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SMR 1550 - 2

WORKSHOP ON THE USE OF RECEPTOR BINDING ASSAY (RBA)

1 - 5 September 2003

Co-organized by the International Atomic Energy Agency (I.A.E.A.)

International Legislation and Regulations that Impact on Saxitoxin Research and Use

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These are preliminary lecture notes, intended only for distribution to participants.

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The Chemical Weapons Convention

- Parties will not
  - develop, produce, acquire, stockpile or retain chemical weapons
  - not transfer or use them
  - will destroy any they possess, together with production facilities
- Must declare chemical weapons and related facilities as well as chemical production for "non-prohibited purposes" in accordance with a list of chemicals in the Convention
- Permit international inspectors to verify declarations, witness destruction of prohibited items and investigate possible non-compliance if one Party challenges another
- Requires each State Party to enact implementing legislation making it a criminal offence to carry out any prohibited activity
- Established the Organisation for the Prohibition of Chemical Weapons to serve the State Parties
- Provides for assistance to State Parties attacked, or threatened with CW and to protect the right of all parties to use chemicals for peaceful purposes

What makes a chemical a weapon?

- It has been developed, produced, stockpiled or used as a chemical weapon
- Has high potential for use in activities prohibited under the Convention because of one or more of the following:
  - It possesses a chemical structure closely related to that of other toxic chemicals listed in Schedule 1, and has, or can be expected to have, comparable properties
  - It possesses such lethal or incapacitating toxicity that would enable it to be used as a chemical weapon
  - It may be used as a precursor in the final stage of production of a toxic chemical listed in Schedule 1, regardless of where this stage takes place
- It has no purposes other than as a chemical weapon

Theory behind chemical & biological weapons

- Killing removes one soldier or person
- An injury removes the victim, the immediate person that helps, medical aide, nurse, doctor, hospital bed, drugs, etc
  - Unit unable to perform mission
  - Casualties consume scarce medical and evacuation assets
- May rapidly overwhelm medical resources
- Even threat of use would create fear, panic
- Perpetrators could escape days before effects (agents with incubation times of several hours/days)
- Potential for secondary/tertiary transmission

Members of the Executive Council

Africa	*Latin America & Caribbean*	*Western Europe & other states*	*Asia*
1. Algeria	1. Argentina	1. Belgium	1. Bangladesh
2. Benin	2. Brazil	2. Canada	2. China
3. Botswana	3. Chile	3. Denmark	3. Iran
4. Cameroon	4. Colombia	4. France	4. India
5. Morocco	5. Mexico	5. Germany	5. Japan
6. Nigeria	6. Panama	6. Italy	6. Pakistan
7. South Africa	7. Peru	7. Portugal	7. Korea
8. Sudan	8. Uraguay	8. Turkey	8. Saudi Arabia
9. Tunisia		9. UK	9. Sri Lanka
		10. USA	
Eastern Europe	1. Belarus	2. Bulgaria	
3. Croatia	4. Hungary	5. Russia	

Scientific advisory board

- Gives specialised advice in areas of science and technology relevant to the Convention, to the Director-General, the Conference, the Executive Council or the States Parties
- Functions of the Board include:
  - assessing and reporting to the Director-General on scientific and technological developments
  - providing advice on proposed changes to the Annex on Chemicals
  - providing scientific and technological advice to the Secretariat upon request
  - assessing the merits of verification methodologies, technologies and equipment, and advising the Conference of scientific and technological developments that need to be taken into account in its review of the operation of the Convention

Chemical "accidents"

- In 1992, an El Al plane crashed into an apartment block in Amsterdam
- Many deaths and victims complained of a mysterious illness for years to come
- After 3 inquiries, it was finally revealed that the plane carried 240 kilograms of dimethyl methylphosphonate, a chemical used in the production of the nerve agent sarin
- Purchased from a U.S. company
- Destination was the Israel Institute for Biological Research in the Tel Aviv suburb of Nes Ziona
- This facility had long been suspected of involvement in Israel's chemical and biological weapons program
- Israel had yet to accede to the BWC or ratify the CWC

The "Australia" group

- Australia Group established in 1985 as an informal forum for like-minded countries to exchange information and to harmonise export control measures on chemical weapon precursors
- Later extended to include controls on chemical production equipment and technology that could be used for chemical weapons purposes
- Extended further in 1990 to include controls on biological weapons agents, precursors and production equipment
- The AG currently maintains controls on the following items :
  - chemical weapon precursors
  - biological agents (including human/animal/plant pathogens, zoonoses and toxins, etc.)
  - chemical and biological manufacturing equipment and related technology

Members of "Australia" group at June 2002

Argentina *	Czech Republic	Iceland	Poland	Switzerland
Australia	Denmark *	Ireland	Portugal *	Turkey *
Austria	Finland	Italy *	Romania	UK *
Belgium *	France *	Japan *	Korea *	USA *
Bulgaria *	Germany *	Luxemburg	Slovakia	
Canada	Greece	Netherlands	Spain	
Cyprus	Hungary *	Norway	Sweden	

European Commission sits as a non-voting member

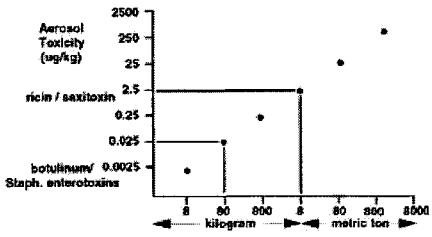
CWC and saxitoxin

- Schedule 1 chemicals can only be shipped between Convention signatories after having received a permit
- Schedule 1 compounds cannot be reexported to another country
- To ship STX, you need a permit from the governments of the country of origin and receipt as well as one from the Organisation for the Prohibition of Chemical Weapons
- ^{3}H-STX was a more difficult problem because Amersham did tritiations in the UK after importing unlabelled STX from USA
- Could not then sell the ^{3}H-STX to another country as this was deemed a re-export and banned under the CWC
- Researchers in the UK were able to use the ^{3}H-STX and a special permit was given to ship hot STX back to the USA, it being the country of origin
- Any changes to the CWC are difficult because it a consensus decision making body

Saxitoxin already a chemical weapon

- Japanese experimented on Chinese POW's with saxitoxin
- CIA reportedly used it in suicide capsules (eg U-2 pilot Gary Powers)
- In 1970, Nixon ordered CIA to destroy entire stock of saxitoxin because of US commitment to the UN bioweapons agreement
- In 1975, the CIA Director revealed to Congress that CIA still had >10 grams of saxitoxin - later distributed to scientists and medical researchers by the NIH
- US Army coated 20,000 rounds of bullets and flechettes with saxitoxin
- USA wanted ricin included because of chemical weapons development in old USSR, and the USSR responded by asking for STX's inclusion
- Chemical synthesis of saxitoxin in the 70's put it into the chemical weapon category because it could now be manufactured at will. Cost and efficiency was irrelevant
- Only STX is covered by the CWC - derivatives are not

Saxitoxin a large scale chemical weapon?



Toxicity in LD_{50} vs. quantity of toxin required to provide a theoretically effective open-air exposure under ideal weather conditions. to an area 100 km^{2}. Ricin, saxitoxin and botulinum toxins kill at the concentrations depicted; the staphylococcal enterotoxins incapacitate.

Getting around the CWC

- Salt forms of STX, have different CAS numbers to STX itself
- Similarly, tritiated saxitoxin had a different CAS number
- There was a precedent for this - a nitrogen mustard salt, which is used as a chemotherapeutant, was being shipped worldwide, despite the free base form being on the Schedule 1
- Canada, UK and Australian governments deemed these different compounds and not subject to the CWC
- Because the Scientific Advisory Board is a consensus body & the other countries were then held to that interpretation by these 3 countries
- IUPAC has produced a report on the above loophole:
  - "Current practice is to regard the salts of saxitoxin as not being Schedule 1 chemicals because they do not have this CAS number and therefore such salts do not need to be declared in the same way and transfer restrictions need not be applied"
  - "....little chemical rationale for this distinction"
  - "In solution a salt and its free base are both present, with equilibrium concentrations depending on the acidity of the solution"
  - "... inevitable that the distinction between the free base and the salt will cause anomalies among States Parties in the way they report such materials"

Biological Warfare

- Next hurdle which scientists in our field should be aware of is the International Biological Weapons Convention
- Biological warfare is the intentional use of microorganisms or toxins derived from living organisms to produce disease or death in humans, animals, or plants
- BWC has long history but a compliance regime yet to be developed
- Compliance regime is agreed procedure to enable inspections and monitoring of biological weapon manufacture
- Difficult process because you have to be mindful of participating country's security rights, commercial-in-confidence issues and the need to maintain some of these weapons for research purposes
- Toxins will again be covered under the BWC
- Rajneeshee cult-Oregon, 1984
  - Contaminated salad bars-*S. typimurium*
  - 751 cases of enteritis
- Aum Shinrikyo-Japan,1995
  - Police raids on compound allegedly recovered cultures of *B. anthracis*, *C. botulinum*, *C. burnetti*, botulinum toxin, and spray tanks

Biological Warfare

- 1972 Biological Weapons Convention Parties agree:
  - Never develop, produce, stockpile, acquire or retain biowarfare agents
  - Facilitate exchange of equipment, materials, and information about peaceful uses for biological agents
- Easy to source:
  - Field samples or clinical specimens
  - Multiple culture collections
  - Universities
  - Commercial biologics supply houses
  - Foreign laboratories
- Genetic engineering to enhance virulence
- Uses common production methods (eg antibiotics, vaccines, foods)
- Easy to do, easy to conceal
- Costs of casualties per square kilometer by weapon type
  - Conventional $2000
  - Nuclear $800
  - Nerve gas $600
  - Biological $1

Australia Group's List of Biological agents for export control - toxins

Aflatoxins
Abrin
Cholera toxin
Diacetoxyscirpenol toxin
T-2 toxin
HT-2 toxin
Modeccin toxin
Volkensin toxin
Viscum Album Lectin 1

Botulinum toxins
Clostridium perfringens toxins
Conotoxin
Ricin
Saxitoxin
Shiga toxin
Staphylococcus aureus toxins
Tetrodotoxin
Verotoxin
Microcystin (Cyanginosin)

CDC Select Agent Program

- *Public Health Security and Bioterrorism Preparedness and Response Act of 2002* required the United States Departments of Health and Human Services (HHS) and Agriculture (USDA) to establish requirements regarding possession, use, and transfer of select biological agents and toxins.
- In order for a laboratory facility or entity to lawfully possess select biological agents & toxins after February, 2003, they must:
  - file an application
  - Entities that previously declared possession of a select biological agent or toxin that determine they are exempt under the provisions must provide details regarding why they are exempt or no longer possess a select biological agent or toxin
  - All transfers of HHS or USDA select biological agents and toxins after March 12, 2003 must be pre-authorized by CDC or APHIS, respectively
- Saxitoxin and tetrodotoxin listed in CDC select agents but amounts less than 100 mg per principal investigator are exempt

United Kingdom's Anti-Terrorism, Crime and Security Act

- Passed December 2001 in response to September 11 terrorist attacks on New York and Washington
- One specific aims is to 'improve the security of dangerous substances that may be targeted or used by terrorists'.
- The Act:
  - restricts transfer of biological agents & toxins to third parties
  - extends the BWA to acts committed abroad by UK nationals or incorporated bodies
  - authorises Customs and Excise to prosecute offences involving movement of biological or chemical weapons, and covers offences of aiding, abetting, conspiracy
  - makes it an offence to assist weapons-related acts overseas
  - provides police with powers of entry, search and seizure if there are reasonable grounds for suspecting an offence
  - places personal responsibilities on managers for offences committed on their premises

United Kingdom's Anti-Terrorism, Crime and Security Act

- Imposes a duty on laboratory managers and occupiers of premises to notify the Home Office before any scheduled pathogen or toxin may be kept or used on the premises,
- Police can require information on the security measures adopted, and on who has access to the substances, including their nationality
- List must be kept up to date, and there is a waiting period of 30 days before the named person can be given access
- Home Secretary can ban named individuals from access
- Police can require reasonable security measures to be put in place, and on 48 hours' notice can inspect them
- Home Secretary, with parliamentary approval, can add toxic chemicals, animal & plant pathogens & pests to the list if the chemical
  - "could be used in an act of terrorism to endanger life or cause serious harm to human health", or
  - if there is a risk that the pathogen or pest "is of a description that could be used in an act of terrorism to cause widespread damage to property", significant disruption to the public, or significant alarm to the public"

World Trade Organisation

- Nearly 150 members, accounting for over 97% of world trade.
- Decisions are made by the entire membership by consensus
- A majority vote is also possible but it has never been used in the WTO, and was extremely rare under the WTO's predecessor, GATT.(General Agreement on Tariffs and Trade)
- WTO agreements have been ratified in all members' parliaments
- The WTO's top level decision-making body is the Ministerial Conference which meets at least once every two years
- Below this is the General Council (normally ambassadors and heads of delegation in Geneva, but sometimes officials sent from members' capitals) which meets several times a year in the Geneva headquarters
- The General Council also meets as the Trade Policy Review Body and the Dispute Settlement Body
- At the next level, the Goods Council, Services Council and Intellectual Property (TRIPS) Council report to the General Council

Regulations for animal and plant products

- Separate agreement on food safety, animal & plant health standards (Sanitary and Phytosanitary Measures) sets out the basic rules
- Intention is to ensure a country's consumers are being supplied with food that is safe to eat by the standards considered appropriate
- At the same time, ensure strict health and safety regulations are not being used as an excuse for protecting domestic producers
- Allows countries to set own standards, but regulations must be based on science
- Regulations should be applied only to the extent necessary to protect human, animal or plant life or health
- Not arbitrarily or unjustifiably discriminate between countries where identical or similar conditions prevail
- Member countries are encouraged to use international standards, guidelines and recommendations where they exist
- Members may use measures which result in higher standards if there is scientific justification
- Countries can also set higher standards based on appropriate assessment of risks as long as approach is consistent, not arbitrary

Regulations for animal and plant products

- Still allows countries to use different standards and different methods of inspecting products
- So how can an exporting country be sure the practices it applies to its products are acceptable in an importing country?
- If an exporting country can demonstrate that the measures it applies on its exports achieve the same level of health protection as in the importing country, then the importing country is expected to accept the exporting country's standards and methods
- The agreement includes provisions on control, inspection and approval procedures
- Governments must provide advance notice of new or changed sanitary and phytosanitary regulations, and establish a national enquiry point to provide information
- The agreement complements that on technical barriers to trade

Technical regulations and standards

- "Agreement on Technical Barriers to Trade" attempts to ensure regulations, standards, testing & certification do not obstruct trade
- TBT recognizes countries' rights to adopt the standards they consider appropriate for human, animal or plant life or health, for environmental protection or to meet other consumer interests
- Members may take measures to ensure standards are met
- Encourages countries to use international standards where appropriate, but not require change of their levels of protection
- The agreement sets out a code of good practice for the preparation, adoption and application of standards by central government bodies.
- Includes provisions describing how local government and non-governmental bodies should apply their own regulations — normally same principles as central governments
- Discourages methods that give domestic goods an unfair advantage
- Encourages countries to recognize each other's testing procedures
- Manufacturers and exporters need to know what the latest standards are in their prospective markets
- All WTO members need to establish national enquiry points

Import licensing

- The Agreement on Import Licensing Procedures says import licensing should be simple, transparent and predictable
- Agreement requires governments to publish sufficient information for traders to know how and why the licences are granted
- Describes how countries should notify the WTO when they introduce new import licensing procedures or change existing procedures.
- Agreement offers guidance on how governments should assess applications for licences.
- Some licences are issued automatically if certain conditions are met.
- Agreement sets criteria for automatic licensing so that the procedures used do not restrict trade
- Agreement says the agencies handling licensing should not normally take more than 30 days to deal with an application — 60 days when all applications are considered at the same time

Whose international standards?

- An annex to the Sanitary and Phytosanitary Measures Agreement names:
  - The FAO/WHO Codex Alimentarius Commission for food
  - The International Office of Epizootics for animal health
  - The FAO's Secretariat of the International Plant Protection Convention for plant health
- Governments can add any other international organizations or agreements whose membership is open to all WTO members

Codex Alimentarius Commission

- Created in 1963 by FAO and WHO to develop food standards, guidelines and related texts such as codes of practice under the Joint FAO/WHO Food Standards Programme.
- http://www.codexalimentarius.net/
- CAC/RCP 18-1978 Recommended International Code of Hygienic Practice for Molluscan Shellfish:

  "……applies to those bivalve molluscan shellfish such as oysters (Ostreidae), clams (Veneridae, Mactridae, Cooperellidee and Arcidae), mussels (Mytilidae), and cockles (Cardiidae), which are filter feeders, may be eaten raw or partially cooked and are normally consumed whole including the viscera. The Code is concerned with hygiene requirements for those species of shellfish intended for human consumption whether in the raw condition or destined for further processing."

Relevant Codex clauses 1

3.1.4 Growing area control.
Areas known to be affected by blooms of toxic dinoflagellates should be monitored at appropriate seasons for the presence of marine biotoxins such as paralytic shellfish poison. The official agency having jurisdiction should close immediately and effectively patrol affected areas when acceptable levels are exceeded in edible portions of shellfish meats.

7.2 Relaying and purification (depuration) of shellstock in tanks, floats and rafts
Shellstock subjected to the purification process should not contain metallic ions, pesticides, industrial wastes or marine biotoxins in such quantities that it presents a health hazard to the consumer. A low rate of removal of these substances makes purification impracticable.

Relevant Codex clauses 2

7.12 Laboratory Control Procedures
Laboratory facilities and technical personnel should be readily available to the official agency having jurisdiction for the hygienic control of the industry and should be able to provide adequate support to the control agency. The official agency having jurisdiction should take water and shellfish samples from the growing area, relaying areas and purification plants,and samples of shellstock from purification plants and processed shellfish from processing plants whenever necessary. Tests should be performed to assure that water and shellfish samples conform to the standards of the official agency having jurisdiction.

....

Tests of shellfish should include microbiological tests for faecal pollution and, where applicable, for spoilage. Biological tests should be made for biotoxins and faecal parasites and chemical and physical tests for other pollutants. Laboratory procedures should be developed and standardized and microbiological and other criteria promulgated to ensure that shellfish are free from pathogenic organisms and do not contain toxins or toxic chemicals at levels that constitute a hazard to health.

Recent experience to order NRC standards

- Australian Safeguards and Non-proliferation Office (ASNO)
  - Import permit
  - Declaration to CWO
- Informal comment and communication to Department of Defense
- Australian Customs
  - Customs clearance (approval of tariff code for import)
  - Request ASNO import permit for any "saxitoxin" compound
  - Request AQIS permit
- Australian Quarantine- Brisbane
  - Quarantine Biologicals- Canberra
    - AQIS Permit
  - Dangerous goods (IATA)
    - permit & clearance
- Contact Customs Brokerage
  - Liason with Customs on arrival
- Contact local customs office
  - Request to inform staff
- ASNO
  - Request import date and confirmation of receipt of order