in a variety of environmental matrices as well as in complex industrial and chemical neutralization process mixtures. In most of the cases a target compound needs to be specifically detected among a myriad of related compounds, reaction products and by-products. The suitable analytical method should therefore fulfill two principal criteria referred to as sensitivity (often down to picogram levels or below) and molecule specificity.

Because of the complexity of the mixtures to be analysed a single analytical technique, either chromatography or mass spectrometry, has turned out to be insufficient to fulfill these criteria. Combinations of both, referred to as hyphenated (coupled) techniques, are therefore required. The most widely extensively used hyphenated technique for the identification of chemical warfare agents in suspect samples has been capillary GC - MS. Despite its undeniable merits, it has limitations, such as high background in the analysis of complex samples resulting in poor detection limits, general unsuitability for the analysis of low volatile compounds, and the low sample throughput (2-4 samples h^{-1}). A limitation may also be the sample preparation step involving the need for rapid preconcentration from very dilute analytes in atmosphere, or headspace over the soil.

The lecture discusses recent advances in GC based hyphenated techniques including the use of micromulticapillary chromatography (MCGC) for analyte preconcentration from headspace and large volume air samples and the use of plasma source detectors. MCGC is based on the use of a bundles of thousands of coated microcapillaries (ca. 20-40 μm) through which sample gas can be passed at flow rates of 1 L min-1. The small diameter of an individual capillary assures a high chromatographic efficiency (ca. 100 TP cm^{-1}) at ambient temperature whereas the number of capillaries offers a high cross-section allowing the use of high flowrates. On the level of detection the use of microwave induced and inductively coupled plasma spectrometric detection of heteroatoms (P, Si, As, S) will be discussed as a means of reducing matrix background and improving detection limits in the analysis of chemical warfare agents. The advances in the GC - ICP MS coupling will be discussed and compared with GC - AED and GC - MS.

Many degradation products of chemical warfare agents are difficult to determine because of poor GC characteristics and low electrospray MS sensitivity. The lecture will discuss progress in direct ICP MS for the ultrasensitive (femtogram level) detection of heteroatoms (arsenic, silicon, phosphorous, sulfur) in capillary LC and capillary electrophoresis effluents.

The last part of the lecture will discuss recent advances in electrospray mass spectrometry aimed at higher sensitivity, improvement of the mass measurement accuracy and higher tolerance to the matrix for the detection of proteinaceous or non-proteinaceus toxins ranging in mass from a few hundred to more than a hundred thousand daltons. The large number of potential candidates and the structural diversity makes identification of these compounds a challenge. The role of

electrospray and MALDI TOF MS and capillary LC - Q-TOF MS/MS for mass mapping and aminoacid sequencing of toxins for their unambiguous identification in small-size samples will be discussed.

Preliminary steps of the analytical process: from sampling to detection

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Preliminary steps of the analytical process are the pending goals of today's analytical chemistry. Meanwhile detection and data treatment have experienced an enormous development in the last twenty years, preliminary steps have improved only some of their different aspects, others being at present based on old-fashioned procedures. The delay is partially due to the variety of samples (*v.g*. matrix, physical state, origin) which in turn require different treatment in each case. An, intended critical, overview of the preliminary steps, starting from sampling and finishing in introduction at the detector will be presented with special emphasis in automation as the only way for eliminating the overload in analytical laboratories.

When starting from a solid problem [1] automation of sampling and development of the subsequent steps in a manner similar to a human analyst is either a robotic station or (in a more dedicated, limited and cheap version) a workstation (the latter can be devoted only to weigh).

After weighing, dissolution, leaching or physical removal (in the case of volatile analytes) is necessary at least that direct solid analysis (*v.g.* glow-discharge emission spectrometry, laser-induced breakdown spectrometry, graphite furnace atomic spectrometry, etc.) is performed.

Dissolution is preferred when: i) the sample is easy to solubilise, ii) analytes of very different chemical characteristics must be determined, iii) the analytes are difficult to separate from the matrix. Dissolution of solid samples required a digestion step most times, which can be accelerated using high temperature-high pressure [2], microwaves [3] or ultrasound assistance [4]. The different chemicals to be used for facilitating this step as a function of the type of sample and auxiliary energy applied, as well as the other working conditions, are well-established [1].

Leaching (or lixiviation) is the term for defining a process which allows removal of some components from a solid. Instead of this specific name, scientists prefer the most generic of "extraction" (*e.g*. supercritical fluid extraction (SFE) [5], microwave-assisted extraction (MAE) [6], etc.) much less self-explanatory. This process, whatever its name, is more desirable than digestion or total dissolution, in general, as the leachate or "extract" contains less potential interferents and so, the subsequent clean-up and separation steps can be either avoided or minimised. In general it can also be assisted for the same types of energy as dissolution.

After the boom of SFE, more than 20 years ago, when it appears as the panacea, subsequent research showed its limitations, specially related with the different behaviour of spiked and natural samples [7], thus establishing its real field of application [8], at the same time that MAE was gaining position. At present, processes assisted by microwaves are an area of intensive research, meanwhile SFE is estabilised. A new perspective is open presently with the use of water as leachant (both without and with additives for enhancing its function) by taking advantage of its characteristic of lowering its dielectric constant by rising the temperature under moderate pressure. The most significant shortcoming of water leaching, particularly when used in a continuous fashion, is dilution of the target analytes, which calls for subsequent preconcentration (and usually also clean-up) steps.

Removal of volatile analytes (or volatile derivatives) from solid (or liquid) samples is a simpler and more selective goal than those above-commented. In addition to well-known techniques such as headspace (both static and dynamic –purge & trap-modes) and gas-diffusion, a more recent technique (namely, analytical pervaporation [9,10]) must be taken into account as more versatile and easy to automate.

When working with liquid samples, less complex preliminary steps are foreseeable dealing with clean up and/or concentration prior to individual (or groups of families) separation. Clean up and preconcentration are mainly based on liquid-solid extraction steps which are developed in either a continuous or discontinuous way using commercial, disposable cartridges. Research on the material packed in these devices is a field of massive interest aimed at obtaining more selective supports which provide higher preconcentration factors. Solid-phase microextraction [11] the miniaturised version of solid phase extraction, is also a technique with a growing application. In addition, other clean up preconcentration steps based on techniques such as liquid-liquid extraction and dialysis (the latter with only clean up purposes) can be applied but in a lesser extension, as also do with the development for research.

After appropriate clean up and concentration, if required, the last step prior to introduction at the detector is individual or in group separation. This step is usually accomplished by a high-resolution separation technique such as chromatography in any of its versions (gas, liquid or supercritical fluid) depending on the mobile phase, diameter of the column, packing, etc. or by capillary electrophoresis. The features of the treated sample to be introduced and the type of detector to be used after the separation step fix the type and specific characteristic of the equipment to be used in this step.

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Immunoassay / Biological analytical techniques

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Why use immunoassays? Why not use LC-MS-MS?

- Sensitivity
- Speed
- Selectivity
- Ionisation

What assay types are available? What are their characteristics? What are their drawbacks? What are their advantages?

- Competitive
- Non-competitive
- Large / small molecules

What detection systems are available? What are their advantages and disadvantages?

- RIA
- ELISA
- DELFIA
- FPIA

How do we develop immunoassays? What are the requirements? What are the reagents?

- Analyte
- Hapten
- Polyclonal antibodies
- Monoclonal antibodies
- Phage-display antibodies
- Artificial antibodies (molecular imprints, peptides)

What are the formats for immunoassays?

- Tubes
- Plates
- Fibres
- Optical systems

What does the future hold?

- SMNCIA
- Fibre-optic systems
- Real-time systems
- Phage-display
- Molecular imprints

Biosensors and Nanotechnological Methods for the Detection and Monitoring of Chemical and Biological Super-Toxins

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State of problem. The modern level of investigations in the chemistry, biology and molecular biology significantly extends the possibility of creation of new compounds and systems potentially applicable as agents of chemical and biological lesion. A number of circumstances promote this situation:

- the growing volume of accessible information about the structure of different compounds appurtenant to various chemical groups and knowledge about their physiological activity;
- the wide application of domestic and agricultural neurotoxins and pesticides which toxicity is comparable with classical poison gases;
- elaboration and development of new methods of synthesis including enzymatic methods;
- development and wide use of gene-engineering methods allowing enough easy transformation of genes of biological super-toxins to the non-pathogenic microflora.

Thereupon, the elaboration of new highly sensitive, reliable and enough express methods for control, quantitative detection and monitoring of various super-toxicants is important in principle. The creation of new methods of protection against the chemical and biological lesion also is extremely important task.

Recently, the Chemical Enzymology department of Moscow State University and coworkers has performed a battery of research and development works on creation of biosensor and nanotechnological methods for the detection of toxins of various classes and super-pathological microorganisms. The works have been performed in terms of the ISTC, IPP and CRDF programs, NATO grants, the governmental research program "Novel bioengineering methods", the agreements with Defense Ministry of Russian Federation and Committee on Conventional Problems of Russian Federation.

Biosensors for neurotoxic compounds. The hypersensitive amperometric enzymatic biosensors have been created for quantitation of neurotoxins of various classes (pesticides and toxins) in the range of the maximum permissible concentrations (MPC) and lower; detection limit is up to 10^{-12}M. Neurotoxins of various chemical classes (heavy metal ions, organophosphorus compounds and carbamates) are discriminated using specific enzymatic and chemical kits. The automatic robot performing all analytic operations without the operator has been created; the instrument has been tested by the US governmental agencies. The biosensor designed for the tasks of chemical safety, for environmental monitoring (water, soil, air), for qualitative control of agricultural industry and food safety.

Test microcolumns and strips. Test columns and strips for express detection of inhibitors of choline esterase, affording the determination of toxins and congenial compounds up to 10^{-14}M.

Delayed neurotoxicity. The phenomenon of delayed toxicity exhibiting by several organophosphorus compounds and its correlation with inhibition of neurotoxic esterase (NTE) in the brain and blood was

definitely demonstrated. New biosensor as well as the new method of diagnostics using the detection of inhibition of NTE in the blood system as criterion for screening of different compounds on their delayed neurotoxicity were created.

Nanotechnological methods of detection of super-toxic microorganisms and viruses. The bases of method of express detection of different microorganisms and viruses by the application of atomic-force scanning microscope as analytical device were developed. This method consists in creation of many-dimensional immunological chip matrix and use of highly specific antibodies followed by the revealing of adsorbed cells with scanning probing microscope. The scope of method was demonstrated by the example of impaired strains of super-pathogens such as yellow fever, smallpox, plague. The protocol of analysis with attraction of computer programs recognizing the samples was elaborated. The ultimate sensitivity of method is a single cell. Now, another one protocol of discovering of microorganisms and viruses with application of biochip matrix based on DNA-probe is under design.

The enzymatic methods of destruction of super-toxins and pathogenic microorganisms. The approach, based on the use of enzymes degrading toxins and pathogenic microorganisms is developed. Several gene-engineering constructions, containing gene encoding the synthesis of recombinant organophosphate hydrolase (OPH) were elaborated. Their transformation to the different E.coli strain-hosts resulted in more than 10 times enhancement of expression of OPH protein in cells compare with the best known OPH-producers. Modification of created gene-engineering construction allowed the obtaining of OPH, containing polyhistidine sequence, and the enzyme purification in one step by the application of metal-chelated chromatography. The method of considerable stabilization of OPH based on the forming of emzyme-polyelectrolite complex was elaborated. The possibility of OPH stabilization by the additional inter-protein interactions also was demonstrated. Chemical immobilization of stabilized OPH on the porous polymer material and different samples of textiles allowed the preparation of highly effective and stable biocatalysts including perspective individual protective means degrading the organophosphorus compounds.
The possibility of effective destruction of pathogenic microorganisms under the action of specific enzymes was demonstrated.