OPCW

Scientific Advisory Board

SAB-II/1
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REPORT OF THE SECOND SESSION OF THE SCIENTIFIC ADVISORY BOARD

1. Introduction

1.1 The Scientific Advisory Board (hereinafter referred to as the "Board") held its second meeting in The Hague from 21 to 23 April 1998.

1.2 Dr Claude Eon of France, Chairman of the Board, presided over the proceedings.

1.3 The Board considered the following issues:

(a) a report on the reporting of ricin production;

(b) a report on the meaning of "production by synthesis";

(c) a progress report on discussions on CW destruction matters;

(d) the work programme for its temporary working groups on analytical procedures and equipment issues;

(e) problems related to adamsite;

(f) problems related to salts of chemicals listed in the Schedules of Chemicals; and

(g) other business.

1.4 The Board received a briefing by the Deputy Director-General on the status of implementation of the Convention and on work priorities. The Board was also briefed by staff from the Verification and the Inspectorate Divisions, on the requirements of and experiences in the conduct of different types of inspection (i.e. industry inspections, inspections of CWSFs and OCW sites, permanent monitoring of the destruction of chemical weapons, challenge inspections and investigations of alleged use).

2. Work on substantive issues

Reporting of ricin production

2.1 The Board considered the preliminary report of its temporary working group on ricin, chaired by Dr Thomas Inch of the United Kingdom of Great Britain and Northern Ireland. In the absence of Dr Inch, Dr Claude Eon of France introduced the report. Several adjustments were agreed and the report was adopted with these amendments. The final report on the reporting on ricin production is attached (annex 1).

2.2 The Board passed the following recommendations to the Director-General (cf. paragraph 6 of annex 1):

(a) Ricin, given its properties and history, is correctly placed on Schedule 1. At present, it has no uses except in very small quantities for research. There may be future medical applications, but they have not come along as quickly as predicted, and may never do so.

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

(c) Castor oil plants should not be subject to the Convention's reporting procedures under Schedule 1, as ricin is destroyed not isolated.

(d) It should be noted that hot pressing of castor beans constitutes the economically preferred technological choice, and it also destroys the ricin contained in the seeds. Cold pressing, which continues to be done at the level of individual farmers, usually involves pre-soaking and steaming of the seeds before pressing. Thus, the Board considered it neither worthwhile nor realistic to establish a system for monitoring each and every producer of castor oil. However, given that castor seeds are a potential source for ricin extraction, the Board recommended that the Director-General encourage National Authorities in castor oil producing countries to promote hot pressing and other techniques that destroy ricin so as to minimise the risk of illicit ricin production. The OPCW may wish to consider establishing contacts with the appropriate authorities of States Parties that produce castor oil in order to be able to address any concerns that may arise.

(e) Were castor oil producing plants to be integrated into larger chemical production complexes with additional capabilities that might give rise to concerns, normal chemical industry reporting procedures under Article VI are likely to apply to these sites, unrelated to the presence of a castor oil pressing plant. Such sites are likely to be DOC sites, which are subject to declaration and eventually inspection under the Convention.

The meaning of the term "production by synthesis"

2.3 The Board considered a report on this issue, which was prepared by some of its members during the intersessional period. The report was introduced by Dr Will Carpenter of the United States of America. The Board approved the report (annex 2). This report concluded that from a scientific standpoint, it is no longer possible to make a clear distinction between "chemical" and "biological and biologically mediated" processes. The emphasis should be on the product rather than on the process. The impact of that approach on declarations would be negligible at this stage. Although no significant additional declarations would be required today, it would be prudent to keep the situation under review in the future, as advances in technology and science may lead to an increased number of chemical products being manufactured in sizeable quantities using biological systems or principles.

The Board draws the attention of the Director-General to annex 2 to this report.

Chemical weapons destruction issues

2.4 The Board received a briefing on the discussions in its temporary working group on CW destruction, by the chairman of that group. The members agreed that:

(a) the OPCW should become the main repository of information on CW destruction technologies. To this end, contacts had been established, inter alia, with the IUPAC Committee on CW Destruction Technologies. The Technical Secretariat should support the setting up of a database on destruction technologies, as required; and

(b) the next meeting of the temporary working group on CW destruction should be scheduled for the autumn of 1999.

A summary of the proceedings of the meeting will be circulated to the members of the Board and to the other members of the temporary working group as soon as possible.

Analytical issues

2.5 The Board appreciated the opportunity to have been given comprehensive factual briefings on the analytical activities carried out by the OPCW. It recognised the professionalism and dedication of the staff involved. Still, for various reasons, analytical chemistry has not been used to the extent initially foreseen, and will probably not be used to that extent in the future either. While the question of when and where analysis would be used needs further discussion, chemical analysis will still be needed to ensure confidence and to diffuse possible doubts or misunderstandings. Thus, the Board feels that its temporary working group on analytical procedures should :

(a) review and suggest alternative inspection methods, with the aim of always using the simplest and least intrusive method possible that will meet the requirements; and

(b) address the use of analytical equipment belonging to the inspected State Party (without prejudice to the OPCW's right to use its own equipment).

The temporary working group on analytical issues should recommend key criteria that should be established in facility agreements to ensure that, when on-site analysis is carried out with equipment belonging to the inspected State Party, the credibility of the results is ensured and protected.

Equipment issues

2.6 The Board received a very informative and important briefing on inspection procedures, which conveyed a wide variety of experiences in the use of inspection equipment. As a result, all members of the Board now have a comprehensive level of information in this respect.

2.7 In relation to the tasks of this temporary working group, the Board agreed to recommend to the Director-General that the group address:

(a) recommendations in relation to equipment for continuous on-site monitoring at CW destruction facilities, with a view to optimising the personnel resources required for permanent monitoring of destruction;

(b) improvements of the equipment used by the OPCW during inspections, mainly in respect to analytical equipment; and

(c) evaluations of simple analytical instrumentation or sensor technology that may be procured as approved equipment in the future.

A more detailed description of these tasks has been prepared by the chairman of this temporary working group, Professor Gerhard Matz of Germany, and will be circulated at a later stage to all Board members and to other members of the group.

Adamsite

2.8 Following a request by the Director-General, the Board conducted an initial discussion of technical criteria that should be taken into account when declaring holdings of adamsite. The issue was brought to the attention of the Board because of the divergence in the ways in which different States Parties have declared such holdings. The Board recommended that this issue be discussed by a temporary working group, and that a technical seminar be convened to study the scientific aspects relevant to declarations of such holdings.

Salts of scheduled chemicals

2.9 The Board received a request from the Director-General to give its advice on whether the listing of certain scheduled chemicals containing amino groups implies that the provisions of the Convention also apply to the salts of these chemicals, such as hydrochlorides, even if the entry in the Schedules of Chemicals makes no mention of such salts.

2.10 In considering this issue with respect to the chemicals listed in Schedules 1 and 2 (for which this question has particular bearing, given the provisions relating to prohibitions on transfers of such chemicals to States not party to the Convention), the Board concluded as follows:

- The salts of these chemicals are chemically distinct from the parent compounds, and have different physical and chemical properties, as well as their own CAS registry numbers. However, the dynamic equilibrium between the base and the salt means that a certain amount of the free base is always present. The equilibrium is reversible, and the salt can easily be re-transformed into the base. In industry, a base is often converted to a salt if it is more convenient to handle a compound in that form. Normally, there is no essential difference between the free base and the corresponding salt from the standpoint of the end user.

- The majority of Board members concluded that there should be no differentiation in relation to the treatment of a free base and the corresponding salts under the Convention. There was a dissenting view that additional data may be needed to substantiate this conclusion.

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

3. Other business

The Board confirmed Dr Claude Eon of France as Chairman of the Board, and Dr Will Carpenter of the United States of America as its Vice-Chairman.

4. Closure

4.1 The Board agreed to convene its next (three-day) meeting during the period 15 - 18 November 1999, and to conclude the next session of its work with a three-day meeting in early April 2000.

4.2 The meeting was closed on 23 April 1999.

Annexes (English only):
Annex 1 Reporting of ricin production
Annex 2 The meaning of the term "production by synthesis"
Annex 3 Second session of the Scientific Advisory Board: list of participants

Annex 1

REPORTING OF RICIN PRODUCTION

1. Introduction

1.1 The temporary working group of the Scientific Advisory Board (SAB) on the reporting of ricin production met on 22 and 23 March 1999 in The Hague. The list of participants at the meeting is attached to this annex. Dr Thomas Inch of the United Kingdom of Great Britain and Northern Ireland served as chairman of the group.

1.2 The group received its task from the Director-General, as set out in Conference decision C-II/DEC.5, dated 5 December 1997. The group was requested to address the scientific and technical aspects of the reporting of ricin production. The group decided that, in order to cover this subject comprehensively, it needed to address a range of scientific and technical issues including chemical and toxicological properties of ricin, as well as the risks associated with ricin with respect to the Chemical Weapons Convention, historical aspects, castor oil production technologies and practices in the castor oil industry, research and medical (if any) applications of ricin or ricin-based treatments, and analytical issues.

1.3 The results of the group's deliberations and its recommendations to the Director-General, as endorsed by the Scientific Advisory Board, are contained in this report.

2. Properties of ricin

2.1 Ricins are proteinaceous toxins contained in the seeds and other parts of the different varieties of the castor plant, *Ricinus communis*. Ricin is a polypeptide molecule (molecular weight approx. 62 kDa) containing an A chain (~30 kDa) and a B chain (~31 - 32 kDa) which are coupled through a disulfide bridge. The A chain is an N-glycosidase and contains the physiologically active site of the molecule, the B chain is a galactose specific lectin and is essential for the binding of the toxin to the cell surface and for the passage into the cell.

2.2 Ricins may vary in degree of glycosylation, between different castor bean plant families, as well as within the same plant (as a result of multigenic expression). There are apparent differences in the primary structure between different ricin isoforms. These may result in differences in functional efficacy and hence toxicity between different isoforms. Different ricin isoforms have been reported and differences between them characterised analytically as well as toxicologically. The term "ricin" should apply to all these isoforms (including toxic mutants; see further below) but not to the individual side chains. In other words, ricin is characterised by the generalised structural formula A-S-S-B.

2.3 Ricin binds via the B chain to cell-surface galactomolecules. Subsequently, the toxin molecule is internalised by endocytosis. The chains separate inside the cell and the A chain reaches the cytoplasm via the Golgi complex (it is assumed that the B chain plays a role in reaching the cytoplasm within the cell). Ricin acts by interference with the rRNA in the protein synthetic apparatus. It prevents the binding of elongation factor-2 and thus the formation of the initiation complex (cleavage of adenine$_{4324}$ in mammalian 28S rRNA). As a result, protein synthesis is arrested and the cell dies. Tissue with high turnover (e.g. the intestine, immune system) is more severely affected than other tissue. Ricin also potentiates the release of inflammatory cytokines TNF-α and IL-1β, which may cause pyrexia and may contribute to the formation of oedema.

2.4 Ricin toxicity varies with species, route of administration (by inhalation, oral, intramuscular), purity of the material used, variety of ricin administered and form of application (for inhalation toxicity: particle size). Different isoforms may vary in toxicity.

2.4.1 The LD_{50} has been reported to be in the order of 9.8 micrograms per kg body weight (purified ricin isolated from *R. zanzabiriensis*, rat model, inhalation). Even crude extracts are still extremely potent (in the same test, a clarified homogenate was shown to have an LD_{50} of 14.5 µg/kg). Typically, all lymph nodes become swollen and haemorrhagic. Spleen, liver, lungs and heart are affected, body cavities contain clear fluid, hypothermia (perhaps related to hypotension) is observed, and death is accompanied by convulsions.

2.4.2 Inhalation toxicity depends on the particle size, with smaller particles able to penetrate deep in to the lungs reaching the alveoli being considerably more toxic than aerosols with larger particles. The animal model used is also important, given the differences in the anatomical structures of different models as well as man. The following lethal dosages have been reported:[1]

	LCt_{50} (mg min m^{-3})		
Particle size Species	1.4	4.6	6.6 µm
Rabbit	4.0	8.0	10.0
Guinea pig	7.0	15.0	-
Mouse	9.0	40.0	45.0
Dog	24.0	45.0	-
Cat	24.0	45.0	-
Rat	50.0	120.0	-
Monkey	100.0	-	-

In another test, an aerosol of 0.9 µm purified ricin of the "Hale Queen" variety had an LCt_{50} of 5.0 mg min m^{-3} in the rat model.

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1 Data submitted to the temporary working group seminar by Gareth D. Griffiths, CBD Porton Down, United Kingdom, in his presentation "Toxicity of ricin (parenteral and inhalation routes)", 22–23 March 1999.

In rat, using a particle size of <2 μm and a low lethal dose (LCt_{20} - LCt_{30}), the following symptoms were observed: damage to conducting airways, the alveolar macrophages became affected between 6 and 12 hours after exposure, type I epithelial cells of alveoli and endothelia were affected from 12 - 15 hours onwards, perivascular oedema commenced from about 20 hours depending on the dose, acute alveolitis (neutrophils), type II alveolar ephitelial cell hyperplasia (24 - 72 hours after exposure), arrival of migratory macrophages (polymorphs), interstitial macrophage congestion and general repair and recovery by about 7 days. Different from intramuscular application, systemic effects were not observed, the damage was confined to the lungs.

2.4.3 In summary, the LD_{50} of ricin is generally given between 1 and 10 μg/kg for parental and inhalation administration. Orally, however, ricin is 100- to 1000-fold less potent.

2.5 As early as during World War I, ricin was assessed as a candidate CW agent. During World War II, ricin was field-tested (but not actually used).[2] There are reports about pilot plant production during the war. Aerosol dissemination tests demonstrated that ricin could be used as an effective weapon. Despite its heat sensitivity, the toxin survived aerosolisation by explosive charges surprisingly well and retained much of its toxicity. Lung-penetrating aerosols could be disseminated. Ricin was thus considered a potent candidate agent.[3]

2.6 Ricin has also acquired notoriety for its more recent uses in assassinations. In one widely publicised case,[4] a minute quantity of toxin (approx. 250 nanoliters) was places inside a spherical device (diameter 1.5 mm, two diametric channels) which was shot into the leg of the victim with a special device hidden in an umbrella. During the night, the victim developed a high fever and nausea. He was hospitalised the next day. Blood tests for blood-borne infections remained negative while the patient's condition worsened (delirium, hypotension). The white blood cell count rose considerably and on the fourth day, the victim died of cardiac arrest. The pathology showed inflammation of the wound, widespread haemorrhagic swollen lymph nodes, small haemorrhages in heart and adrenals, fluid around the lungs, fatty changes in the liver and damage to the gut lining. The conclusion of the investigation of this death was that the agent used in the attack must have been very potent indeed.

2.7 There are also reports about ricin being extracted by individuals (using primitive extraction equipment), for criminal or terrorist activities. It appears that ricin is not difficult to isolate in a crude way; even purification has been reportedly attempted. Given its high toxicity, this potential needs to be looked at with concern.

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2 See for example Summary Technical Report of Division 9, NDRC Vol. 1 (Chemical Warfare Agents, and Related Chemical Problems), Part 1 (1946), Office of Science Research and Development, Washington, DC.

3 As a toxin, it would at the time have been associated with biological warfare agents.

4 See reference under footnote 1.

Protection against ricin

2.8 Studies have shown that the therapeutic window for the treatment of ricin intoxication is very narrow. Even if timely detection is available, that short window of opportunity severely limits post-attack treatment efficacy. Pre-treatment is thus essential for survival. To date, work on ricin intoxication therapy (passive immunisation or chemical treatment) has not been successful. Vaccination pretreatment seems the only viable option. Work is under way in several countries, and initial success has been reported in the development of a ricin vaccine. Current interest is reported to focus on the optimisation of the formulation of a vaccine.

Summary on ricin

2.9 Ricin is a potent toxin when administered parentally or by inhalation. Some ricin varieties are 20 times more toxic than the nerve agent sarin. It can be disseminated in aerosol form, or in terrorist attacks against individuals. Victims would not be aware of the attack until symptoms would appear, as the toxin has neither smell nor taste, nor any acute intoxication effects. Its toxicity profile is steep and the time window for effective treatment very narrow. Thus, pre-treatment is the only effective option to counter its possible abuse as a chemical weapon. Ricin has a history as a CW agent and its inclusion in Schedule 1 is fully justified.

3. Castor oil production and ricin

3.1 Ricin can be acquired by acidic extraction and purification[5] from the seeds of the castor plant *Ricinus communis*. This plant grows abundantly in tropical and subtropical regions. *R. communis* is a highly variable species, with different characteristics of capsules, seeds, size, form and colour of the plant. It also shows a remarkable capacity to hybridise. The seeds of *R. communis* are the source of a vegetable oil ("castor oil"), which has a wide range of applications. In addition to ricin, the seeds also contain two other toxic compounds: ricinine and CB-1A. Ricinine is a mildly toxic alkaloid. CB-1A is a powerful thermo-stable allergenic protein-polysaccharide which is difficult to remove or detoxify. In fact, it is today the main occupational hazard in the handling of the seeds and the castor meal.[6]

3.2 During castor oil production, ricin is destroyed in a number of process steps given its thermo-lability. It has been reported, for example, that ricin will be destroyed during moist cooking of flaked castor bean meals at temperatures between 65 and 77°C, irrespective of the presence of chemical additives.[7],[8]

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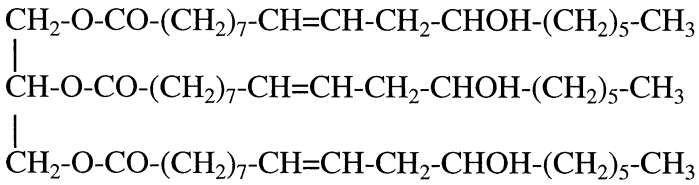
5 Crude extracts of the de-oiled seeds with acidified water are already highly toxic.

6 For details of castor meal toxicity and its treatment, see "The processing of castor meal for detoxification and deallergenation", International Castor Oil Association Technical Bulletin no. 1/1989, Ridgewood, New Jersey. This publication also summarizes the history of the castor oil industry's efforts to curtail the toxicity problems associated with the handling of castor seeds and castor meal.

7 Jenkins, F.P., "Allergenic and toxic components of castor bean meal - review of literature and studies of inactivation of these components", J. Sci. Fd. Agric. 14 (1963) 773-780

8 Gardener, H.K. Jr., D'Aquin, E.L., Koltun, S.P., McCourtney, E.S., Vix, H.L.E. and Gastrock, E.A., "Detoxification and deallergation of castor beans", JAOCS 66 (1989) 227

3.3 Castor oil is the only commercial source of the hydroxylated fatty acid ricinoleic acid, also known as hydroxoleic acid:



This key component comprises 80 - 90 percent of the fatty acid composition of castor oil. Uniformity is thus a key characteristic of castor oil. Its ricinoleic acid content is quite independent of crop variations in good or bad years. This is unusual for vegetable oils and an asset for the applications of castor oil. Other constituents of castor oil include palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachidic acid and dihydroxy stearic acid. Castor oil is non-toxic, a renewable resource, non-comedogenic, and biodegradable - all interesting properties in relation to its applications.[9]

3.4 Castor oil is produced to specifications (standards) which include requirements in respect to, inter alia, acid value, clarity, colour, hydoxyl value, loss on heating, refractive index, saponification value, solubility in ethanol, specific gravity, unsaponifiable matter, viscosity and iodine value. Other standards are also applied, such as optical rotation, peroxide value, absorption. The ricin content in castor oil is not subject to regulation in the castor oil standards as it is not distributed into the oil. Ricin contained in the seeds is effectively destroyed during the process (soaking of seeds with hot water, hot pressing if applied, toasting of press cake after solvent extraction).

3.5 Castor oil is further processed by the industry using a variety of chemical processes, such as pyrolysis, hydrogenation, dehydrogenation, sulfonation, oxidation, polymerisation, esterification and the like. Castor oil and its derivatives have a vast range of applications. Typically, these are specialty applications given the price advantage that products based on crude oil have today. However, if the price relationship between castor oil and crude oil would change in favour of castor oil, it is conceivable that castor oil could be a competing raw material also for the products which as of today are made from crude oil. Products made from or containing castor oil include, inter alia:

- Nylon 11, engineering resin and textile fibre
- lubricants, lubricating grease
- different types of coatings
- casting resins including electrical casting resins
- thixotrop
- textile processing agents
- pharmaceuticals and cosmetics

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9 More details can be found in "The chemistry of castor oil and its derivatives and their applications", International Castor Oil Association, Ridgewood, NJ, 1992.

- a variety of industrial derivatives using castor oil as starting material
- plasticisers
- castor soaps
- castor esters as polyols and for other uses
- petroleum de-emulsifiers
- electrical and sonar applications
- surfactants
- perfumes and flavours

3.6 The main producers of castor oil are Brazil, China and India. Sizeable quantities are also produced elsewhere. The main process steps include:

- the seeds are screened, sorted and conveyed to screw expellers,
- the seeds are passed through screw expellers heated with open and jacket steam (feed stock temperature in the expeller 80 - 90°C, passage time approx. 30 minutes),
- the castor oil and the meal are separated,
- the castor meal (which still retains approx. 5 - 9 percent of the oil) is extracted with hexane at 60 - 65°C ,
- the castor cake after solvent extraction is drained and toasted at 110 - 120°C for 30 to 40 minutes. This ensures improved solvent recovery and reduces fire risk during storage,
- the castor oil is refined as per required specifications (see paragraph 3.5 above), and
- the de-oiled cake is used as organic manure as well as fuel.

In smaller castor oil plants, castor oil is still manufactured by a less efficient cold pressing process. Even in this process, however, the seeds are pre-soaked with steam or boiling water in order to facilitate the pressing process. Most of the ricin content is so destroyed. The press cake from cold pressing is normally sold to industrial castor oil manufacturers who, using solvent extraction and hot pressing, will recover additional castor oil and convert the press cake into the de-oiled cake sold as manure or fuel. In the final process step, the castor meal is toasted at 110 - 120°C, which destroys any residual ricin that may still be present. The transfer of press cake from smaller cold pressing plants to industrial scale castor oil producers which use hot pressing and solvent extraction followed by thermal treatment of castor meal, is important for the economy of the small producers using cold pressing technology.

3.7 As a result of these technological steps, and given the market relationships between smaller (cold-pressing) and larger (steam pressing/solvent extracting) manufacturers, the entire content of the heat labile ricin is destroyed during castor oil manufacture. A summary of the technological steps involved in castor oil production is contained in figure 1.

3.8 The castor meal is an important by-product of the castor oil industry. Notwithstanding constituent proteins, the presence of large quantities of allergic material forbids today its use as cattle feed. However, by virtue of its content of nitrogen, phosphorus, potash

and trace metals (zinc, copper), the cake is considered a versatile manure. It is used on cash crops like tobacco, sugar cane and cotton. Castor oil cake fertiliser is made to specifications. Castor cake also has an excellent calorific value; one-third of it is used by the castor oil industry itself for steam generation.

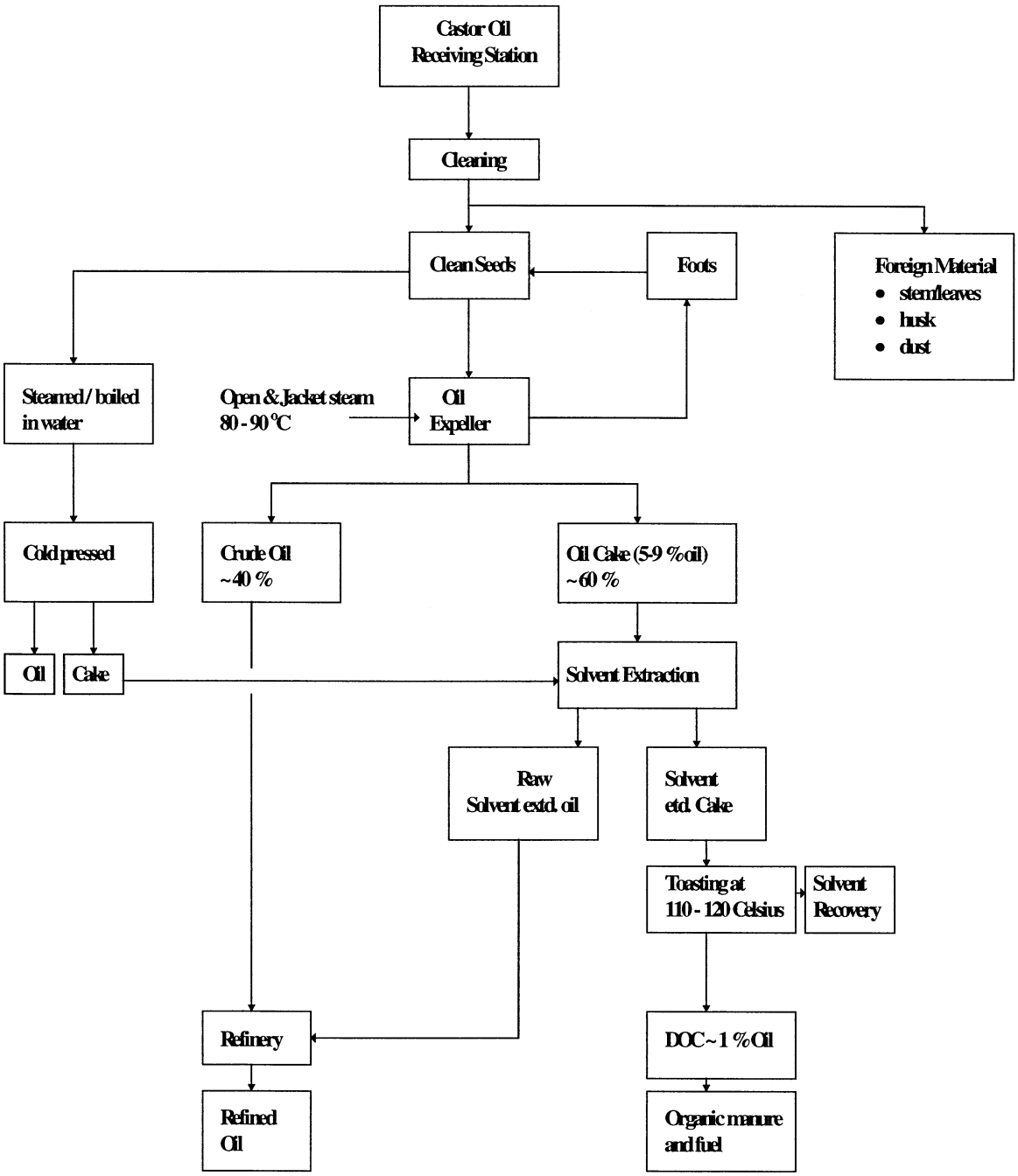
3.9 The castor oil industry is driven presently by economies of scale. Irrespective of the pressing process, their activities do not involve the extraction of ricin from the plant material. Ricin is not a product of that industry given the demand situation for ricin. Furthermore, economic as well as technical reasons have resulted in the widespread elimination of cold pressing techniques in favor of fully utilising the raw material (the castor plant). Most processes and certainly all large-scale techniques used today involve a sequence of heat treatments, as a result of which the toxin is destroyed. The economy of the industry depends on maximum castor oil extraction and refinement as well as on full utilisation of the press cake. As a side effect of this approach, the ricin content that enters the process with the raw material is eliminated.

3.10 At the same time, the castor oil industry handles a very large amount of material that contains the Schedule 1 chemical ricin, if in small amounts. The average concentration of ricin in the seeds is around 120 mg/100 g, and the world's castor oil production utilises in the order of 900,000 tonnes of castor seeds per annum. This material stream contains a potential 1,080 tonnes of ricin, a fact that should not altogether be ignored, given the ease with which ricin could be extracted. Even though the industry does not extract the toxin and has no intention to do so, there is a potential risk that should be addressed. Hence, where castor oil plants are operating as stand alone facilities, it may be prudent to ask national authorities to advise companies that hot pressing and other process steps should be used that destroy the ricin in the raw material. This would also add to the safety of workers. More importantly, national authorities would be well advised to perform some sort of safety monitoring for all castor oil production. This would add transparency and simultaneously be a contribution to workplace safety.

3.11 Converting a castor oil plant into a ricin producer would require the installation of process equipment for acidic extraction (and possibly the purification) of the toxin, and a change in the process conditions (avoidance of heating of the seed soak before pressing). Such changes would be highly visible and distinct from current industrial practices. It is important to note that ricin has no commercial value for the castor oil industry. Thus, the castor oil industry is unlikely to develop dual use processes for ricin extraction/purification.

3.12 At the same time, it should be noted that some castor oil producers are moving towards integrating their production and the manufacture of castor oil derivatives into larger chemical production complexes. While such sites may well have the technical capability to perform acidic extraction and purification of toxic material, it is very likely that these sites also would, for reasons unrelated to their castor oil production, be declarable as DOC plant sites and thus be subject to declaration and, eventually, verification provisions under Article VI.

Figure 1
Production Flow Sheet for Castor Oil



4. Uses of ricin for purposes not prohibited by the Convention

Research

4.1 Ricin is used in research because of its potency in blocking protein synthesis in, inter alia, mammalian cells. This property can be used as a tool to study cell mechanisms in a variety of organisms. The amounts used in such experiments are minute (micrograms).

Medical treatments

4.2 Until quite recently, there were hopes that ricin could become a potent anti-cancer treatment and even find application in HIV treatment. The basic idea was to exploit the fact that tissue with high turnover is affected to a larger degree by ricin than other tissue. If, for example, it were possible to specifically deliver ricin to a cancer cell and to contain its toxic action within the cancer, the hope was to be able to specifically kill the cancer without affecting the healthy tissue surrounding it. In reality, the high toxicity of ricin meant that it could not safely be delivered to a cancer without causing an intoxication of other tissue. When attempts were then made to only use the A chain of the molecule (which carries the active site of the toxin but is non-toxic without the B chain), it emerged that the B chain was essential for the passage into the cell and to the target sites. Work with mutant ricin molecules or constructs involving the A chain and other delivery vehicles have not succeeded and, at this moment, it appears unlikely that ricin could become the basis for either cancer or HIV treatments in the near future.

4.3 Thus, there are no medicinal uses of ricin at this moment. If medicinal uses would in the future become viable, it is unlikely that more than kg quantities would be involved on the manufacturing side. It appears thus unlikely that novel biotechnological manufacturing means would become attractive for such small-scale production. Ricin production for such (potential) future uses would likely involve extraction from natural sources.

The vaccination issue

4.4 As indicated above, research is under way to develop a vaccine that would act as a pre-treatment against ricin intoxication. If vaccine production would become reality, it could involve ricin as a starting material (this seems however not the most promising approach given the toxicity of the molecule). In such a case, consequences for the application of the Convention's provisions would have to be assessed. It appears much more likely, however, that a different route would be chosen for the manufacture of a vaccine (i.e. not extraction of ricin from castor seeds and subsequent work-up). For example, it seems feasible that a mutant A chain coupled with the "normal" B chain could be used as the active principle of the vaccine. It needs to be seen whether such vaccines would actually involve ricin as an intermediate step, or, more likely, be manufactured using genetic engineering techniques. If there is no involvement of ricin at any stage of the vaccine production, the mutant - if it is not toxic - should not be considered covered under the provisions of the treaty. If,

however, the manufacturing of the vaccine would at any stage involve ricin as an intermediate, it should be expected that the required quantities could easily exceed the amounts permitted under Part VI of the Convention. If that happens, the situation would need to be reassessed. The restrictions contained in Part VI of the Verification Annex would not permit such larger-scale production.

5. Ricin and the provisions of the Chemical Weapons Convention

5.1 Ricin is a Schedule 1 chemical.[10] Those few legitimate uses of ricin which today exist are of course subject to the provisions of the Convention in relation to Schedule 1 chemicals. These include restrictions on its use and the amounts any State Party may possess, declaration and verification requirements, and restrictions (prohibitions of transfers to States not party and of re-transfers) and notification regulations in respect to transfers.

5.2 Within the life cycle of ricin, the first activity to be considered as a declarable activity is its extraction from plant material/seeds (the manufacturing of a crude extract). As long as the toxin molecule is not broken up into its sub-units, it meets the structural criterion for ricin and remains accountable as a Schedule 1 chemical in accordance with Convention provisions, irrespective of possible variations in the finer molecular structure of different ricin isoforms. The same principle must be applied to toxic mutants of ricin. Once the molecule is broken up (the S-S bond hydrolysed), however, the resulting products no longer constitute ricin and any activities involving them would remain outside the scope of the provisions under Part VI of the Convention's Verification Annex.

5.3 Non-toxic mutant ricin, however, should not be considered as ricin under the Convention, also if the A or B chain were acquired by genetic techniques in host organisms (rather than by splitting the protein).

5.4 The production of castor oil does not constitute a declarable activity. While ricin is present in the raw material, it is not extracted from the plant material. Furthermore, the ricin that is contained in the seeds is destroyed in a number of process steps that involve heat treatment. Thus, irrespective of the ricin content, the quantities of seeds processed and the pressing mode used in the castor oil production, the provisions contained in Part VI of the Verification Annex cannot be applied.

6. Summary and recommendations

6.1 Given its properties and history, ricin is correctly placed on Schedule 1. At present, it has no uses except in very small quantities for research. There may be future medical applications, but they have not come along as quickly as predicted, and may never do so.

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10 It should be noted that ricin, being a toxin, is also covered under the 1972 Biological and Toxin Weapons Convention. At present, negotiations are underway that may result in a protocol to that treaty setting out, inter alia, declaration and verification procedures. Ricin could also be a candidate toxin to be covered under the measures related to that protocol.

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

6.3 Castor oil plants should not be subject to the Convention's reporting procedures under Schedule 1, as ricin is destroyed not isolated.

6.4 It should be noted that hot pressing of castor beans constitutes the economically preferred technological choice, and it also destroys the ricin contained in the seeds. Cold pressing, which continues to be done at the level of individual farmers, usually involves pre-soaking and steaming of the seeds before pressing. Thus, the Board considered it neither worthwhile nor realistic to establish a system for monitoring each and every producer of castor oil. However, given that castor seeds are a potential source for ricin extraction the Board recommended that the Director-General encourage National Authorities in castor oil producing countries to promote hot pressing and other techniques that destroy ricin so as to minimise the risk of illicit ricin production. The OPCW may wish to consider establishing contacts with the appropriate authorities of States Parties that produce castor oil in order to be able to address any concerns that may arise.

6.5 Were castor oil producing plants to be integrated into larger chemical production complexes with additional capabilities that might give rise to concerns, normal chemical industry reporting procedures under Article VI are likely to apply to these sites, unrelated to the presence of a castor oil pressing plant. Such sites are likely to be DOC sites, which are subject to declaration and eventually inspection under the Convention.

Attachment

LIST OF PARTICIPANTS AT THE MEETING OF THE TEMPORARY WORKING GROUP ON RICIN

A.K. **Datta**	India
Claude **Eon**	France
Shintaro **Furusaki**	Japan
Bernard **Goupry**	France
Gareth **Griffiths**	United Kingdom of Great Britain and Northern Ireland
Tom D. **Inch** (Chairman)	United Kingdom of Great Britain and Northern Ireland
Li Weimin	China
Michael **Lord**	United Kingdom of Great Britain and Northern Ireland
Ali Akbar **Mohammadi**	Iran
Toshiya **Oda**	Japan
Abbas **Shafiee**	Iran
Kaushal Kishore **Srivastava**	India
Wiktor **Tyszkiewicz**	Poland
Stanislaw **Witek**	Poland

Annex 2

THE MEANING OF THE TERM "PRODUCTION BY SYNTHESIS"

1. Introduction

1.1 The issue of whether or not the term "production by synthesis" used in Part IX of the Verification Annex includes biochemical and biologically mediated processes was brought to the SAB by the Director-General on the basis of a decision adopted by the Conference of the States Parties during its Third Session (C-III/DEC.5 of 19 November 1998). The Conference had requested that the Scientific Advisory Board "address, solely from a scientific and technical aspect, the qualitative and quantitative implications of this issue in relation to their impact on declarations and inspections and, without making any recommendations or in any way prejudging the nature of any future decision on the issue, to report its findings to the Director-General".

1.2 The Scientific Advisory Board decided not to request the establishment of a temporary working group to deal with this issue as it considered that adequate scientific and technical expertise was available within the Board itself. During a planning meeting in The Hague from 28 to 29 January 1999, several members of the Board discussed the issue and prepared a draft text on it. The following considerations were recorded, and endorsed by the Board at its annual meeting.

2. Consideration of the issue

2.1 From a scientific standpoint, it is no longer possible to make any clear distinction between "chemical" and "biological and biologically mediated" processes. The more that is learnt about the events that occur at the molecular level in biological processes, the more such processes will be recognised as chemistry. Indeed the next century may well become "the age of the molecule". Consequently, increasingly more and more chemicals will be produced using combinations of traditional chemistry, chemistry mimicking biology, and biologically mediated processes. In the above circumstances there would appear to be little purpose (or scientific justification) in refining the term "production by synthesis" in relation to biological processes.

2.2 In relation to the term as used in Part IX of the Verification Annex, attention should be focused on the product rather than the process. Under such an approach, industrial alcohol produced by fermentation would fall under the coverage of Part IX of the Verification Annex, alcoholic beverages would not.

2.3 This approach of placing emphasis on the nature of the product (i.e. whether it meets the terms of a DOC or not) should have little effect on current declarations. The same applies to the expected inspection loads, even after DOC inspections will be begun.

2.4 In particular, there are few discrete organic chemicals today that are manufactured in declarable quantities using biological processes. It is only when a single PSF chemical is produced in excess of 30 tonnes per year per facility, or when aggregate facility

production of DOCs totals more than 200 tonnes per year, that declaration requirements are triggered. With these thresholds established by the Convention, there should be little or no effect on declarations. The commercial confidentiality of research activity particularly in fledgling biotechnology companies would remain protected given the small amounts of product involved at that stage of process or product development.

2.5 At the same time, any biological production of scheduled chemicals, should it be attempted, would of course be declarable under the terms of the Convention and the decisions taken by the Conference.

2.6 While no significant additional declarations would be required today, it would be prudent to keep the situation under review in the future as advances in technology and science may lead to an increased number of chemical products being manufactured in sizeable quantities using biological systems or principles.

Annex 3

SECOND SESSION OF THE SCIENTIFIC ADVISORY BOARD
LIST OF PARTICIPANTS

Will D. **Carpenter**	USA
Claudio **Costa Neto**	Brazil
A.K. **Datta**	India
Claude **Eon**	France
Alfred **Frey**	Switzerland
Shintaro **Furusaki**	Japan
Li Weimin	China
Gerhard **Matz**	Germany
Brahim Youcef **Meklati**	Algeria
Giorgio **Modena**	Italy
Viktor Alkeseevits **Petrunin**	Russian Federation
Erno **Pungör**	Hungary
Marjatta **Rautio**	Finland
Stanislaw **Witek**	Poland
Burkhard **Seeger**	Chile
Abbas **Shafiee**	Iran
Theodoros **Solomon**	Ethiopia

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