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VERIFICATION METHODS, HANDLING, AND ASSESSMENT OF UNUSUAL EVENTS IN RELATION TO ALLEGATIONS OF THE USE OF NOVEL CHEMICAL WARFARE AGENTS

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PREFACE

This paper was first published in June 1989 for distribution to Canadian government agencies in order to promote discussion on issues related to the proposed Chemical Weapons Convention. The issue of allegations of use is a complex one, especially where the agents are unknown and it is possible that the event, although unusual, may be of natural occurrence. The paper develops a methodology for the examination of such events including the possibility that a novel chemical warfare agent had been employed. It focuses upon the need for epidemiological studies and the type of national infrastructure that might be appropriate to oversee such investigations for a National Authority in Canada.

The paper was written by a consultant from the University of Saskatchewan in conjunction with the Verification Research Unit of External Affairs and International Trade Canada. The paper and its recommendations do not necessarily reflect the views of the Canadian government.

It is believed that the material herein might be useful to other States involved in the negotiations on a Chemical Weapons Convention and is offered to promote discussion on the difficult problem of novel chemical weapons.

Executive Summary

The purpose of this study is to identify, if possible, and to describe verification, handling, and assessment methods with respect to unusual events in relation to possible allegations of the use of novel chemical warfare agents, including toxins.

Novel chemical warfare agents may include a newly discovered or existing chemical used for the first time to produce casualties because of its toxic properties.

After a brief review of the relevant part of the "rolling text" of the chemical weapons negotiation in the Conference on Disarmament, the potential for developing novel chemical warfare agents is discussed. The discussion sometimes strays into areas which some might reserve for biological weapons, but this is because the receptor system (i.e., the mammalian body) has only a limited way to respond to injury and also because an unusual event needs to be examined from a variety of angles.

In order to provide examples of unusual events, which incidentally have nothing to do with chemical weapons (novel or old), some recent dramatic events are highlighted.

It is suggested that any investigation of novel chemical weapons has to go through the time-proven method of epidemiological investigation as a first step. Initial assessment of the situation, whether obtained through carefully conducted epidemiological studies or through critical evaluation of preliminary data, should not be handled by a large standing group of specialists, because it is not known what type of event, if any, might have occurred. Instead, a very small (3 persons maximum) standing national advisory committee should be established to monitor events and developments on a continuing basis. This

advisory committee would become the nucleus for further action. It is assumed that the necessary special expertise to address the problem(s) can be found nationally.

1.0 Introduction

The Conference on Disarmament (CD) has been negotiating for many years to develop a structure for a chemical weapons convention (CWC), and it appears that a CWC could be concluded in the not-too-distant future.

Not surprisingly, the definition of chemical weapons and the role of the international "machinery" required to monitor a CWC have required much time and effort. Although not all contentious issues have been resolved, there is now tentative agreement on the various organs to be created and on many of the functions to be carried out. In particular, the issues of verification of declaration, storage, destruction and transfer of existing chemical weapons (Art. III and IV); declaration, cessation/closure, destruction/dismantling, temporary conversion/destruction of chemical weapons production facilities (Art. III and V); and activities not prohibited by the convention (Art. VI) all appear close to the point of substantial agreement.

Despite this progress, how a CWC would deal with a situation where a novel chemical agent were to be developed and used for warfare purposes is less clear. In the case of development of novel chemicals, guidelines are being developed which would allow such chemicals to be added to existing schedules of chemicals of concern. With regard to the unexpected use, or allegation of use, of novel chemicals not appearing on any schedule, further consideration will be required in due course.

This study paper considers aspects of the potential use of novel chemical warfare agents that do not fall under the current schedules of chemicals deemed to be of particular concern to the CWC. For the purpose of this paper, which focuses on investigations of use, a novel chemical warfare agent may be a newly discovered or existing chemical which, because of its toxic properties, has been used for the first time to produce casualties.

Chemical weapons are chemical substances in either gaseous, liquid, or solid form that could be used for hostile purposes because of their direct toxic effects on plants, animals, and humans. The agents are inanimate and incapable of self-reproduction. The effects of biological agents are dependent on their ability to multiply in a person, animal or plant attacked, and include bacteria, viruses, rickettsia and fungi. Toxins are inanimate chemical poisons usually produced by living organisms such as lower forms of life (algae, bacteria or fungi; fish and plants) and by higher organisms. Some such substances may also be synthesized in the laboratory.

It has been argued that the advent of biotechnology, i.e., man's ability to engineer and alter genetic information, has made the distinction less clear between chemical agents (toxicants), toxins, and biological agents. Because of its relevance to a number of CWC-related issues, including procedures for investigation of allegations of the use of chemical weapons and the problems posed by novel agents, this matter will eventually require further consideration.

2.0 Chemicals Addressed in the CWC Negotiations

Article VI of the "rolling text" states that each State Party:

"(a) has the right, subject to the provisions of this Convention, to develop, produce, otherwise acquire, retain, transfer and use toxic chemicals and their precursors for purposes not prohibited by the Convention.

(b) shall ensure that toxic chemicals and their precursors are not developed, produced, otherwise acquired, retained, transferred or used within its territory or anywhere under its jurisdiction or control for purposes prohibited by the Convention."

It is noteworthy that sub-paragraph (b) above would suggest that concerns and obligations in relation to toxic chemicals go beyond the three schedules of chemicals currently included under Article VI for international monitoring because of the particular risks they pose to the objectives of the Convention. The intention is that under the "general purpose criterion," discussed at length in the CD negotiations but no longer specifically included in the "rolling text," the overall prohibition would apply to the production, stockpiling and use of any toxic chemicals for chemical warfare. Such a notion is difficult to express in simple terms because there are usually legitimate civilian uses for many of the chemicals. In relation to the prohibition on use of chemical weapons, the "bottom line" is that it applies to any chemical substance used for the purpose that its toxic properties cause death or harm to man or animals. This places the burden of verification with regard to the alleged use of a novel agent on the body responsible for investigating any such allegations (or even concerns) which may arise. It is possible that unusual events involving sickness or death could lead to requests for

investigative assistance even without, or as a preliminary to, an allegation of use.

3.0 Potential to Develop Novel CW Agents

3.1 Chemical Agents (Toxicants)

The search for novel chemicals, useful in preventing or combating disease, is a laudable goal. To some, it may appear that human inventiveness has its limits, and that just about everything that can be invented has been invented. This is most certainly not the case. Indeed, the chemical and pharmaceutical industries are constantly searching for better, more effective chemicals to be used for peaceful purposes. One good example is the family of pesticides, which includes insecticides, herbicides, fungicides, etc. The heavy use of some pesticides has led to the evolution of pesticide-resistant pests, and the industry has to experiment with novel compounds, including modifications of existing ones. This does not necessarily mean that the new compounds are more toxic. The contrary is true in some instances, because environmental concerns dictate that new generations of pesticides ought to be less harmful to non-target species than "older" pesticides. However, during this search for novel compounds, it is equally possible that new, more lethal compounds may be found.

A parallel - in many ways much more disturbing - may be found in the activities of producers of illicit drugs who modify the structure of these substances to make "designer drugs" that either do not fall under the currently valid legal restrictions/ descriptions or are cheaper to make.

Finally, "old," existing and already used compounds may undergo review with respect to novel use. Robinson (1982) has referred to training/riot control agents, or immobilizing drugs intended for use in animals, that may seem as suitable for warfare purposes.

Another example, actually belonging under the heading of biotoxins, is the mycotoxin, T-2, about which much has been written in recent years and which is more lethal when administered together with lipopolysaccharides from Salmonella typhimurium, an ubiquitous bacterium. Such lipopolysaccharides can be considered an endogenous component of the gastrointestinal tract; thus there is a great potential for interaction with trichothecenes, even in the absence of a systemic bacterial gram-negative infection (Tai and Pestka, 1988).

At this point, one has to conclude that science and technology will continue, knowingly or unknowingly, to produce novel means for waging chemical warfare (see also Chapter 8, Developments in Chemical and Biological Weapons, in Murphy et al., 1984).

With respect to the "rolling text" of the CWC and its definitions and schedules, the following statements can be made:

1. it is likely that novel chemicals, suitable for warfare purposes, will be developed; and

2. such novel chemicals may not appear on any schedule of the CWC.

Since Article II is essentially a blanket statement, in relation to allegations of use, it may not be worthwhile to worry too much about what is on which schedule. Instead, one should turn to the question of how to identify hostile use of any toxic agent. This will be discussed in Section 5, Methodology.

3.2 Biotoxins, Genetic Engineering and New Technologies as Sources of Novel Weapons

Piller and Yamamoto (1988) list the following applications of biotechnology as examples of novel weapons (verbatim quotations indicated by page numbers in parentheses):

- "Drug resistance. The genetic basis for bacterial resistance to antibiotics and viral resistance to other drugs is well understood. Genes that confer such resistance can be transferred to a Biological Weapon (BW) agent to thwart medical countermeasures" (page 22).

- "Increased hardiness. Finding a way to keep aerosolized microorganisms from dying once they are sprayed from aircraft or exploded from bombs has been one of the most vexing questions for BW planners. Solar radiation, drying, and temperature fluctuation easily kill most agents adapted to live within humans or animals. But microencapsulation—a novel method of protecting individual BW organisms within organic compounds—has already extended the range of agents that can be weaponized effectively" (pages 22-23).

- "Defeating vaccines, natural resistance, and diagnosis. Our immune system's antibodies can overcome a virus or other BW antigen by targeting the organism's specific surface structure. Using [recombinant deoxyribonucleic acid] rDNA to make minute changes in this antigenic surface could render antibodies ineffective.[.....] Virtually anyone exposed [to a novel agent] would contract the new disease. Through rDNA methods a form of [a] virus could be created that would frequently mutate—in essence making many "mistakes" as it self-

replicates. This would lead to diseases of longer duration because the body's defences would have to learn to recognize each of the various forms of the new .... virus" (page 23).

"Similarly, many diagnostic methods are based on the detection of certain sites on a disease organism's surface. Altering these sites could render a BW agent "invisible," thereby frustrating appropriate detection and treatment" (page 23).

- "Unlimited vaccine development and new biodetection abilities. A nation probably would not use a BW agent unless it could protect its own people from infection.[.....] Just as they have become tools to thwart vaccines, [monoclonal antibodies] MCA and rDNA technologies have revolutionized vaccine research. Under modern bioprocess methods vaccines are simple to mass-produce, and in the foreseeable future they will be created for nearly all known potential BW agents. Meanwhile, MCA technology can detect the presence of biological agents in the environment with a sensitivity unthinkable a decade ago. These developments may reduce an aggressor's fears of backfire and retaliation" (page 23).

- "Increased virulence. Disease symptoms often stem directly from toxins secreted by a pathogen. Anthrax toxin, for example, is the active ingredient of the anthrax bacterium. The genes that regulate toxin production may be manipulated to enhance an organism's virulence. The result would be a more powerful, faster-acting, and invasive weapon, one that would infect and kill more reliably" (page 23).

- "Weaponization of innocuous organisms. Certain harmless microorganisms, such as E. coli, are a normal part of the body's ecology. By the transfer of genes that regulate the production of disease-causing toxins to these helpful microbes, they may become lethal toxin factories, already well adapted for survival inside the human body" (pages 23-24).

  "It is technically and economically unfeasible to extract militarily significant quantities of many potent toxins, such as shellfish toxin, from their natural sources. But, prolific microorganisms fitted with toxin-producing genes can easily and cheaply mass-produce many of them. Further genetic manipulation could yield more efficient toxins—possibly stable under a range of temperatures and resistant to degradation in the body" (page 24).

- "Safer experimentation. Improvements in physical and biological containment, since the advent of rDNA technology have made the potentially grave dangers of BW experimentation far less daunting" (page 24).

- "Enhanced production efficiency. In the past a genuinely military BW production capability required massive, dangerous facilities and storage tanks that were difficult to conceal and maintain. New bioprocess technologies have drastically slashed the minimum size required for a BW production plant. The time for the manufacturing process has been reduced by several thousand-fold over earlier methods [....]" (page 24).

- "Ethnic weapons. BW planners have dreamed for decades about targetable weapons that would devastate the enemy,

but could never backfire or be used in retaliation. Since the advent of rDNA this fantasy has entered the realm of possibility. Specific ethnic or racial groups are susceptible to certain diseases or chemical poisoning, as a result of variations in natural resistance in the human gene pool" (page 24).

- "Biochemical weapons. The body produces tiny amounts of hormones and other substances that exert profound regulatory influence over moods, perceptions, organ function, temperature, and other essential physiological processes. The smallest imbalance can lead to severe illness, even death. Genetic engineering methods have made possible the manufacture of nearly unlimited quantities of these rapidly acting substances. This capacity has led to speculation about the weaponization of man's own biochemical endowment" (page 24).

- "More potent chemical agents. The mode of action of nerve gas is being carefully studied for the development of antidotes. But elucidation of their mechanisms of action, combined with work in the chemical synthesis of toxins, is expected to lead to neurotoxic agents up to hundreds of times more potent than existing CW agents" (page 25).

A more scientific review of this topic can be found in a report written by the National Defense Research Institute in Sweden (1987) and in the publication edited by Geissler (1986).

4.0 Historic Review of Some Recent "Unusual Events"

4.1 Methyl Isocyanate; the Bhopal Tragedy, 1984

During the night of December 2-3, 1984, methyl isocyanate, an intermediate chemical in the production of the insecticide carbaryl (Sevin), escaped from a ruptured tank. About 2,500 people were killed, and 50,000 to 60,000 seriously affected. About 150,000 persons suffered damage to lungs and eyes. The technical details of the manufacturing process, the various aspects of how the explosion of the methyl isocyanate tank could occur, and the medical and environmental effects have been discussed in detail by J.M. Dave (1985). The animal death toll was equally large, and all broad-leaved trees suffered maximum damage.

From the very beginning of the tragedy, there was little doubt as to the principle event (i.e., the explosion of a tank filled with methyl isocyanate). It is interesting to note, however, that debate of the precise mechanisms which caused the widespread death and damage to health is still going on. Numerous hypotheses have been advanced, and at times it appears that one has lost sight of the actual, instant tragedy that occurred on that December night. It may be worthwhile to remember this in the case of novel chemical weapon use.

4.2 Carbon Dioxide from Lake Nyos in Cameroon, 1986

On August 21, 1986, Lake Nyos in Cameroon erupted with a loud rumbling noise. A cloud of vapour and smoke, 50 metres high, burst out of the lake and flowed 16 km down into surrounding valleys. More than 1,700 people were killed instantaneously, and the carcasses of over 3,000 cattle and innumerable other animals littered the area the following morning.

Field investigators of the Lake Nyos tragedy were at first baffled by the event, but focused quickly on carbon dioxide (confirmed by lake water analysis), questioning where all the gas had come from and why it has been released so violently.

The event was eventually traced to the sudden release of one billion cubic metres of carbon dioxide gas from the lake, which dropped the lake level by more than a meter. Carbon dioxide escaping from hot rock into ground water and eventually into the lake was held in a dissolved state by the weight of the water above it until it shot to the surface (Stager, 1987). An earth tremor, an eruption of a volcanic pipe connected to a magma source, a landslide, or turbulence from strong wind or rain may have caused a disruption of the water stratification and released the gas.

Similar events, although not well documented, have been reported from other lakes located close to the so-called Cameroon Line, a volcanic chain stretching from the Atlantic Ocean island of Annobon to the mountainous mainland of Africa, where it forks to the north and east. A few months after the eruption, Lake Nyos's carbon-dioxide levels were still dangerously high. Claims of chemical burns, heat sensation and foul odours later proved to be unsubstantiated, but attest to the difficulty in unravelling what first appeared to be a most unusual, probably unnatural, event.

4.3 Domoic Acid; Amnesic Shellfish Poisoning in Canada, 1987

Between mid-November and mid-December, 1987, 156 people (mainly in Quebec [Bird et al., 1988]) suddenly became ill after eating cultured blue mussels. The most obvious symptoms were acute (within 12 hours) and included nausea, vomiting, abdominal cramps or diarrhea, followed by confusion, disorientation and loss of memory (in about 24% of cases) after 24 to 48 hours. Most affected

individuals recovered, but 22 people were hospitalized, 10 admitted to intensive care, and four (age 73 to 84) had severe impairment of speech. These patients were unable to communicate, developed coma and seizures, and died 7, 12, 24 and 98 days, respectively, after ingesting the toxic mussels. All seriously affected patients were elderly and several still suffered neurological effects, particularly memory loss, many months after the initial event. This clinical feature was the reason for proposing the term, Amnesic Shellfish Poisoning (ASP) (Bates et al., 1988).

All patients had eaten cultivated mussels from the Cardigan River in Prince Edward Island. There were about 3 reported cases of illness for every 1,000 servings of mussels, suggesting a low morbidity. Appropriate regulatory actions were taken to prevent further consumption of mussels or other shellfish from the area.

No previous problems with mussels from this area had been experienced. Testing of shellfish at risk is routinely carried out by the Federal Department of Fisheries and Oceans, using a mouse bioassay. Paralytic shellfish poison (due to saxitoxin) had never been detected in the Cardigan River area, although this type of shellfish poisoning is an annual occurrence on the Atlantic seacoast.

When mussels from the Cardigan River area were investigated more closely, it was determined that there was no evidence of heavy metal or pesticide contamination, nor of existence of bacterial toxins. The unknown toxin did not cause instant death (within 5 minutes) of mice, as would be the case with saxitoxin. Instead, mice died 2-3 hours after injection, preceded by unusual, yet characteristic, scratching motions which started within 10-30 minutes, followed by tremors, circling movements, "praying gestures" and "wet dog shakes." Such symptoms have also been observed in cases of Sarin or Tabun poisoning.

In view of the publicity, and the possibility that the mussel industry in that area might remain closed for a long time, considerable resources were committed to the investigation. A mussel contamination task-force was set up on December 3, 1987, and an entire analytical laboratory dedicated. In total, more than 100 people were engaged in sampling, transportation, recording of data and laboratory studies, etc. The responsible agency was the Department of Fisheries and Oceans. The Department of National Health and Welfare conducted toxicological studies, and the National Research Council, i.e., the Atlantic Research Laboratory of NRC in Halifax, provided analytical expertise.

The toxic component from the mussels was found to be extractable in aqueous methanol. High voltage paper electrophoresis (HVPE) and reversed phase high pressure liquid chromatography (HPLC) were used to isolate the toxic principle (Bird et al, 1988). The UV-spectrum and the mass spectrum of the compound was determined, and nuclear magnetic resonance (NMR) and Fourier Transform Infra-Red (FTIR) spectra gave further clues about the structure. A computer search of chemical databases revealed that the structure was identical to domoic acid. This stage was reached about two weeks after the full-scale investigation had started (Quilliam et al., 1988).

Domoic acid was found to be present at levels up to 1,000 mg/kg (= ppm). Domoic acid has been known to occur in the Pacific macroalga, Chondria armata (a seaweed). Domoic acid is actually used in Japan as an anthelmintic at a dose of 0.5 mg/kg body weight (BW), which is less than what one serving of mussels provided to the persons affected. That dose was calculated to be 10 times more, i.e., about 5 mg/kg BW, and poisoning occurred after consumption of one serving of mussels, typically about 750 g of mussels (including shells).

Chondria armata occurs very rarely on the Canadian Atlantic seaboard. In fact, the predominant food found in the intestinal tract of toxic mussels was the diatom, Nitzschia pungens, and a heavy bloom of these organisms had occurred in late 1987. To the surprise of many, it was found that Nitzschia pungens (isolated from plankton samples in December 1987) contained domoic acid, and that these diatoms are actually capable of producing domoic acid (Bates et al., 1988; Subba Rao et al., 1988).

With respect to the basic neuropathology, it was eventually determined that the damage in the brain occurs in the astrocytes and their dendrites (Iverson et al., 1989; Tryphonas et al., 1989, 1990; Tryphonas and Iverson, 1990). The assumed pathogenesis of this particular intoxication is: (1) depletion of energy, (2) potentiation of excitatory action (the "glutamate hypothesis"), or (3) inhibition of neurotransmitter uptake. The lesions are said to resemble kainic acid intoxication, but the debate is still continuing.

Various hypotheses have been advanced as to why the mussels were able to collect toxic levels of domoic acid. Considered were: run-off of herbicides used on potatoes and blueberries; increased nutrient supply into the water after heavy rainstorms; low rainfall in July and August, 1987, which could have caused higher than normal levels of dissolved nutrients, followed by warm and sunny days; and the fact that culture of mussels is a recent introduction into this area (Bates et al., 1988).

While there was never any suggestion that the event may have been due to a hostile act, the challenge faced by the investigators is much like the challenge posed by a hostile use of a novel toxin or toxicant weapon. One particularly interesting observation is that speakers at a Symposium on Domoic Acid (April 10-11, 1989, in

Ottawa) were only willing to state that there is strong circumstantial evidence to support the idea that the adverse health effects, or deaths, were due to domoic acid. The reluctance to say more is probably attributable to fear of legal implications rather than scientific opinion, particularly in view of the fact that persons in Ontario consuming mussels from the same source suffered only minor effects. Also, there has not been one single report of adverse health effects from the United States, into which a considerable amount of mussels was shipped at the same time (Domoic Acid Symposium, April 10-11, 1989). At the moment, there are no answers to the question: why would only elderly persons, in one particular geographic location, suffer severe adverse health effects, but not other exposed populations?

4.4 Stachybotryotoxicosis (Mycotoxicosis) in a Hospital in Quebec (Canada)

In June 1982, the media reported a severe "fatigue syndrome" among 50 employees in a hospital in Quebec. The place in question is a general hospital with 836 beds and a staff of about 2,000 employees. The total number of employees affected rose to 600 by the end of 1988.

Employees reported a variety of symptoms, such as exhaustion, fatigue, headaches, memory loss, irritation of eyes and skin, sore throats, rhinitis, etc. More importantly, though, many employees contracted Cytomegalovirus and Epstein-Barr virus infections, suggestive of a suppression of their immune system.

The hospital building had a record of leaking roofs, with the possibility of fungal growth either within the building structure or in the ventilation system, and a microbiological examination was conducted. A variety of fungi was found in the ventilation system, the most prominent being Stachybotrys atra. Air sampling yielded

a high count of spores of S. atra, and it was eventually determined that the spores contained large amounts of macrocyclic trichothecenes.

In spite of these findings, the medical authorities, particularly the Hospital Board, discounted the possibility of employees experiencing such symptoms as the result of being exposed to macrocyclic trichothecenes. The reason for this lack of understanding or recognition of the biological/toxicological effects of macrocyclic trichothecenes is not known. While much has been written in the French press (in Quebec), no scientific publications have emanated from this event to date, except for a paper presented at the Conference on Healthy Buildings, 1988; Stockholm, Sept. 1988 (C. Mainville, P.L. Auger, W. Smoragiewicz, D. Neculca, J. Neculca, and M. Levesque).

This case of a mycotoxicosis is of particular interest because of two aspects:

(1) the symptomatology echoes symptoms reported from the "Yellow Rain" event in Southeast Asia;

(2) the reluctance of the medical profession even to consider mycotoxins as a possible cause of the symptoms are rather typical for the presence of a "novel event."

At the writing of this report, the events in the hospital are still awaiting a final decision, but the case serves as a good example of the hesitancy to accept basic scientific findings as a cause of a disease or syndrome that is unusual or has not previously been documented in textbooks or in the medical literature.

5.0 Methodology

5.1 Interdisciplinary Tier Approach to Problem Solving

Perhaps an obvious first step is to realize that an event is, in fact, unusual. The second step is to conduct a critical review of all data at hand at the time, followed by focused and specialized investigations.

In order to meet the challenge of a suddenly occurring unusual event, it is proposed that Canada should establish a small Standing (national) Advisory Committee (see Table 1), consisting of no more than three persons, meeting on a regular basis. This "think tank" would be very much akin to existing expert groups that consider potential and actual terrorist threats. Members of this Standing Advisory Committee (SAC) have to be versed in problem solving, and the majority should have an interdisciplinary background, preferably in general or forensic pathology. The SAC would report to the National Authority established to ensure fulfilment of obligations under the Chemical Weapons Convention.

Table 1:	**Tier Approach to Examining Unusual Events Involving Toxic Chemicals**
Tier 1:	Standing Advisory Committee (3 persons)
Tier 2:	Ad hoc Advisory Group (six to twelve persons, selected on the basis of tentative assumptions)
Tier 3:	Specialists (called together on the basis of specific needs; membership may have to be re-structured, depending on findings; may include involvement of specialized laboratories)

Once this Standing Advisory Committee (Tier 1) has been made aware of an unusual event, an ad hoc Advisory Group (Tier 2) could be called upon. Members of this Group would be chosen not from an existing list, but on the basis of the expertise required for the specific problem at hand. This Group should number about six (6), but in any case no more than twelve (12). As the investigation unfolds, it may be necessary to replace some or all members of this Advisory Group. The ad hoc Advisory Group, together with the Standing Advisory Committee, would determine the specific expertise needed to solve the problem, and they would select experts for further (various) investigations to be conducted (Tier 3). It is likely that many of the specialists in this third body would be associated with laboratories with equipment necessary to conduct whatever laboratory investigations required.

Once the problem is solved, the specialists, called together for the Tier 2 and 3 activities, would discontinue their activities. However, their names should be kept on file for future reference.

There are various reasons for proposing such an approach. Firstly, with the exception of military personnel trained in known chemical (and biological) weapons, it is highly unlikely that scientists (in government, industry or university laboratories) would be available on short notice if an unusual event occurs. Secondly, substantial and precious time would be lost in getting together an Advisory Group from an existing but possibly outdated list of volunteers: such a list might not include the required experts for the specific study. Thirdly, the members of the Standing Advisory Committee (Tier 1) would know each other and each other's limitations very well, since they would likely have gone through simulations or models, as training exercises. Finally, the SAC's knowledge would allow for the selection of the most appropriate persons at that time for the ad hoc Advisory Group

(Tier 2). Also, the Standing Advisory Committee could make suggestions for further investigations, even before assembly of the ad hoc Advisory Group (Tier 2).

As suggested in Sections 3.1 and 3.2, and on the basis of the experience of the examples listed in Section 4.0, any investigation of an unusual event involving a toxic chemical will need:

- a strong scientific leadership to ensure that a multidisciplinary investigative team remains focused on the problem at hand; and

- the rapid establishment of a multidisciplinary investigative team comprising all necessary expertise. As the toxicant or toxin with which one is dealing, will not be known, flexibility and innovative approach are most important.

These needs can be met by the Standing Advisory Committee, as described above. It is proposed, therefore, that Canada establish such a permanent Standing Advisory Committee. Should similar bodies be created in other countries, it would be advantageous to arrange for occasional bi- or multi-lateral meetings of such groups in due course, perhaps under the umbrella of a Scientific Advisory Committee established pursuant to the Chemical Weapons Convention.

5.2 Investigations to be Conducted

5.2.1 Introduction

Leaving aside for a moment the thorny question of how, when, and where to collect samples while hostile actions are under way, most chemical and biological warfare agents can be detected and identified by a variety of methods. However, the first, and

probably most important, step is the recognition and documentation of the fact that an unusual event, such as adverse health effects in humans or animals, has occurred. The time-tested and best method is a careful review of events, a tabulation of the adverse health effects, and the tentative conclusion that something of an unusual nature has occurred. This critical appraisal is best achieved by an epidemiological study.

5.2.2 Gathering of Epidemiological Data

The effects of the use of chemical weaponry (CW) would likely be more predictable in a society where conditions of sickness, malnutrition, or crowding would intensify the toxic response. These same populations, however, already have a high rate of morbidity and mortality. Identifying an outbreak of disease with high mortality and investigating it must, therefore, be undertaken against a background of illness that could obscure much of the potential effect of CW. Another problem is discriminating between an outbreak as the result of a CW attack and a natural disaster, such as the tragedy in Cameroon, or between a CW attack and a technological disaster, such as Bhopal (Dave, 1985; Sutherland, 1985; Suitcliffe, 1985), or Chernobyl (USSR).

As in the investigation of an epidemic, the immediate task is to confirm the existence of an outbreak (i.e., the occurrence of an excess number of events over what would be expected within a defined time and population [Binder and Sanderson, 1987]). If an outbreak is under way, the next task is to rule out most likely causes while investigating for CW. Since the effects of some CW could mimic diseases normally seen in the population, they can be reliably excluded only if the age/sex/socio-demographic pattern of the outbreak does not resemble the normal/background pattern for the disease it resembles. Pathological evidence will assist in

discriminating between CW and epidemics due to natural causes or breaches of public health measures (Schiefer, 1982).

5.2.2.1 Recognition of an Outbreak

Three possible scenarios can be discussed relating to the use of a novel chemical warfare agent:

(1) An Attack on the General Population

This scenario would be most obvious to public health authorities since the objective of such an attack would only be useful operationally under three conditions:

(1.1) to immobilize resistance by paralysing the population's ability to respond

(1.2) to terrorize the population in order to induce dissent and to cause morale to collapse

(1.3) to annihilate the population in an act of genocide.

Operational objectives (1.1) and (1.3) would require massive disability or death rates. Objectives (1.1) and (1.2) would require a sudden effect, developing over hours or days, to be effective. Objectives (1.1) and (1.2) would very probably be combined in a sudden attack in order to maximize the effect; the aggressor would have every incentive to execute the attack quickly and visibly. Objective (1.3) could be subtle, but would more likely be combined with military objectives. If Objective (1.1) were primary, the outbreak would probably be visible first in militarily sensitive industries and communities.

The most likely scenarios in an attack on the population would result in a sudden, visible effect clearly evident to medical and public health authorities. If the nation's health care system were at all advanced, such an attack would immediately be detected and documentation of its medical characteristics could be obtained from health authorities.

(2) An Attack on Operational Military Personnel

The purpose of this scenario would be to cripple operational readiness or fighting strength. The only likely scenarios for an attack on military personnel involve a sudden, overwhelming outbreak of disability or deaths in an operationally important unit. This scenario would rapidly come to the attention of military medical personnel, although it may be concealed from the general population by security measures and to prevent panic. For security reasons, an attack on more than one unit at a time would be unlikely in the absence of full-scale, obvious combat assault.

There are two plausible variations on this scenario:

(2.1) an operationally critical unit experiences sudden and massive health problems of unknown cause;

(2.2) an entire army or major portion thereof experiences an assault with the aggressor employing military delivery systems (shells, bombs, missiles) that would be obvious in a combat situation.

(3) An Attack on Key Military or Civilian Leaders

Such a scenario, involving the targetting of small numbers of key personnel, would be very difficult to detect without an on-going occupational health monitoring program for the periodic

evaluation of such personnel in sensitive positions. The scenario more properly belongs to the realm of counter-espionage, sabotage, and security than to the documentation of overt chemical warfare. Nevertheless, it is possible that allegations could be made, followed by requests for international assistance to investigate the allegations.

Such an operation would probably be carried out over a long period using techniques to elude detection and result in insidious health problems that would impair but perhaps not kill the victim(s). The health effects would have to mimic natural diseases or accidents and not be suspiciously uniform among all victims. The disorders may not be rare or bizarre, as this would attract undue attention. The agents employed would have to be administered reliably through a concealed delivery system, relatively nontoxic in the short-term in order to avoid detection and identification of the delivery system, and certain to act over weeks or months in producing an effect. A fast-acting compound or drug would likely be too conspicuous. An agent with a very long latency period would be operationally useless, since the advantage would be lost over the intervening years. The most likely health outcome of interest would be dementia or mental illness, since the "quality of work" would decline over time without a cluster of deaths to trigger an investigation.

5.2.2.2 Confirmation of an Outbreak

The investigation of incidents involving chemical warfare agents and of patients exposed to such substances may focus on a specific agent, but need not do so. A specific exposure may not be identifiable at first or may require extensive analyses for its identification. Also, many exposures are nonspecific in their actions and are treated with supportive care. When an incident occurs in a community, residents with real or suspected exposure

may be presented for evaluation or management of acute effects (Guidotti, 1986). Very often, individual patients will believe that they have sustained a toxic exposure, however unlikely this may be. These misleading cases must be recognized quickly and with some accuracy by medical personnel on short notice.

The investigation of an outbreak suspected to be associated with CW is best managed by a team of specialists with training in toxicology and epidemiology, but such specialists are in short supply and probably not on the scene when an incident occurs. Some simple guidelines are needed, therefore, for personnel on the scene. Table 2 provides a checklist of questions to be answered in the event that a nonspecialist physician is called to assist in managing a hazardous substances incident. A careful, methodical approach is at least as important as a detailed knowledge of the toxicology and safety hazards involved.

From these preliminary data, a physician may have to decide the magnitude of risk to the population and revise his or her opinions. At the very beginning, one needs the most accurate information possible. It is imperative that a log be kept during such an incident. Each entry has to be dated and timed, and the source of the report identified.

Correct identification of the substances involved is important and requires technical expertise (see below). Once the substance is identified, the hazard potential must be determined. If an emergency forces action before the substance is identified, the only prudent move is to assume the worst unless one has exceptionally strong circumstantial evidence that the substance is not highly toxic.

Table 2: Checklist for Physicians Involved in an Outbreak

1. What is the apparent target group? 1.1 Are operational personnel affected? 1.2 What sectors of the general population appear to be at risk? 1.3 What appears to have been the motive for the suspected attack? 1.4 What other populations might be targeted?
2. How many persons have been affected and how many are likely to be at risk in the near future? 2.1 What groups seem to have the highest concentration of health effects? 2.2 How many cases are resulting in deaths? 2.3 What clinical findings are being observed?
3. What technical resources are available on short notice to assist in evaluation and control?
4. Is the community or military adequately handling the casualties? 4.1 What local hospitals, clinics, and physicians are available as informants? 4.2 Should military resources be mobilized? 4.3 Are medical specialty services adequate or available to provide the information needed? 4.4 Are local physicians experienced and knowledgeable about this kind of problem? If not, what is the best way to reach them quickly with information to help them manage the problem?
5. What toxic substances could produce this effect? 5.1 At what concentrations in air, water, or food? 5.2 What are the most readily available technologies to detect CW concentrations? 5.3 What other potential health effects would be seen with this agent? Are they observed?

5.2.2.3 Health Monitoring for Populations at Risk

When the risk of a particular disease outcome is known to be increased in a particular industry (Guidotti, 1985), a strategy to determine the group experience with that outcome is called surveillance. When a particular outcome is not the focus of attention and the overall health experience of the individual or group is to be observed, the strategy is termed monitoring. This strategy might be suitable for the identification of a more subtle incident involving CW.

Monitoring may be applied to individuals or to groups. When the experience of a group of workers is followed over time, patterns of illness may appear which suggest either unusual characteristics for that population or suggest possible exposures. Monitoring an operationally significant group of military or civilian personnel is one way to detect a suitable CW assault [see Section 5.2.2.1]. Monitoring programs limited to key personnel may protect them and the responsible agency from unexpected losses due to the effects of CW. In any case, monitoring would only be practical for small groups of individuals and would have to be conducted by physicians knowledgeable about such matters in order to be effective. Monitoring by a general, but sensitive, battery of clinical and performance tests, however, could contribute to the discovery of previously unrecognized health problems and to separate potentially suspicious outbreaks from background illnesses. Such monitoring programs would be restricted to certain high-risk groups and be required of all in those groups. Since mass screening depends for its utility (as measured by predictive value) on three components, namely the sensitivity, specificity and population prevalence of a condition, these approaches are unlikely to be useful in the context of novel CW.

5.2.2.4 Principles of Screening

The identification of an outbreak rests on identification of the illness (Guidotti, 1985; Lilienfeld and Lilienfeld, 1980). When the attack results in mortalities, detection is obvious. If the outcome is illness, however, diagnosis rests on presented symptoms and clinical tests. These have intrinsic limitations that must be understood for their application to be meaningful. With very few exceptions, there are no clinical tests in common use that could specify a novel CW during the course of an outbreak. The tests apply only to the characterization of the health effects they produce.

The selection of an appropriate screening test is based on three variables: (1) the sensitivity of the test; (2) the specificity of the test; and (3) the prevalence of the disease in the "community." These terms describe essential concepts that apply to the use of tests in detecting any disease. Sensitivity refers to the proportion of diseased persons in the population who are identified by the test. The higher the sensitivity of the test, the more likely the test will identify the diseased individuals. The specificity of a test refers to the proportion of non-diseased individuals in the population who will have a negative result. The higher the specificity of a test, the more reliably it will exclude non-diseased individuals. The ideal is a combination of high sensitivity and high specificity. Most tests in clinical use fall well short of this ideal. During an outbreak with many casualties, conditions in the field are likely to be suboptimal and tests will fall well below their usual performance.

A test with low sensitivity but high specificity will detect only a small fraction of diseased individuals, but a positive

result will be a more reliable indication that disease truly is present in an individual. However, a negative test result will not reliably rule out the disease. A test with high sensitivity and low specificity will correctly identify most true cases, but will also yield positive results for many individuals who do not, in fact, have the disease. In other words, an insensitive but specific test may yield many false-negative results, whereas a sensitive but nonspecific test may give many false-positives. If a disease is rare in the population, the false-positive results of a sensitive but nonspecific test may outnumber the true positives, requiring additional diagnostic tests to confirm the result. The diagnostic efficiency of a test is called its predictive value.

Studying the specificity and sensitivity of diagnostic tests, and calculating their diagnostic yield in a population with a given prevalence of a disease, constitute one aspect of clinical epidemiology. When physicians order diagnostic tests for their patients, they are applying the same concepts, but the diagnostic yield is higher because the predictive value of the tests is much higher. The tests are used in a small population of persons who have a high prevalence of the disease because they were selected for testing because of their symptoms. When tests are used for surveillance or monitoring, however, the predictive value is low because most of those tested are, in fact, normal. During an outbreak associated with CW, these tests may be exceptionally uniform in abnormal findings.

To be useful in the evaluation of outbreaks associated with novel CW, a screening test must detect an exposure-related abnormality with as much certainty. The scenario for such operational use of CW suggests that the health effects will not be subtle. The risk of an error, however, could precipitate an international incident. Sensitive but highly specific tests for

toxic exposures fall into two categories: biological monitoring and toxicological screening.

Biological monitoring includes techniques to determine the magnitude of an effect the exposure is having on the body without direct measurement of the toxic substance. Measuring serum and red cell cholinesterase levels after low-level exposure to organophosphate agents is a well-known example and is one of the very few common tests that would be useful in an outbreak suspected of being associated with CW.

Toxicological screening includes tests to determine, by direct measurement, the levels of a toxic substance or its residues in tissue, body fluids, or excreta. Testing for blood levels is a common example of this more traditional approach. Usually, these tests must be done at a qualified reference laboratory if they involve agents other than common drugs.

With both biological monitoring and toxicological screening, the intent is usually to detect potentially toxic exposures before their effects become manifest. Often, however, disease due to hazardous exposure cannot be detected during the subclinical phase. In outbreaks resulting from an attack by novel CW, the effects are likely to be already in an advanced stage or lethal by the time detection is undertaken. Any test applied should, therefore, be considered a screening technique for evaluation and identification of the novel compound and for documentation of their health effects, rather than as diagnostic.

5.2.2.5 Actual Investigation of an Outbreak

Epidemiologic methods have long been used for identifying epidemic events where somewhat sizeable proportions of defined groups develop illness within a relatively short time of exposure

to a putative cause. Such epidemics fall into two classes: point source (i.e., common source contamination) outbreaks, and propagated (i.e., person-to-person transmission) epidemics (Lilienfeld and Lilienfeld, 1980). One can follow the other.

Since the early 1960s, more slowly progressive epidemics of low intensity have been analyzed by the methods of Knox (1963). Dealing with smaller numbers of affected persons, investigating small clusters, or cases involving longer incubation periods all add complexity not only to the analysis of the data, but also to the interpretation of the findings (Chakraborty and Szathmary, 1985).

Descriptive epidemiology involves three principal components for adequate analysis of an epidemic: the persons affected; the place(s) impacted; and the time sequence of outcome events. When large numbers of persons are affected, the analysis and interpretation of the findings are simplified, and little statistical sophistication is needed (Milliken and Johnson, 1984; Cox, 1982; Cutler et al., 1954).

Novel CW, however, could have outcomes that are manifested after a short, moderate or long incubation period. The outcomes themselves may be ill-defined and indeterminate, pending the identification of the agent itself. Since the preventive effectiveness of any strategy must be maximized, the outcome events will have to be analyzed at two levels. The first level will be broadly based, such as self-reported/unexpected illness events. The second level will include more complete case finding/ confirmation of a specific diagnosis for one disease or a class of diseases.

Exposure must eventually be determined through a broad-based environmental assessment, or from the victim(s), and/or through

through biochemical or other studies. Epidemiologic and medical features of the outbreak may provide clues that could lead to identification of the agent (Schiefer, 1982, 1988; Government of Canada, 1985).

Analytical epidemiology could be useful at two levels. Firstly, a determination of incident case rates would facilitate a comparison of rates. Secondly, where time would permit, case-control studies would help elucidate exposures of interest. These approaches, however, may require time beyond that which is available. For those countries having vital statistics registration systems and which publish disease patterns by person, place and time, a comparison of current observed rates against background rates will contribute more definitively to the verification of suspected excesses. This could be done quite rapidly if that baseline information is available (Gladen and Rogan, 1979; Goldsmith, 1983, 1986). However, in countries which lack such reporting systems, response will be very slow, if available at all.

To avoid false accusations, more likely diagnoses must first be ruled out. Care is needed to ensure that an outbreak is not falsely attributed to CW. Therefore, suspected outbreaks due to CW attacks must be differentiated from outbreaks due to the following causes:

- naturally occurring etiologic agents;
- breakdowns in public health systems serving the population;
- natural disasters;
- technological disasters due to failures of complex systems.

One important aspect is the prevention of public over-reaction. Any unusual incident provokes rumours, misinformation and replication of misinformation, which must be controlled, if possible, to avoid panic and misguided interference in public safety measures. Indeed, in an alleged CW attack, misinformation can seriously impede investigators.

Another important role is the protection of persons engaged in the investigation on site. They should be equipped with suitable protective gear, trained in decontamination procedures, have back-up personnel, and emergency telecommunications from the site, and proper security and emergency provisions (see Government of Canada, Handbook for the Investigation of Allegations of the Use of Chemical or Biological Weapons, 1985).

Obviously, attacks involving CW are likely to be much less common than ambiguous exposure situations in which a person or a group believes that they have been exposed to a toxic substance. Once the substance is known, an appropriate medical evaluation can be derived. But when the substance is not known or could involve a complex mixture or unusual route of exposure, the appropriate medical evaluation may be quite difficult to determine (Guidotti, 1986).

It is absolutely essential to establish a central registry of individuals exposed. This registry is invaluable for final decisions concerning the event, for future epidemiologic studies, and to document the incident and to identify victims for future reparations. Such a registry may also help in tracing victims who can provide useful information or testimony while the incident is being investigated.

In summary, the stepwise approach to investigating an epidemic where CW are suspected is:

(1) establish that an epidemic (unusual event) is under way; verify initial reports; define putative cause according to symptoms;

(2) eliminate causes other than unknown or novel agents; obtain pathological assessment consistent with potential cause;

(3) describe the event with respect to time, place and persons; calculate rates of illness in the population at risk by age, sex, occupation, eating habits, etc.

(4) formulate hypotheses and exposure-based questions in a case-control design.

5.3 Novel Methods That Could Be Used

An algorithm for eliminating most point-source and propagated outbreaks needs to be developed. Such a method of analysis should be achievable in a single day if it is to be operationally useful. While time-place clustering methods have been developed, the development of person-place analogues may be necessary for novel CW (MacMahon and Pugh, 1970). For example, if certain individuals employed in a particular activity (i.e., place) are possible targets of a CW attack, the very person-place combination could be prima facie evidence of the deployment of CW. The development of a weighting scheme could be desirable, in which evidence contributed from the different levels of epidemiologic assessment will be summed to attain a maximum possible score (Milliken and Johnson, 1984). The contributing components will include:

(1) epidemic investigation, excluding case-control study findings (Lilienfeld and Lilienfeld, 1980; Mausner and Kramer, 1985).

(2) cluster analysis (time-place, person-time, person-place) (MacMahon and Pugh, 1970; Mantel, 1967; Mustacchi et al., 1967; Pike and Smith, 1968).

(3) rates comparisons (in the presence of established background data) (Knox, 1963).

(4) case-control study findings (Feinstein, 1979; Poole, 1986; Cole, 1979).

(5) pathologic confirmation (Schiefer, 1982).

If the sum attained exceeds a predetermined value, then it may be inferred that CW has been used. This threshold could probably be established through simulation studies. It is recognized, however, that such an approach may not be considered as conclusive by an international body.

Other approaches may be possible if proper methodological development occurs, but all must take into consideration the essential concepts of toxicology. Among the most critical are the role of individual susceptibility in determining the response to toxic exposure and the limitations of conventional clinical tests in identifying non-overt, "subclinical" illness (Guidotti, 1985). These aspects are discussed in detail in the literature on toxicology and epidemiology, but seldom addressed as general principles (Guidotti, 1988).

5.4 Evaluation of Environmental Effects

It is interesting to note that much of what has been written about verification of alleged use of chemical or toxin weapons focuses solely on adverse health effects in humans. However, with

the exception of diseases that affect specifically humans (most of these would be caused by infectious agents, i.e., biological warfare agents of the known variety and possibly the more novel ones discussed earlier; see Section 3.2), other agents will also affect mammals, birds, other small animals, and even some plants. It is unlikely that an agent aimed at humans would have no effects on animals. In fact, animals may be a useful indicator of the effects of use of a novel weapon against humans.

On the other hand, the destruction of either plants or animals might be the sole purpose of using chemicals, for instance, to force populations to abandon their place of living. It is unlikely that use of such agents would exclude any possibility of causing adverse health effects in humans.

It is necessary, therefore, to apply the method of epidemiological study not only to humans, but also to other living creatures. That need for environmental studies has to be translated into appropriate action, i.e., specialists from disciplines other than human medicine will have to be added to an investigative team, as suggested already in the Handbook for the Investigation of Allegations of the Use of Chemical or Biological Weapons (1985) and summarized in Section 6.0 of this report.

5.5 Tentative Analytical Tests in the Field

Should a novel weapon be used, analytical tests carried out in a mobile laboratory in the field, if available, would be of very limited value. The role of a mobile laboratory (if in place) should be to exclude already known agents that can tentatively be determined; to ensure that samples are properly selected, packaged, stored, and shipped (see Government of Canada, 1985); and to attempt to prepare crude extracts for further analysis.

The main tasks (see also Sutherland and Schiefer, 1984) during the investigation of a truly unusual event would be:

(1) to conduct an epidemiological survey;

(2) to obtain tissue samples (blood, urine, or tissue of deceased casualties), etc., for future investigations;

(3) to collect any other necessary samples, be they remnants of delivery systems or environmental samples, according to standard procedures;

(4) to use the basic information obtained to make a very tentative assessment of the situation;

(5) to transmit the findings (documentation in general, samples, tentative conclusions, etc.) to a central agency.

With respect to biological weapons (not part of this review), the reader is referred to Vol. 6, Technical Aspects of Early Warning and Verification, SIPRI, 1975.

As shown by the domoic acid example, (see Section 4.3), dedicated instrumentation and the availability of a computerized data bank were necessary to identify the toxin. Clearly, such a task is beyond the possibility of a field laboratory. On the other hand, the field laboratory plays a pivotal role in securing/preparing samples suitable for further work. If the field laboratory selects only one method of extraction (just to give an example), or stores the samples at inappropriate temperatures or in inappropriate containers, future investigations might be severely hampered by this first step. It should be a conditio sine qua non, therefore, that the field laboratory does the following:

(1) stores samples under various temperature conditions;

(2) ensures that various types of packaging (containers) are used;

(3) prepares polar and non-polar extracts from some sample materials;

(4) oversees packaging and shipping (preferably multiple shipments);

(5) organizes raw data of observations in a tentative fashion to allow for speedier appraisal in other laboratories, but retains all raw data for future review.

5.6 Further Analyses/Activities

5.6.1 Review of Field Data

The ad hoc Advisory Group or a group of specialists (see Section 5.1 and Table 1) would have to review the field data very carefully and in a scientific manner. It might be possible to detect any missing data at this stage, and to request provision of such data with high priority. The review should also include an assessment of the methods used by the field laboratory, such as appropriateness of containers and storage/shipping conditions used and of extraction procedures employed, and to suggest further investigations, as appropriate.

5.6.2 Analysis or Re-analysis of Samples

It will be the duty of the designated laboratories to conduct analyses as speedily as possible. This may mean employment of a

computerized data bank for comparison of mass spectra. A few countries maintain very large data banks that contain information about almost every compound imaginable. Efforts should be made to link up with such facilities via satellite communication means.

5.6.3 Employment of SAR-Methodology

Structure Activity Relationship (SAR) evaluation is a rapidly developing field in toxicology. SAR evaluations have been used for many years for the development and optimization of pharmaceutical and agricultural chemicals, and have been applied to the development of SAR models of toxic endpoints (Enslein, 1988). These models permit the estimation of the toxic effects from the structure of chemicals.

The elements needed for the development of an SAR model are:

(1) a data base of verified assays for the endpoints in question;

(2) a set of parameters which describe the chemical structures so that the endpoint can be modelled in terms of these parameters;

(3) statistical techniques, principally multivariate regression and discriminant analysis, for weighting these parameters in a near-optimum fashion for the explanation of the endpoint;

(4) computer technology to make it all practical.

Toxicology estimates derived from SAR models can be used for the following types of applications (Enslein, 1988):

- In compound discovery, to select for further investigation those chemicals from among a set of candidates which are less or more likely to have toxic effects.

- Priorization of chemicals of environmental concern to permit the selection of those most in need of bioassay, inasmuch as the great majority of chemicals have not been, and never will be, tested.

- Investigation of detoxification by studying the effects of modifications of the structure on the toxic effect.

- Investigation of the toxic effects of putative metabolites.

- Identification of compounds for risk assessment.

- Assessment of mutagenicity and carcinogenicity indicators (Ashby and Tennant, 1988).

The SAR method can also be used to understand the potential toxic action of a novel compound, once the molecular structure has been determined. In theory, at least, it should be possible to compare the salient clinico-pathological findings, obtained from a thorough epidemiological study, with the GC/MS data and molecular configuration of the found compound, and to try to match the two sets of observations. There is, however, one severe limitation to the SAR method: current models cannot handle mixtures if there is any presupposition of interaction between compounds, i.e., synergism or antagonism, because very few data exist for such mixtures.

6.0 Requirements for Investigations in the Field

Although this section draws on material from the Canadian Verification Research Programme, there are studies conducted under the auspices of the United Nations which are particularly relevant to these issues (Report of the Group of Qualified Experts Established in Pursuance of General Assembly Resolution 42/37C, August 1989).

6.1 Personnel

It is difficult to foresee all the circumstances and possible questions that may arise when alleged use of a novel chemical warfare agent is investigated. It is not possible, therefore, to suggest a "standard" team or approach. Instead, the following list is suggested:

- military personnel who can advise on traditional chemical and/or biological warfare agents;
- physician with epidemiological training, preferably with some knowledge of known chemical and/or biological warfare agents;
- medical specialist in infectious diseases (e.g., pathologist, dermatologist, neurologist, hematologist, specialist in internal medicine);
- chemist, preferably with knowledge of known chemical weapons;
- microbiologist with knowledge of known biological warfare agents;

- veterinarian, preferably veterinary pathologist, with knowledge of the effects of known chemical or biological warfare agents on animals and/or infectious/exotic diseases;

- psychologist, familiar with interviewing techniques;

- sociologist, ethnologist and/or cultural anthropologist with knowledge of the area where the alleged attack occurred;

- plant expert, ecologist, etc., depending on what problems have been encountered.

6.2 Equipment

The basic requirements for a field laboratory, should it be possible to establish such a facility, have been detailed in the Handbook for the Investigation of Allegations of the Use of Chemical or Biological Weapons (Government of Canada, 1985; see pp. 23-36). Hence, there is no need to repeat this here. However, it should be stressed that this laboratory, if established, would essentially be restricted to the collection and preservation of samples for further investigation.

7.0 Requirements for Analyses in Specialized Laboratories

7.1 Personnel

It must be assumed that a laboratory, selected by the Ad hoc Advisory Group (see Section 5.1), has the qualified personnel, plus the necessary support staff, including persons trained in computer retrieval of technical information.

7.2 Facilities

The required laboratories will have to be fully equipped with state-of-the-art instruments and be capable of working under pressure to identify the problem chemicals contained in the samples received as part of the investigation of allegation of use of novel chemical weapons. At the present there would be a need for designated laboratories to carry out such investigations. One would have to make use of existing government, university or consulting laboratories capable of complying with the high standards enunciated by many countries for clinical and non-clinical studies of novel drugs and chemicals, i.e., the principles of Good Laboratory Practice and Quality Control.

If the Chemical Weapons Convention has already entered into force, the Technical Secretariat will almost certainly have its own central laboratory. These facilities would be properly equipped to carry out such investigations. The costs of establishing and maintaining such a laboratory mainly for the investigation of suspected breaches of a CWC might be prohibitive. However, as has been pointed out earlier (Schiefer and Sutherland, 1984) and suggested also by Cassell (1983) such a laboratory could serve other useful purposes if it had excess capacity. It could investigate global pollution, toxic waste problems and unusual disasters like those described in Section 4. Such duties would

keep it in a constant state of alert and continually test its functional ability. This would give the laboratory public visibility and allow it to earn international reputation and respect.

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