



the sunshine project

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A Survey of Biological and Biochemical Weapons Related Research Activities

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About the Sunshine Project Country Studies

The Biological Weapons Convention (BWC) prohibits the development, production and stockpiling of biological weapons, while permitting defensive research. Although biodefense research programs may be necessary for protection against biological warfare, there is often only a very fine line separating defensive and offensive activities, and offensive capabilities may be generated in the course of defensive work.

Accordingly, there is an ongoing need for governments to exercise sound judgment and restraint in their biodefense programs and to guarantee full transparency in all aspects of biodefense research, so as to increase confidence between countries, avoid suspicions and uninformed allegations, and prevent a race for offensive capabilities under cover of defense.

State Parties to the BWC have committed themselves to 'Confidence Building Measures' (CBMs), i.e. an exchange of information on biodefense programs, biological capabilities and other relevant fields. Many countries, however, do not comply with their obligation to submit annual CBMs, and those CBMs that are submitted frequently contain inadequate detail and omissions that defeat their purpose of building confidence.

To increase transparency and to contribute to building confidence in this critical area of international arms control, the Sunshine Project has initiated a series of in-depth country studies to publish additional information on BW-related activities in a variety of countries. Three major questions are addressed in these studies:

- What are the parameters (e.g. type, size, location) of the country's biodefense program insofar as can be judged from open sources?
- How transparent is the respective government with regard to BW-related research and development activities?
- Is the country engaged in the development of new biological or biochemical weapons (e.g. so called 'non-lethal' chemical weapons) and, if so, what is the nature of these activities?

The country studies are based on open sources such as scientific publications, general media, government publications and the internet as well as direct contacts with relevant institutions and individuals.

As aspects of biodefense programs may be classified, the Sunshine Project country studies may not be comprehensive as they reflect the parts of national biodefense programs that are accessible through open sources. The reports provide a review of the country's contemporary research and do not necessarily cover other aspects of a country's history, policy, and law with respect to biological weapons.

The reports name names, of individual researchers, research groups, and facilities. It is important to note that, unless it is specifically stated, these individuals or institutions are not accused of doing something illegal, immoral or of involvement in the development of offensive biological weapons. There is nothing inherently improper about biodefense research provided it is pursued within strict limits and if a maximum transparency is ensured. We call on all researchers as well as on all governments to adopt the '*Undertaking on Biodefense Programs*', which outlines basic principles on transparency and limits for biodefense research (see back cover).

In 2004, the following four Country Studies will be published; more will follow in 2005:

No. 1: Germany

No. 2: France

No. 3: Turkey

No. 4: USA: 'Non-lethal' (bio)chemical weapons

Individuals, institutions, or governments wishing to bring forward information on BW-related activities in their country are warmly welcomed.

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1. Summary

1.1.1. Incomplete and inconsistent information on the French biodefense program

France is not in compliance with its obligations under the Biological Weapons Convention (BWC). There is no indication that the French Armed Forces are engaged in any illicit activities related to an offensive biological warfare program, but the French government violated its obligation to submit annually to the United Nations comprehensive information about its biodefense program, in order to enhance transparency and build confidence among the States Parties to the BWC.

The French government has submitted only fragmentary, incomplete and contradictory information about its military biodefense activities to the United Nations, although the Confidence Building Measures (CBMs) adopted by the BWC are binding for France as a State Party to the Convention. Major information on the nature, scope and location of the French biodefense program has consistently been omitted from the CBMs. The French government is also not using other means to inform the French public about its biodefense activities, and it did not respond to written questions about its biodefense program. The CBM filed by the French government in 2002 is now available on the homepage of the Sunshine Project.

Based on a comprehensive analysis of open sources we conclude that biodefense work in France is performed in a variety of institutions. The two most important ones are the military research centers *Centre d'études du Bouchet* (CEB) and *Centre de recherches du service de santé des armées* (CRSSA). Other military research facilities such as the *Hôpital d'instruction des armées Bégin* near Paris and the *Institut de médecine tropicale du service de santé des armées* (IMTSSA) in Marseille as well as a range of academic research institutions are also involved in French biodefense efforts. Due to the opacity of the French government, we were unable to determine exact figures for the French military's biodefense budget.

The French biodefense program includes most of the core elements of a comprehensive biodefense program: detection, protection, and treatment/decontamination. In addition, so-called 'threat assessment' studies are performed, which may involve the practical imitation of offensive capabilities to assess an enemy's possibilities. As this kind of research smudges the line between defensive and offensive work, 'threat assessment' type projects are a major concern for international arms control. We were able to confirm that French threat assessment projects exist; but we were not able to elucidate their concrete nature.

Based on open sources it appears that the French government

- recently built mobile biological laboratories in the course of its biodefense program;
- engaged in the past in the production of possible biowarfare agents by means of genetic engineering; the exact nature and extent of this production could not be identified;
- has initiated a study on microencapsulation techniques for microorganisms;
- maintains a strain collection of infectious agents at its main military biodefense facility;
- has performed and/or performs research on aerosol generation in the course of its biodefense research;
- has its reference laboratory for poxviruses at one of its major military biodefense laboratories;
- has a comparatively strong emphasis, in its biodefense program, on animal toxins.

None of these activities necessarily indicate illicit programs, but they warrant further clarification. Based on the fragmentary and incomplete information available we were not able to establish the nature, extent and – most importantly – the likely objectives of these activities. Clarification on the following questions is warranted to enable a more thorough assessment of the French biodefense activities:

1. Which specific experiments were conducted in the past years as part of the French biological ‘threat assessment’ program?
2. What is the extent and nature of work with biological aerosols in the French biodefense program, e.g. the number, size and location of aerosol chambers, the availability of explosive aerosol chambers, the extent of indoor and outdoor aerosol studies, and the type of agents (type of chemical/microbial simulants or active agents) used in these studies?
3. In addition to research *with* aerosols, some work *on* aerosols has been conducted in the French biodefense program, including meteorological studies and the development of aerosol generating devices. What is the purpose and current scale of this type of aerosol research?
4. What capabilities and capacities for the production of biological agents exist in French biodefense facilities, and which agents were produced, in the recent past, in the French biodefense program?
5. To what extent have genetic engineering experiments performed or commissioned in the French biodefense program created organisms with an enhanced offensive BW potential, e.g. the overexpression of toxins, the transfer of genes that confer resistance to treatment, enhanced pathogenicity, or environmental stability, or the production of animal toxins in microorganisms?
6. What is the purpose of the mobile biological laboratories that were built at CEB/CRSSA and where are they regularly stationed and maintained?
7. What is the overall budget for all French biodefense activities?
8. What is the extent and nature of the biodefense research or development projects contracted to civilian institutions, and to whom were projects contracted?

These questions – which we have submitted in writing to the French Ministry of Defense and to French biodefense institutions (with no reply made) – could and should have been addressed in the CBMs submitted by France to the United Nations. If the French government is supportive of the international ban on biological weapons, and if it supports a strengthening of the Biological Weapons Convention, it should contribute to building confidence by submitting future CBMs that are complete, consistent and unambiguous.

1.1.2. Indications for an illicit R & D program on ‘non-lethal’ chemical weapons

A variety of indirect evidence suggests that France may be working in the area of so called ‘non-lethal’ chemical weapons and thus may be in violation of the Chemical Weapons Convention. French military scientists have investigated a broad range of incapacitating agents – from tear gas to neurotoxins and psychoactive drugs – and a variety of delivery devices for ‘non-lethal’ chemical weapons have been developed, patented, and marketed by French companies.

French defense companies are strongly engaged in the development of weapons to deliver so called ‘non-lethal’ chemical agents. Several companies from the defense sector are actively developing and manufacturing delivery devices for tear gas and potentially other non-lethal chemicals. Etienne Lacroix, which has been linked to chemical weapons since the 1980s, developed a training system for chemical weapons that may also be used for combat. In early 2004, salespersons from Etienne Lacroix offered us payloads with non-lethal chemical agents, including malodorants.

France’s main biological and chemical defense laboratory CEB maintains a *Behavioural Pharmacology Laboratory* that works on a variety of psychoactive drugs including opiates and has established a broad range of behavioural animal tests. The objective of these experiments remains obscure. They may be related to the development of ‘non-lethal’ chemical agents, but could be related to performance or memory enhancing compounds for the French soldier. Absent a clarification from the French government, the appearance remains that some illicit ‘non-lethal’ chemical weapons research or development activities are pursued at CEB.

In summary, the secretive and intransparent behaviour of the French government with regard to its biodefense and its putative non-lethal weapons activities may give rise to a broad range of suspicions. If these are indeed unfounded, only a radical change towards transparency and improved confidence building measures may counter similar suspicions in the future.

2. Biodefense activities in France

The French government's official information about military biodefense activities is fragmentary, incomplete and contradictory. For example, within one official document – the BWC *Confidence Building Measure* (CBM)¹ submitted in 1992 – incoherent and contradictory information is provided. In one chapter, three biodefense facilities that are run by the defense ministry are declared, while in another chapter of the very same document only one such facility is listed.²

We were not able to establish even rough numbers for the French military's biodefense budget. The numbers given in the CBMs are of unclear origin and probably only reflect the biodefense budget of one facility, the *Centre d'études du Bouchet* (CEB), most likely without staff costs. For example, the French CBMs 1992 and 2000 gave the same amount of money for the overall biodefense program and for CEB – although in the 1992 document it was stated that two other military research facilities were also involved in biodefense. According to the 2002 CBM, the total biodefense budget was €8 million, 60% of which was spent on contractors. Accordingly, €3.2 million were available for military biodefense research and development. These figures clearly do not account for all biodefense activity in France.

Based on a comprehensive analysis of open sources we conclude that biodefense work in France is performed in a variety of different institutions. The two most important are the military research centers *Centre d'études du Bouchet*³ (CEB) and *Centre de recherches du service de santé des armées*⁴ (CRSSA). While CEB is a dedicated NBC-defense institution, CRSSA performs both standard medical research and biodefense activities. Other military research facilities as well as a range of academic research institutions are also involved in the French biodefense program.

Defining biodefense

Not all research involving typical biowarfare agents such as anthrax can be characterised as 'biodefense'. It is obvious that no categorical distinction can be made between research to combat natural disease and research performed in the context of BW, as the areas are overlapping and interdependent. A great deal of medical and veterinary research performed on natural occurring microbes is unrelated to biodefense.

No agreed definition for the term 'biodefense' exists. During the negotiations for a verification protocol to the Biological Weapons Convention in the 1990s, the following definition was suggested: "*activities involving research (...) development, (...) and (...) production (...)* **designed to detect (..) the impact of any use of (...) biological agents (...) for hostile purposes (...) and/or to (...) reduce (...) the impact of biological (...) weapons (...)"⁵ (emphasis added).**

Accordingly, for the purpose of this report all activities that are explicitly performed in the context of BW issues are subsumed under the term biodefense. We also assume that all activities run (or financed) by the military that involve typical BW agents such as anthrax, tularaemia, plague, smallpox and/or botulinum are biodefense activities.

The term 'military biodefense' comprises all activities that are performed in facilities run by the defense ministry or another government entity dedicated to military or counterterrorism issues (such as the Department of Energy in the USA).

¹ State Parties to the Biological Weapons Convention (BWC) agreed in 1987 and in a revised version in 1992 to submit annually 'Confidence Building Measures' (CBMs), i.e. information on biodefense programs, biological capabilities and other relevant fields. See chapter 5 for more information on French CBMs. The 2002 CBM from France is available on the Sunshine Project website at www.sunshine-project.org.

² Under Measure A, part 2(iii), only the Centre d'études du Bouchet is listed as a biodefense facility, while under Measure F (page 100) two additional facilities are declared: the CRSSA and the Centre de recherches de médecine tropicale du service de santé des armées.

³ *Centre d'études du Bouchet* translates as *Le Bouchet Research Center* (please see also the glossary of French names on page 35).

⁴ *Research Center of the Armed Forces' Health Service*.

⁵ See chapter 'definitions' of the so called Rolling Text (BWC/AD HOC GROUP/55-1 of 1 March 2001), online available at <http://www.opbw.org/ahg/docs/rolling%20text%20and%20annexes.pdf>.

In this chapter, the major relevant institutions and some of their biodefense projects are listed, as indicated by open sources. It may well be that other French military facilities are also involved in biodefense activities, and it is likely that the facilities listed below are engaged in additional activities that we are unable to document.

The general outline of the French biodefense program is not very surprising and comprises all basic elements of such a program: detection, protection, and treatment/decontamination.⁶ It is important to note, however, that France also performs so called ‘threat assessment’ (according to the French CBM 2002). Threat assessment may involve the practical imitation of offensive capabilities to assess a – perhaps hypothetical – enemy’s possibilities and limits. As this kind of research smudges the line between defensive and offensive work, ‘threat assessment’ type projects are a major concern for international arms control and confidence building measures.

The exact nature of French ‘threat assessment’ projects remains unclear. The French 1992 CBM gave one example of an experiment that generated a pronounced offensive capability in the course of allegedly defensive ‘threat assessment’ work: The generation of genetically engineered bacteria producing large quantities of a deadly snake venom (see below for further details). Another interesting example was given in the 2000 CBM: “*In collaboration with the Armed Forces’ Health Service, studies are carried out on the ability of certain strains of Bacillus thuringiensis employed in agriculture*”.

The 2002 CBM describes ‘threat assessment’ as follows: “*Simulation studies (...) on risks linked to bioterrorist attacks in closed environments*“ (see French original on our homepage).

At the end of this chapter, after outlining the individual biodefense facilities, some general issues of concern including aerobiology, genetic engineering and French military toxin research are discussed.

2.1. Centre d’études du Bouchet (CEB)

The *Centre d’études du Bouchet* (CEB) is a key element of the French biodefense program. It is consistently featured as the expert centre for NBC defense of the French Armed Forces in official French publications, and it has repeatedly been named as the (only) French biodefense facility in confidence building measures (CBMs) submitted by France to the United Nations. According to the French government, parts of its former offensive biowarfare program (initiated after the Second World War) were performed at CEB.⁷ CEB research is not restricted to the biological field – it is also involved in chemical defense⁸ and other R & D projects for the French military. In 2001, its total annual turnover (not just biology) was €21 million, with a total staff of 201.⁹ In 2003, CEB’s microbiology department tendered new research equipment worth €3 million.¹⁰

Organisational

The principal CEB facilities are located 40km south of Paris in Vert-Le-Petit,¹¹ but there is a little known CEB branch on an air force base at Cazaux in Southern France,¹² where CEB conducts some of its biodefense work.

⁶ According to the French CBM 2002, the general objectives of its biodefense program are: “*Development of reactivities and equipment for detection with a view to develop quick detection field systems. Studies on applications of antibodies or genetic probes to biosensors. Research on biologic background in the environment. Studies on genetic diversity of agents.*”

⁷ French CBM 1992, Measure F, page 92.

⁸ CEB is also a ‘designated laboratory’ for chemical weapons related analysis for the Organisation for the Prohibition of Chemical Weapons (OPCW).

⁹ www.ixarm.com

¹⁰ According to a tender published on 23 April 2003 in the Supplement of the European Commission Official Journal.

¹¹ Address: BP No. 3, 91710 Vert-Le-Petit,

¹² Address: CEB – Section de mesures et d’études de décontamination (SMEDD), base aérienne 120, bâtiment PC, 33240 CAZAUX (department Gironde).

Biodefense at CEB in Vert-Le-Petit is performed in a variety of departments or laboratories, including a microbiology, a biotechnology and a biological effects unit. According to official government information, a staff of 31 (including 20 scientists) at CEB were involved in biodefense work in the year 2001; no maximum containments lab is available at CEB, but a 50 m² high security lab (BL3).¹³

The CEB facility in Cazaux has never been mentioned in official government publications in a biodefense context. According to its name – Section de mesures et d'études de décontamination¹⁴ (SMEDD) – it is tasked with decontamination experiments. Some of this work seems to be related to chemical weapons decontamination, as one source indicates two NATO tests on enzymatic nerve gas decontamination at CEB/Cazaux.¹⁵ SMEDD is located on the air force base BA120-Cazaux, which also houses the airforce security technicians training center (CFTSAA) of the French Army, which is tasked with NBC training and has a training range, mobile equipment for decontamination and, according to its website, a “gas training simulator”.¹⁶

In 2002, CEB invited a tender for the reconstruction of a “biology laboratory” for the SMEDD.¹⁷ Another tender, published on 5 August 2004, mentions also explicitly chemical and biological laboratories and air filtration systems at CEB-Cazaux. This clearly indicates that also biological defense work is or will be performed in Cazaux. It may be that this work includes outdoor testing, as there is little other reason for CEB maintaining a biology outlet some 600km away from its headquarters, on an air force base with a firing range adjacent to one of France’ biggest military testing grounds, the Centre d’Essais des Landes (CEL). It should be noted that CEL was created in 1963 to replace the former French military’s special devices test center CIEES.¹⁸

Projects

Considering that 20 scientists at CEB are involved in biodefense studies, scientific publications from CEB in the biological field are rare. This could reflect a rather low scientific standard, but more likely it is an indication of classified or non-public research. Only a minor part of the biodefense related research activities at CEB is accessible through open sources. In this analysis, we have only included more recent publications, mainly from the late 1990s through mid-2004:

- **Mobile BW laboratory:** In 2002/2003, CEB built a mobile lab such as those that were never found in Iraq. A public tender, first issued on 12 June 2002 and in a revised version on 5 February 2003, asked for the “realization of a BL3 lab, equipped, modular, self-contained and movable” for a total of €3 million.¹⁹ As this tender has never been withdrawn we assume that the mobile lab was built and is operational. Concurrently CRSSA published a tender for the purchase of an autoclave “intended to equip a BL-3 self-contained modular lab”.²⁰
- **Agent production:** According to the titles of two presentations given by CEB scientists, in the late 1990s CEB produced and purified “epsilon toxin”,²¹ presumably the lethal toxin produced by *Clostridium perfringens*. As CEB is rather secretive about this project and no other open source is

¹³ French CBM 2002.

¹⁴ SMEDD translates as *Decontamination Studies and Measurement Division*.

¹⁵ US CBDCOM 1998 Annual Report, page 38. URL: <http://mmrs.fema.gov/PublicDocs/cbdcom98.pdf>.

¹⁶ <http://www.defense.gouv.fr/air/orga/bases/ba120/unit1.html>. CFTSAA stands for Centre de formation des techniciens de sécurité de l’armée de l’air. For more information on NBC-related activities at BA120-Cazaux see also http://www.defense.gouv.fr/air/orga/ecoles/speciali/f_pompier.html.

¹⁷ As published in the official journal of the EC, the *Journal Officiel de la Communauté Européenne* (JOCE), 4 June 2002. This tender has been closed for unknown reasons in March 2003.

¹⁸ http://www.cheur.defense.gouv.fr/fr/histoire/guide_du_chercheur/source/site/monographies%20_des_etablissements_armement/direction_des_centres%20_expertises%20_essais/direction_des_centres_expertises_et_essais.html. CIEES stands for Centre Interarmées d’Essais d’Engins Spéciaux.

¹⁹ Journal Officiel de la Communauté Européenne (JOCE), 5 February 2003.

²⁰ According to the 22 May 2003 issue of the Bulletin Officiel des Annonces de Marchés Publics.

²¹ According to two presentations given by CEB scientists Didier Hilaire, as listed in the French CBM 1998, page 230, and Valérie Morineaux, as listed in French CBM 1999, page 49.

available about this toxin production, the aim, scope and result of this exercise remains unclear. Some additional information may be available from publications of the Institut Pasteur, *Unité Bactéries anaérobies et Toxines*,²² which cooperated with CEB on the production of clostridial toxins (see below section 2.6.2 on page 18).

- **Microencapsulation:** In 2004, CEB contracted a “*Study on microencapsulation technologies, adapted to microorganisms, and bioterrorist risks related to it*” to the University Paris-Sud. It remains unclear whether this is purely a desktop study to analyze possible threats from new microencapsulation studies, or whether actual experimental work – i.e. the development of microencapsulated microbes – is involved. The contract is worth nearly €150,000.²³
- **Strain collection:** CEB maintains extensive strain collections of potential BW agents, at least of anthrax and *Yersinia pestis*, the causative agent of plague. One research report states that most of some 180 strains of *Yersinia pestis* that were used in that experiment came from the CEB collection.²⁴ In another experiment, all 31 anthrax strains came from CEB.²⁵
- **Detection:** One focus of biological defense work at CEB appears to be research on the rapid detection of biological agents, including the development of specific antibodies²⁶ or genetic markers e.g. for anthrax²⁷, the development of a laser-based detector for bacteria²⁸, or the use of mass spectroscopy for biological detection.²⁹
- **Protection:** Little information is available about this section of CEB, but one job description indicates that new filter systems to protect against chemical and biological agents are developed at CEB, in cooperation with academic and industrial institutions.³⁰
- **Therapy:** Basic research into therapies against microbial infections is pursued,³¹ including studies on antibiotic susceptibilities of anthrax and plague.³² Also prophylaxis against influenza virus infections was developed at CEB in cooperation with academic scientists.³³

²² Anaerobic Bacteria and Toxin Unit. See also the glossary of French names on page 35.

²³ According to a the 31 January 2004 issue of the official French bulletin on public tenders, the *Bulletin Officiel des Annonces de Marchés Publics* (BOAMP). Contractor is CNRS 8612 at the Faculty of Pharmacy at the Université Paris Sud, 5 Rue Jean Baptiste Clément, 92296 Chatenay-Malabry.

²⁴ Pourcel C, André-Mazeaud F, Neubauer H, Ramisse F, Vergnaud G (2004) Tandem repeats analysis for the high resolution phylogenetic analysis of *Yersinia pestis*. *BMC Microbiology* 4:22.

²⁵ LeFlèche P, Hauck Y, Onteniente L, Prieur A, Denoed F, Ramisse V, Sylvestre P, Benson G, Ramisse F, Vergnaud G. (2001) A tandem repeats database for bacterial genomes : application to the genotyping of *Yersinia pestis* and *Bacillus anthracis*. *BMC Microbiology* 1:2.

²⁶ According to a CEB job advertisement (code IDFSTO7) at http://www.defense.gouv.fr/dga/fr/travailler/recrutement_volontaires/ile_de_france/fdp_idf_vhn_set.pdf, as of 8 August 2004.

²⁷ Ramisse, V, Patra, G, Vaissaire, J, Mock, M. (1999) The Ba813 chromosomal DNA sequence effectively traces the whole *Bacillus anthracis* community. *Journal of Applied Microbiology* 87:224-228.

Ramisse V, Patra G, Garrigue H, Guesdon JL, Mock M (1996) Identification and characterization of *Bacillus anthracis* by multiplex PCR analysis of sequences on plasmids pXO1 and pXO2 and chromosomal DNA. *FEMS Microbiol Lett.* 145:9-16.

²⁸ Morel S, Leone N, Adam P, Amouroux J (2003) Detection of bacteria by time-resolved laser-induced breakdown spectroscopy. *Appl Opt.*42:6184-6191.

²⁹ Wind FL, Stephan P, Tabet JC (2000) Biological detection using self-ionization optimization in an ion trap mass spectrometer. *Eur J Mass Spectrom* 6:415-419.

³⁰ http://www.defense.gouv.fr/dga/fr/travailler/recrutement_volontaires/ile_de_france/fdp_idf_vhn_set.pdf, as of 8 August 2004 (job ad code IDFST19).

³¹ DeHennezel L, Ramisse F, Binder P, Marchal G, Alonso JM (2001) Effective combination therapy for invasive pneumococcal pneumonia with ampicillin and intravenous immunoglobulins in a mouse model. *Antimicrobial Agents and Chemotherapy* 45:316-318.

³² Cavallo JD, Ramisse F, Girardet M, Vaissaire J, Mock M, Hernandez E (2002) Antibiotic susceptibilities of 96 isolates of *Bacillus anthracis* isolated in France between 1994 and 2000. *Antimicrob Agents Chemother* 46:2307-2309

Hernandez E, Girardet M, Ramisse F, Vidal D, Cavallo JD (2003) Antibiotic susceptibilities of 94 isolates of *Yersinia pestis* to 24 antimicrobial agents. *J Antimicrob Chemother* 52:1029-1031.

- **Basic genetic/genomic research** on plague and anthrax bacteria genomics³⁴ as well as on *B. thuringiensis* and *B. cereus*.³⁵ Based on several scientific publications it can be concluded that one research group at CEB is focussing entirely on genomic techniques, which are applied to a variety of organisms, including microorganisms such as *Legionella pneumophila*³⁶, *Burkholderia sp.*³⁷ and *Pseudomonas aeruginosa*³⁸ as well as humans.³⁹ One publication states that ‘work on the typing and molecular epidemiology of dangerous pathogens is supported by the French ministry of defense.’⁴⁰ A co-author of all these genomics-related publications is Gilles Vergnaud who is, according to the publications, affiliated with CEB as well as the University Paris-Sud. G. Vergnaud is also the corresponding author of a recent study on a correlation between chromosomal deletions and mental retardation in humans.⁴¹ Whether this work aims, in the long run, at selection brighter soldiers or brighter scientists, remains unclear.
- **Molecular modelling:** According to a CEB job advertisement, work on structure-activity relationship of enzymes is performed at CEB. No additional information on this unit is available, but according to the job ad, the research unit on molecular modelling seems to be well established and equipped. This unit may be predominantly working on chemical weapons issues, but – absent further information – may also work on toxins or bacterial pathogenicity factors in the course of so called ‘threat assessment’ work.⁴²

It should be noted that the biodefense work at CEB appears to be entirely devoted to bacteria. With the notable exception of influenza (see below section 2.6.4 on page 20), no work on viruses or prions is performed at CEB, according to the CBM 2002.

Some of the work at CEB was undertaken in cooperation with CRSSA (see below), other military institutions or civilian scientists.

³³ Ramiisse F, Deramoudt FX, Szatanik M, Bianchi A, Binder P, Hannoun C, Alonso JM (1998) Effective prophylaxis of influenza A virus pneumonia in mice by topical passive immunotherapy with polyvalent human immunoglobulins or F(ab')₂ fragments. *Clin Exp Immunol* 111:583-587.

Dreffier C, Ramiisse F, Dubernet C (2003) Pulmonary administration of IgG loaded liposomes for passive immunoprophylaxy. *Int J Pharm* 254:43-47.

³⁴ LeFlèche P, Hauck Y, Onteniente L, Prieur A, Denoëud F, Ramiisse V, Sylvestre P, Benson G, Ramiisse F, Vergnaud G. (2001) A tandem repeats database for bacterial genomes : application to the genotyping of *Yersinia pestis* and *Bacillus anthracis*. *BMC Microbiology* 1:2.

³⁵ Salamiitou S, Ramiisse F, Brehelin M, Bourguet D, Gilois N, Gominet M, Hernandez E, Lereclus D (2000) The pIcR regulon is involved in the opportunistic properties of *Bacillus thuringiensis* and *Bacillus cereus* in mice and insects. *Microbiology* 146:2825-2832.

³⁶ Pourcel C, Vidgop Y, Ramiisse F, Vergnaud G, Tram C (2003) Characterization of a tandem repeat polymorphism in *Legionella pneumophila* and its use for genotyping. *J Clin Microbiol* 41:1819-1826. F. Ramiisse and G. Vergnaud are CEB staff members, this work was also supported by two military grants (from DGA – Délégation Générale de l'Armement).

³⁷ Ramiisse V, Balandreau J, Thibault F, Vidal D, Vergnaud G, Normand P (2003) DNA-DNA hybridization study of *Burkholderia* species using genomic DNA macro-array analysis coupled to reverse genome probing. *Int J Syst Evol Microbiol* 53:739-746. This is a cooperative publication from CEB, CRSSA, and University of Lyon.

³⁸ Onteniente L, Brisse S, Tassios PT, Vergnaud G. (2003) Evaluation of the polymorphisms associated with tandem repeats for *Pseudomonas aeruginosa* strain typing. *J Clin Microbiol* 41:4991-4997.

³⁹ Denoëud F, Vergnaud G, Benson G (2003) Predicting human minisatellite polymorphism. *Genome Research* 13:856-867.

⁴⁰ Fabre M, Koeck JL, LeFlèche P, Simon F, Hervé V, Vergnaud G, Pourcel C (2004) High genetic diversity revealed by VNTR genotyping and analysis of hsp65 gene polymorphism in a large collection of ‘*Mycobacterium canettii*’ strains indicates that the *M. tuberculosis* complex is a recently emerged clone of ‘*M. canettii*’. *J Clin Microbiol* 42:3248-3255.

⁴¹ Giraueau F et al. (2001) Use of a set of highly polymorphic minisatellite probes for the identification of cryptic 1p36.3 deletions in a large collection of patients with idiopathic mental retardation. *J Med Genet* 38:121-125.

⁴² <http://www.defense.gouv.fr/dga/index.html> (recruitment web page of DGA on 5 August 2004).

The activities of one specific research group at CEB, the Biological Effects Unit (*Service Evaluation des Effets Biologiques*) remain obscure. Some toxin work, e.g. on the venom of the stonefish, is performed here that may be related to chemical warfare or, specifically, so called non-lethal chemical agents.⁴³ See chapter 4 for an in-depth discussion of this issue.

There are also clear indications from several job and internship advertisements that aerosol work is performed at CEB. The specific nature of this work, and whether it is at all connected to biodefense work, remains unclear. French aerobiology research issues are further discussed in section 2.6.1.

2.2. Centre de Recherches du Service de Santé des Armées (CRSSA)⁴⁴

Although CRSSA in La Tronche has only once been listed in French CBMs as a biodefense facility under CBM Measure A2,⁴⁵ it is clearly a key element of the French biodefense program, perhaps as important as CEB. According to an official French government website, CRSSA's key obligation is "research on the medical protection against effects of biological, chemical, nuclear or radiological weapons".⁴⁶

CRSSA and CEB are the only two laboratories that are tasked by the French civilian biodefense plan, the so called 'Plan Biotox', to test all biological samples thought to pose a potential threat. Within Plan Biotox, CRSSA is responsible for Lyons, Bordeaux, and Marseille *zones de défense* (defense sectors), which is essentially the whole south of France. Following the anthrax attacks in the USA 2001, CRSSA and CEB analyzed a deluge of hoax letters in France.⁴⁷ Recently, three CRSSA scientists co-authored – with scientists from other French biodefense institutions – a general introductory article on biological weapons defense.⁴⁸ CRSSA is also the official French reference lab for pox-viruses.⁴⁹ Taking this into consideration there is no reasonable doubt that CRSSA is a key biodefense facility of the French military and should have been mentioned as such by the French government in its annual CBMs submitted to the United Nations.

A major part of CRSSA biomedical research activities is related to BW defense work, although other medical research into infectious diseases/agents (such as HIV, Hepatitis) with no direct link to BW issues is also performed.

Organisational

The CRSSA laboratories are located in La Tronche near Grenoble.⁵⁰ According to an official website,⁵¹ it has a staff of 300 and operates in four departments, two of which are linked to BW defense:

⁴³ Breton P, Delamanche I, Buee J, Goudey-Perriere F, Perriere C (2002) Evidence for a neurotoxic activity in crude venom of the stonefish (*Synanceia verrucosa*). *J Nat Toxins* 11:305-313.

Deurveilher S, Delamanche IS, Hars B, Breton P, Hennevin E (1999) Chronic, low-level exposure to the cholinesterase inhibitor DFP. I. Time course of neurochemical changes in the rat pontomesencephalic tegmentum. *Pharmacol Biochem Behav* 64:95-103.

⁴⁴ Research Center of the Armed Forces' Health Service.

⁴⁵ CRSSA La Tronche was only listed and described in the CBM 2001 as a biodefense facility. In addition, it was mentioned in CBMs 1992 and 1998 under Measure A1 as a research center with high containment labs. There, it was also stated that some of the work of CRSSA is connected to biodefense, but the more detailed information required under CBM Measure A2 for biodefense facilities was only delivered in CBM 2001.

⁴⁶ <http://www.defense.gouv.fr/actualites/publications/defactu/n78/dossier.html>, as of 11 August 2004.

⁴⁷ Vidal D, Léveque F : The Biotox experience in fall of 2001. Abstract of a presentation at a symposium on 'Biology and Defense' in Strasbourg, October 2002. More at <http://www.cnrs.fr/cw/en/pres/compress/ScienceDefense/index.html>.

⁴⁸ Binder P, Attre O, Boutin JP, Cavallo JD, Debord T, Jouan A, Vidal D (2003) Medical management of biological warfare and bioterrorism: place of the immunoprevention and the immunotherapy. *Comp Immunol Microbiol Infect Dis* 26:401-421

⁴⁹ Utilisation du virus de la variole comme arme biologique. Report of the Institut de Veille Sanitaire, 25 October 2001, page 39. http://www.invs.sante.fr/publications/variole_2001/variole_vf.pdf.

⁵⁰ Address : 24 Avenue des Maquis du Grésivaudan, 38702 La Tronche. Key biodefense scientists at CRSSA are Alain Jouan, Daniel Garin and Dominique Vidal; key scientist in the department of neuropharmacology is Guy Lallement.

The *département de biologie des agents transmissibles* (infectious disease department) works on a variety of infectious diseases, including BW agents, and develops rapid diagnostic tools for viruses as well as new antibacterial and antiviral compounds. This department was listed in the French CBM 2001 as a biodefense institution. In 2000 it had a total staff of 36, including 16 scientists.⁵² It appears to be subdivided into several laboratories, including a virology lab⁵³ and a molecular biophysics lab.⁵⁴ The *département de toxicologie* (toxicology department) is dedicated to chemical defense including enzymatic degradation of nerve gases and the development of a neuroprotective substance, but it is also working on animal toxins and may thus be related to BW.

According to French CBMs, 290 m² of BL3 laboratory space are available at CRSSA/La Tronche, 200 of which are part of the *département de biologie des agents transmissibles* according to CBM 2001. An additional BL3 lab as well as an A2 (ABSL-2) animal testing facility at CRSSA was under construction in 2003/2004, according to public tenders.⁵⁵ In 1992, 42 m² of BL4 lab were projected to be available by 1993, but later CBMs did not mention this maximum containment facility.

Projects

The virology lab of CRSSA is working on a broad range of pathogenic viruses, including poxviruses, hantavirus and flaviviruses. Some projects are explicitly related to biodefense, while others are more focused on other natural diseases.

- **Smallpox research** : As mentioned above, CRSSA is the French reference laboratory for poxviruses. Research on vaccinia virus has been undertaken at CRSSA to develop new antiviral compounds to treat smallpox.⁵⁶
- **Detection**: A variety of scientific publications from CRSSA scientists focus on the rapid detection of pathogenic viruses, including hantavirus,⁵⁷ Rift Valley Fever virus,⁵⁸ or flavivirus⁵⁹ as well as the plague causing bacterium *Yersinia pestis*⁶⁰ and Burkholderia species.⁶¹

⁵¹ http://www.defense.gouv.fr/sante/sante_vue10a1.html, as of 11 August 2004.

⁵² French CBM 2001, page 208.

⁵³ Head: D. Garin; interview with D. Garin: Le CRSSA et Roche Diagnostics répondent ensemble aux besoins du plan biotox. Journal d'Information Biomédicale Vol. 65, May 2003, p. 6.

⁵⁴ J.C. Debouzy ; <http://master-ism.imag.fr/listelaboimag.pdf>

⁵⁵ The tender for the BL 3 lab was published in the Journal Officiel de la Communauté Européenne (JOCE), 7 June 2002. A year later, CRSSA published in the 30 May 2003 issue of JOCE that the company Labover, Montpellier, supplied the lab. The A2 animal facility was published in the 27 december 2003 issue of the Bulletin Officiel des Annonces de Marchés Publics (BOAMP).

⁵⁶ Scaramozzino N, Sanz G, Crance JM, Sapparbaev M, Drillien R, Laval J, Kavli B, Garin D (2003) Characterisation of the substrate specificity of homogenous vaccinia virus uracil-DNA glycosylase. Nucleic Acid Research 31:4950-4957.

⁵⁷ Garin D, Peyrefitte C, Crance JM, LeFaou A, Jouan A, Bouloy M (2001) Highly sensitive taqman PCR detection of Puumala hantavirus. Microbes Infect 3:739-745.

⁵⁸ Garcia S, Crance JM, Billecoq A, Peinnequin A, Jouan A, Bouloy M, Garin D (2001) Quantitative real-time PCR detection of Rift Valley fever virus and its applications to evaluation of antiviral compounds. J Clin Microbiol 39:4456-4461.

⁵⁹ Scaramozzino N, Crance JM, Jouan A, DeBriel DA, Stoll F, Garin D (2001) Comparison of Flavivirus Universal Primer Pairs and Development of a Rapid, Highly Sensitive Heminested Reverse Transcription-PCR Assay for Detection of Flaviviruses Targeted to a Conserved Region of the NS5 Gene Sequences. J Clin Microbiol 39:1922-1927

⁶⁰ Thullier P, Guglielmo V, Rajerison M, Chanteau S (2003) Short report: Serodiagnosis of plague in humans and rats using a rapid test. Am J Trop Med Hyg 69:450-451.

⁶¹ Sprague LD, Zysk G, Hagen RM, Meyer H, Ellis J, Anuntagool N, Gauthier Y, Neubauer H (2002) A possible pitfall in the identification of Burkholderia mallei using molecular identification systems based on the sequence of the flagellin fliC gene. FEMS Immunol Med Microbiol 34:231-236.

Hagen RM, Gauthier YP, Sprague LD, Vidal DR, Zysk G, Finke EJ, Neubauer (2002) Strategies for PCR based detection of Burkholderia pseudomallei DNA in paraffin wax embedded tissues. J Clin Pathol: Mol Pathol 55:398-400.

- **Treatment:** Basic research aiming at developing specific compounds to stop dengue virus infections was performed in a collaborative project of CRSSA and the Institut Pasteur in Paris.⁶² A variety of basic research projects in the area of immunology are also performed at CRSSA.⁶³
- **Decontamination** methods to inactivate anthrax spores have recently been investigated at CRSSA.⁶⁴

A special area of research at CRSSA is related to animal venoms and toxins. The department of neuropharmacology at CRSSA works predominantly (and publishes abundantly) on chemical defense issues and classical nerve agents. But it is also undertaking biodefense work related to animal toxins. We identified publications on the mode of action of the rattlesnake poison crotoxin⁶⁵ and on the venom of the green mamba, called dendrotoxin.⁶⁶ Both venoms are neurotoxins. Another project, funded by the French Ministry of Defence with grant number 93/3, 14/96, focuses on the snake venom paradoxin.⁶⁷ Interestingly, the snake producing this toxin (*Oxyuranus microlepidotus*, 'taipan') is only living in areas of Australia, a place where a deployment of the French Army is rather unlikely. Obviously, this work does not aim to protect French soldiers from snakebites, rather it is clearly related to chemical and biological weapons. The snake is considered to be the most venomous landliving snake in the world. Toxin research in France is further discussed in section 2.6.3.

2.3. Hôpital d'instruction des armées Bégin (HIA Bégin)⁶⁸

In this army hospital near Paris⁶⁹, one research group is working on biodefense. According to an official website of the French defense forces, HIA Bégin's medical biology lab cooperates with CRSSA in research projects on pulmonary anthrax.⁷⁰ Several publications from the past 2 years suggest that the *Laboratoire de Biologie Médicale* of the HIA Bégin has recently become involved in research related to the treatment of typical BW agents. Most of these publications were co-authored with CEB and/or CRSSA staff. In addition to a general introductory article on biological weapons defense,⁷¹ HIA Bégin

⁶² Thullier P, Demangel C, Bedouelle H, Megret F, Jouan A, Deubel V, Mazié JC, Lafaye P (2001) Mapping of a dengue virus neutralizing epitope critical for the infectivity of all serotypes: insight into the neutralization mechanism. *J Gen Virol* 82:1885-1892.

⁶³ Pollet S, Bottex-Gauthier C, Li M, Potier P, Favier A, Vidal D (2002) Insight into some of the signaling pathways triggered by a lipid immunomodulator. *Immunopharmacol Immunotoxicol* 24:527-546.

Tournier JN, Hellmann AQ, Lesca G, Jouan A, Drouet E, Mathieu J (2003) Fever-like thermal conditions regulate the activation of maturing dendritic cells. *J Leukocyte Biol* 73:493-501.

⁶⁴ Clery-Barraud C, Gaubert A, Masson P, Vidal D (2004) Combined Effects of High Hydrostatic Pressure and Temperature for Inactivation of *Bacillus anthracis* Spores. *Appl Environ Microbiol* 70:635-637.

⁶⁵ Dorandeu F, Hesters R, Girard F, Four E, Foquin A, Bon C, Lallement G, Faure G (2002) Inhibition of crotoxin phospholipase A2 activity by manoalide associated with inactivation of crotoxin toxicity and dissociation of the heterodimeric neurotoxic complex. *Biochem Pharmacol* 63:755-761.

⁶⁶ Dorandeu F, Wetherell J, Pernot-Marino I, Tattersall JEH, Fosbraey P, Lallement G (1998) Effects of excitatory amino acid antagonists on dendrotoxin-induced increases in neurotransmitter release and epileptiform bursting in rat hippocampus in vitro. *J Neurosci Res* 48:499-506.

⁶⁷ Dorandeu F, Antier D, Pernot-Marino I, Lapeyre P, Lallement G (1998) Venom phospholipase A2-induced impairment of glutamate uptake: an indirect and nonselective effect related to phospholipid hydrolysis. *J Neurosci Res* 51:349-359.

⁶⁸ *Bégin Military Teaching Hospital*

⁶⁹ Address: Hôpital d'instruction des armées Bégin, 69 Avenue de Paris, 94163 Saint Mandé. Researchers affiliated with the HIA Bégin and working on biodefense issues include Eric Hernandez, Jean-Didier Cavallo, M.onique Girardet, and Thierry Debord.

⁷⁰ <http://www.defense.gouv.fr/actualites/publications/defactu/n78/dossier.html>.

⁷¹ Binder P, Attre O, Boutin JP, Cavallo JD, Debord T, Jouan A, Vidal D (2003) Medical management of biological warfare and bioterrorism: place of the immunoprevention and the immunotherapy. *Comp Immunol Microbiol Infect Dis* 26:401-421

staff co-authored articles on anthrax⁷² and plague antibiotic resistance.⁷³ They are also involved in a CEB project on influenza treatment.⁷⁴

2.4. Institut de médecine tropicale du service de santé des armées (IMTSSA)⁷⁵

The IMTSSA near Marseille⁷⁶ is predominantly working on tropical diseases which pose a natural threat for French soldiers deployed abroad.⁷⁷ Most areas of research at IMTSSA are probably not connected to biodefense work. No publicly available information indicates that IMTSSA is engaged in biodefense work, but according to French CBMs submitted to the United Nations IMTSSA is the relevant facility for biodefense activities relating to flaviviruses (e.g. Dengue fever) in France. The 1998 CBM mentions IMTSSA as working on the protection against and detection of flaviviruses, both in the context of natural outbreaks and use as BW, and the 1999 CBM lists many IMTSSA publications. Recently, an IMTSSA scientist co-authored – with scientists from other French biodefense institutions – a general introductory article on biological weapons defense.⁷⁸ According to one official website, IMTSSA is cooperating with CRSSA on “*emerging biological risks*”.⁷⁹

2.5. Biodefense contractors

A significant part of French biodefense R & D is performed in civilian research institutions. According to the French CBM 2002, 60% of the biodefense budget is spent on contractors.⁸⁰ The French military uses a broad range of instruments to finance military oriented biodefense work in civilian institutions. These include formal framework agreements between the national research organisation CNRS and the Délégation Générale de l'Armement (DGA),⁸¹ research grants from DGA to specific institutions, scholarships from DGA to individual scientists, or research cooperation between one of the abovementioned military biodefense institutions and civilian researchers. In the following section, all institutions and individuals are listed that, according to publicly available documentation, cooperated with military research institutions or received money from DGA for biodefense research. It should be noted that this information may not be up-to-date, as some sources are several years old and research grants, scholarships or cooperation agreements may have run out in the meantime.

⁷² Cavallo JD, Ramisse F, Girardet M, Vaissaire J, Mock M, Hernandez E (2002) Antibiotic susceptibilities of 96 isolates of *Bacillus anthracis* isolated in France between 1994 and 2000. *Antimicrob Agents Chemother* 46:2307-2309.

⁷³ Hernandez E, Girardet M, Ramisse F, Vidal D, Cavallo JD (2003) Antibiotic susceptibilities of 94 isolates of *Yersinia pestis* to 24 antimicrobial agents. *J Antimicrob Chemother* 52:1029-1031.

⁷⁴ Hernandez E, Ramisse F, Lhonneux A, Noury J, Bazin H, Cavallo JD (2003) Compared protective effect of nasal immunoprophylaxis using a new human monoclonal IgM antibody, human polyclonal antibodies, F(ab')₂, amantadine, and zanamivir for prophylaxis of influenza A virus pneumonia in mice. *Mil Med* 168:246-251

⁷⁵ Institute for Tropical Medicine of the Armed Forces' Health Service.

⁷⁶ Address: BP 46, Parc du Pharo, avenue Pasteur, 13998 Marseille Armées

⁷⁷ <http://www.defense.gouv.fr/actualites/publications/defactu/n78/dossier.html>.

⁷⁸ Binder P, Attre O, Boutin JP, Cavallo JD, Debord T, Jouan A, Vidal D (2003) Medical management of biological warfare and bioterrorism: place of the immunoprevention and the immunotherapy. *Comp Immunol Microbiol Infect Dis* 26:401-421

⁷⁹ <http://www.defense.gouv.fr/actualites/publications/defactu/n78/dossier.html>.

⁸⁰ It should be noted though that the budgetary information in the CBMs appear to be not very reliable (see page 6).

⁸¹ DGA translates as *General Armament Authority*. It is the department of the Ministry of Defence that is responsible for the development and procurement of military materiel in France. It also oversees CEB. The agreement with CNRS was signed in 2001 and includes specifically research on ‘*biological threats*’. It was online available at www.defense.gouv.fr/dga/fr/pdef/dp_recherche1.pdf but was recently removed from the DGA-website.

2.5.1. *Commissariat à l'Énergie Atomique (CEA)*

The French nuclear energy commission CEA is a state owned research giant with a budget of over € 2.8 billion in 2003, nearly half of which comes from the Ministry of Defence. CEA maintains a huge life sciences division (CEA-SDV). In the department on protein engineering and research (*Département d'Ingénierie et d'Études des Protéines*) in Gif-sur-Yvette, some 25km southwest of Paris, one research team is explicitly working on anthrax and botulinum toxins in the context of biological defense.⁸² One project related to possible vaccinations against botulinum toxin A was conducted in cooperation with the Institut Pasteur (Dr. Popoff, see below).⁸³ The *Département d'Ingénierie et d'Études des Protéines* of CEA-SDV is also intensively working on a variety of other toxins and animal venoms.

CEA is also involved in biodefense work for CEB. In early 2004 they received a contract from CEB for a “*Study of a nucleic acid hybridization device*” for more than €1.3 million.⁸⁴

2.5.2. *Institut Pasteur, Paris*

The Institut Pasteur in Paris⁸⁵ is one of the cradles of microbiology and a worldwide center of microbiological research. Formally, it is a private non-profit foundation.⁸⁶

Considering its expertise in microbiology and infectious diseases, it is not surprising that at least two departments of the Institut Pasteur have been or still are involved in biodefense related work:

- The *Unité Toxines et Pathogénie Bactériennes* (head: Michèle Mock) is specialised on anthrax.⁸⁷ A variety of publications on anthrax were co-published with CEB personnel,⁸⁸ indicating a close cooperation of the Institute Pasteur and the Armed Forces on biodefense. Whether or not there is a formal contract between the Ministry of Defense and the Institute Pasteur remains unclear. One staff member (Guy Patra) working on the molecular characterization of anthrax strains was financed through a DGA grant (no. 96/44133).⁸⁹
- The *Unité Bactéries anaérobies et Toxines* (head: Michel R. Popoff) works on botulinum and other clostridial toxins. Recent work on *Clostridium perfringens* toxin at this lab was funded by DGA⁹⁰ and two scientists received, according to the unit's 2003 annual report, DGA grants.⁹¹ In this institute's 1998 annual report, the work on clostridial toxins is explicitly discussed in the context of biological defense and it is stated that “*in cooperation with CEB, we study the expression*

⁸² http://www-dsv.cea.fr/content/cea/d_dep/d_diep/d_lsp/cristallo/toxines-bacteriennes.htm, as of 12 August 2004.

⁸³ Tavallaie m, Chenal A, Gillet D, Pereira Y, Manich M, Gibert M, Raffestin S, Popoff MR, Marvaud JC (2004) Interaction between the two subdomains of the C-terminal part of the botulinum neurotoxin A is essential for the generation of protective antibodies. *FEBS Letters* 572:299-306.

⁸⁴ According to the 9 February 2004 issue of the Bulletin Officiel des Annonces de Marchés Publics (BOAMP).

⁸⁵ Address: 28 rue du Docteur Roux, 75724 Paris.

⁸⁶ More at <http://www.pasteur.fr/english.html>.

⁸⁷ For example: Fouet A, Smith KL, Keys C, Vaissaire J, LeDoujet C, Levy M, Mock M, Keim P (2002) Diversity among French *Bacillus anthracis* isolates. *J Clin Microbiol* 40:4732-4734.

⁸⁸ Ramisse, V., Patra, G., Vaissaire, J. & Mock, M. (1999) The Ba813 chromosomal DNA sequence effectively traces the whole *Bacillus anthracis* community. *Journal of Applied Microbiology* 87:224-228.

Cavallo JD, Ramisse F, Girardet M, Vaissaire J, Mock M, Hernandez E (2002) Antibiotic susceptibilities of 96 isolates of *Bacillus anthracis* isolated in France between 1994 and 2000. *Antimicrob Agents Chemotherap* 46:2307-2309.

⁸⁹ Patra G, Vaissaire J, Weber-Levy M, LeDoujet C, Mock M (1998) Molecular characterization of *Bacillus* strains involved in outbreaks of anthrax in France in 1997. *J Clin Microbiol* 36:3412-3414.

⁹⁰ As stated in the following publication: Marvaud JC, Stiles BG, Chenal A, Gillet D, Gibert M, Smith LA, Popoff MR (2002) *Clostridium perfringens* iota toxin. *J Biol Chem* 277:43659-43666.

⁹¹ <http://www.pasteur.fr/recherche/RAR/RAR2003/Batox-en.html>

and the regulation of epsilon toxin⁹² (more about this particular work see below section 2.6.2 on page 18).

A variety of other research departments of the Institut Pasteur received DGA grants or cooperated with military institutions, but these focused on organisms other than the classical BW agents. These departments include the *Laboratoire des fièvres hémorragiques virales*,⁹³ the *Unité des Interactions Bactéries-Cellules* (work on Rickettsia⁹⁴ and Listeria⁹⁵), the *Unité génétique moléculaire des Bunyaviridés* (work on Rift Valley fever⁹⁶), the *Unité des Neisseria* (work on new antibacterial therapies⁹⁷) as well as the *laboratoire d'ingénierie des anticorps* and the *Unité de Biochimie* (work on dengue fever⁹⁸).

2.5.3. Université Paris Sud

As described in the CEB section, Dr. Gilles Vergnaud is affiliated with both institutions, CEB and the *Université Paris Sud, Institut de Génétique et Microbiologie*. Work on plague and anthrax bacteria genomics, conducted with CEB, was supported by two grants from the DGA.⁹⁹

The research group CNRS 8612 at the Faculty of Pharmacy of the *Université Paris Sud* recently received a contract from CEB to study microencapsulation techniques.

2.5.4. Institut Gustave Roussy and Etablissement Français du Sang-Alsace

Scientists from the *Groupe Réparation de l'ADN*¹⁰⁰ (UMR 8113) of the Institut Gustave Roussy in Villejuif near Paris and from the *Etablissement Français du Sang-Alsace* in Strasbourg cooperated with CRSSA in a project on smallpox treatment which was funded by the French military.¹⁰¹

2.5.5. Centre National d'Etudes Vétérinaires et Alimentaires (CNEVA)

A scientist from the *Unité des Zoonoses Bactériennes* from CNEVA in Maisons-Alfort cooperated with CEB on anthrax detection¹⁰² and anthrax antibiotic susceptibility.¹⁰³

2.5.6. Ecole Nationale Supérieure de Chimie de Paris

A scientist from the *Laboratoire de Génie des Procédés Plasmas et Traitement de Surfaces*¹⁰⁴ at this institutions cooperated with CEB scientists in the development of a laser-based detector for bacteria¹⁰⁵,

⁹² See www.pasteur.fr/recherche/RAR/RAR1998/Anaer.html.

⁹³ According to the French CBM 1992.

⁹⁴ Gouin E, Egile C, Dehoux P, Villiers V, Adams J, Gertler F, Li R, Cossart P (2004) The RickA protein of Rickettsia conorii activates the Arp2/3 complex. *Nature* 427:457-461.

⁹⁵ Braun L, Ghebrehiwet B, Cossart P (2000) gC1q-R/p32, a C1q-binding protein, is a receptor for the InIB invasion protein of Listeria monocytogenes. *EMBO journal* 7:1458-1466.

⁹⁶ <http://www.pasteur.fr/recherche/RAR/RAR2002/Gmbun.html>.

⁹⁷ See footnote 31.

⁹⁸ Thullier P, Demangel C, Bedouelle H, Megret F, Jouan A, Deubel V, Mazié JC, Lafaye P (2001) Mapping of a dengue virus neutralizing epitope critical for the infectivity of all serotypes: insight into the neutralization mechanism. *J Gen Virol* 82:1885-1892.

⁹⁹ See footnote 34.

¹⁰⁰ DNA Repair Group.

¹⁰¹ Scaramozzino N, Sanz G, Crance JM, Saparbaev M, Drillien R, Laval J, Kavli B, Garin D (2003) Characterisation of the substrate specificity of homogenous vaccinia virus uracil-DANN glycosylase. *Nucleic Acid Research* 31:4950-4957.

¹⁰² See footnote 27.

¹⁰³ See footnote 32.

¹⁰⁴ Plasma devices and surface treatment engineering laboratory.

¹⁰⁵ See footnote 28.

2.5.7. Université de la Méditerranée, Faculty of Medicine

The CNRS research group *Unité des Rickettsies* of the *Université de la Méditerranée*¹⁰⁶ is working on anthrax infections in the context of biodefense.¹⁰⁷ It also received a DGA grant for basic research on *Rickettsia*.¹⁰⁸

2.5.8. Centre Hospitalier Régional Universitaire de Lille

The *Laboratoire de Bactériologie-Hygiène* of this university hospital in the town of Lille developed a rapid diagnostic test for plague explicitly in response to possible bioterrorist attacks.¹⁰⁹

2.6. Special aspects of French biodefense R & D

2.6.1. Aerosol research

The most effective way to disseminate biological agents for hostile purposes is by aerosol, i.e. their fine dispersion in the air. Accordingly, aerobiology is often an integral part of biodefense efforts. Even for defensive purposes, some capability to produce bioaerosols has to be developed: To test detectors or the efficacy of vaccines against airborne particles, BW agents or simulants must be aerosolized. Different from offensive programs, however, indoor bench-scale testing should be sufficient for defensive purposes.

It remains unclear if outdoor aerosol testing is performed by the French biodefense program. According to all French CBMs available to us, no outdoor studies are performed at CEB, but no information is given for other facilities or for the CEB outlet in Cazaux.

There is no doubt that at least some aerosol work is performed at CEB. Internships for aerosol studies have been advertised,¹¹⁰ a master thesis on aerosol detection was performed at CEB,¹¹¹ and a scientific course on aerosols at the Paris University involved CEB scientists.¹¹² According to a job advertisement for a specialist in chemical and biological detection, published by CEB, aerosol detection is one area of research at CEB.¹¹³ A reference given in the 1992 CBM indicates that an aerosol chamber was built for biodefense purposes.¹¹⁴

A European patent from the early 1990s shows that the French military was – at least at that time – actively involved in the development of large scale aerosol generation devices. EP 0 446 134 A1, a patent filed in 1991 by the DGA, is about a “*device generating a monodispersal aerosol with a high flow*”. According to the patent, the aerosol generator is for “*applications in experimental research and agriculture*”. As the patent does not mention specifically any biological material, it is unclear whether or not it is in any way related to biological defense work.

¹⁰⁶ Adress: Université de la Méditerranée - UMR 6020 - IFR Pathologies Transmissibles & Pathologies Infectieuses Tropicales, 27 boulevard Jean Moulin, 13385 Marseille Cedex 05. Head : Prof. Didier Raoult.

¹⁰⁷ Final presentation by Mme. Berger on 8 October 2002 at the symposium on ‘Biology and Defense’ in Strasbourg, October 2002. More at <http://www.cnrs.fr/cw/en/pres/compress/ScienceDefense/index.html>.

¹⁰⁸ <http://www.timone.univ-mrs.fr/medecine/recherche/crecherche.html>.

¹⁰⁹ Loiez C, Herwegh S, Wallet F, Armand S, Guinet F, Courcol RJ (2003) Detection of *Yersinia pestis* in sputum by real-time PCR. *J Clin Microbiol* 41:4873-4875.

¹¹⁰ http://www.defense.gouv.fr/jeunes/stage/dga_04.pdf, page 10.

¹¹¹ By Ms. Audrey Soric on ‘time detection and identification of aerosols by laser induced breakdown spectroscopy (TRELIBS), in the department of Mr. P. Adam. <http://www.upmc.jussieu.fr/Fdoct/CAPICAPI/anglais/master20022003.htm>.

¹¹² At Université Paris XII, http://www.univ-paris12.fr/fst/formations/formation_initiale/3eme_cycle/dess/dess_saga.htm.

¹¹³ http://www.defense.gouv.fr/dga/fr/travailler/recrutement_volontaires/ile_de_france/fdp_idf_vhn_set.pdf, as of 8 August 2004 (job ad code IDFSTO6).

¹¹⁴ Labarre A, Silvestre P, Sarciaux JY, Bouteville G, Binder P (1991) Réalisation et validation d’une enceinte confinée pour l’étude “in-vivo” et “in-vitro” d’aérosols microbiologiques. Presentation on the 8th aerosol congress in Paris, November 1991.

Another patent, registered in France in 1990 and assigned to the DGA, covers a “*Device generating aerosols with a rotating disc.*”¹¹⁵ It was registered on 03/08/90 (nr 90 02914).

It might well be that some of these aerosol studies are performed in the context of chemical – and not biological – defense. The specific nature of aerosol research at CEB, and whether aerosol work is performed elsewhere in the French military, remains unclear. No scientific publications from French military aerosol scientists are available. But the development of a large scale aerosol generator 15 years ago, the CEB outlet on a large airforce base in Southern France, and the secrecy of the French government with regard to aerosol research do not promote confidence in the French biodefense program. A clear explanation of current activities and commitment to transparency about the purpose and scale of its aerobiology work is warranted, as is a restriction of active BW agent aerosolization to bench-scale experiments.

2.6.2. Genetic engineering – toxin production

New biomedical technologies can contribute to offensive BW activities in many ways. Classical bio-warfare agents such as anthrax or plague may be made more efficient weapons, barriers to access to agents such as smallpox and Ebola are being lowered, and completely new types of weapons are becoming possible.

It is thus especially important to ensure the fullest transparency in the area of genetic engineering. Any use or construction of novel biological agents with an enhanced offensive potential, such as treatment resistance or enhanced environmental stability should be off limits for any biodefense program.

Only very limited information is available about genetic engineering experiments in the French biodefense program. Some evidence suggests that at least two different BW agents were produced by the means of genetic engineering by CEB researchers in the 1990s.

In 1991, CEB scientists presented a pilot scale production of a snake toxin at a US biodefense conference. According to this presentation, the gene for Erabutoxin A, from an Asian sea snake, was introduced into *E. coli* bacteria to produce this toxin on a pilot scale.¹¹⁶ While this appears to be a rather offensive application, the experiment is explained in the French CBM 1992 as an example for ‘threat assessment’ work.

According to the titles of two presentations given by CEB scientists, CEB engaged in the late 1990s in the production and purification of “epsilon toxin”,¹¹⁷ presumably the lethal toxin from *Clostridium perfringens*. CEB is rather secretive about this project, but additional information is available from publications of the Institut Pasteur, *Unité Bactéries anaérobies et Toxines*, which cooperated with CEB on the production of clostridial toxins.

This unit’s annual report 1998 stated unambiguously: “*The epsilon toxin could be used as a biological weapon, and the Armed Forces’ Health Service is interested in this toxin. Pharmacology studies on this toxin have been undertaken at the Centre d’Etudes du Bouchet (CEB). In collaboration with the CEB, we study the expression and the regulation of epsilon toxin (...)*” “*We have transferred this gene [for epsilon toxin] (...) into different vectors E.coli-C.perfringens (...) and we have transformed non-toxic E.coli and C.perfringens strains. We have obtained a strain producing about 10 times more epsilon toxin than the wild strain.*”¹¹⁸

Thus, in cooperation with CEB the gene for a potential BW agent was inserted into non-pathogenic strains to produce 10 times as much of the agent as natural strains. In another study mentioned in the

¹¹⁵ French patent # 90 02914.

¹¹⁶ P Silvestre, M A Labarre and P Binder, "Expression of erabutoxin-a gene in Escherichia coli cultivated in pilot fermenter", US Army CRDEC Scientific Conference on Chemical Defense Research, 19-22 November 1991, abstract book, p 27.

¹¹⁷ According to two presentations given by CEB scientists Didier Hilaire, as listed in the French CBM 1998, page 230, and Valérie Morineaux, as listed in French CBM 1999, page 49.

¹¹⁸ www.pasteur.fr/recherche/RAR/RAR1998/Anaer.html.

same annual report, the beta-2 toxin from *C. perfringens* was genetically engineered into another strain and produced with a 40-80 times higher concentration than the wild strain. In the same laboratory studies on (and gene transfer with) botulinum toxin genes were also performed, by a visiting scientist from the US Army center for medical biodefense, USAMRIID.

While this type of experiment might be explained as being defensive, its offensive applications are obvious and raise concern. Considering the secrecy of CEB around these types of experiments – after all we only know about them through an annual report from 1998 accidentally left over on the website of an academic institution – many questions with regard to the general purpose of the experiments, its current status, its possible connection to the pilot scale production capability at CEB, and possible additional experiments with other toxins remain open.

2.6.3. *Animal toxin research in France*

One specific aspect of French biodefense activities that is worth mentioning is its rather strong emphasis on snake, fish and other animal venoms, as well as fungal toxins.

France has a long colonial history, and it still retains territories in tropical regions. France continues to be regularly involved in military missions in tropical areas, particularly in its former colonies in Africa. Hence it is not surprising that animal venom research is of interest to French researchers, in academia as well as in the military research community, and it can be assumed that some of this research is related to treatment and prevention of natural poisoning, rather than BW incidents.

A variety of factors, however, indicate that there is also a specific biodefense component to this venom research:

- CEB, which is a dedicated biodefense research facility, published work on fish venoms¹¹⁹ as well as on a fungal toxin.¹²⁰
- At least one CRSSA project focussed on the venom of a snake that is restricted to Australia and thus an unlikely threat to French soldiers¹²¹ (see chapter 2.2 on page 12).
- Two papers on green mamba toxin were co-authored by CRSSA staff and the British biodefense unit at Porton Down.¹²²
- Venom research was repeatedly mentioned in French CBMs, e.g. as an example for threat assessment experiments in 1992, or as examples for international cooperation in 1995 and 1996.¹²³

The overall objective of the venom research remains unclear. Most of the investigated toxins are neurotoxins, and a variety of neurological studies were performed, including the analysis of neurotoxic effects of crude venoms,¹²⁴ basic research on toxicity mechanisms,¹²⁵ effects of fish toxin on brain

¹¹⁹ Breton P, Delamanche I, Buee J, Goudey-Perriere F, Perriere C (2002) Evidence for a neurotoxic activity in crude venom of the stonefish (*Synanceia verrucosa*). *J Nat Toxins* 11:305-313.

¹²⁰ Breton P, Bizot JC, Buee J, DeLaManche I (1998) Brain neurotoxicity of penitrem A: electrophysiological, behavioural and histopathological study. *Toxicon* 36:645-655.

¹²¹ Dorandeu F, Antier D, Pernot-Marino I, Lapeyre P, Lallement G (1998) Venom phospholipase A2-induced impairment of glutamate uptake: an indirect and nonselective effect related to phospholipid hydrolysis. *J Neurosci Res* 51:349-359.

¹²² Dorandeu F, Wetherell J, Pernot-Marino I, Tattersall JEH, Fosbraey P, Lallement G (1998) Effects of excitatory amino acid antagonists on dendrotoxin-induced increases in neurotransmitter release and epileptiform bursting in rat hippocampus in vitro. *J Neurosci Res* 48:499-506.
Lallement G, Fosbraey P, Baille-Le-Crom V, Tattersall JE, Blanchet G, Wetherell JR, Rice P, Passingham SL, Sentenac-Roumanou H (1995) Compared toxicity of the potassium channel blockers, apamin and dendrotoxin. *Toxicology* 104:47-52.

¹²³ In the CBMs under Measure D, countries should declare activities for the active promotion of contacts with scientists in other countries. France listed in these two years some scientific conferences as well as several foreign students that worked in French laboratories. Nearly all of these entries related to neurobiology, animal venoms, and toxins.

¹²⁴ See footnote 119

¹²⁵ See, for example, footnotes 65, 121 and 122.

activity¹²⁶, and behavioural effects of mycotoxins.¹²⁷ A broad range of snake toxins was investigated at CRSSA, including dendrotoxin, paradoxin, crotoxin, and ammodytoxin.¹²⁸

It can be assumed that the published research is only part of military venom research in France and that a variety of other, unknown projects were and still are performed at CEB and CRSSA. Considering the broad range of toxins mentioned in available publications and the many different staff members from CEB and CRSSA that co-authored these publications, it is extremely unlikely that such a work force and broad expertise has limited itself to the studies reflected in the handful of publications that are publicly available.

This toxin research corresponds with work performed at CRSSA more than a decade ago, which focused on fungal toxins such as trichothecenes and Fusarium T-2 toxin.¹²⁹ In 1994, a comprehensive paper on ‘facts on venomous animals’ such as snakes, scorpions and cone snails was published by a CRSSA scientist.¹³⁰

One hint towards the nature of possible additional projects may be the pilot scale production of the snake toxin Erabutoxin A (see section 2.6.2). It is not known to us whether or not CEB still maintains the capability for the pilot scale production of biological agents, and whether or not they do work on the production of animal venoms. As CEB scientists gave presentations in the late 1990s on the production of bacterial toxins (see above in chapter 2.1), it seems to be likely that biological production capability is available at CEB.

It should also be noted that the CEB animal toxin research group is also engaged in non-lethal chemical agents research (see chapter 4), but it remains unclear whether the neurotoxicity aspect of the venom research is in any way related to the development of neuroactive compounds.

A variety of academic institutions in France also specialize in neurotoxic animal venoms. Most notably, the *Commissariat à l’Energie Atomique* (CEA), a state-run research institute with a long history of nuclear weapons research (see section 2.5.1), has strong expertise in venoms and their chemical synthesis¹³¹ Apart from some work on microbial toxins, however, no visible connection between this venom research and the French biodefense activities exists.

2.6.4. *Influenza research*

It is notable that one constant element of French biodefense work has been and remains research on influenza. Influenza is the only virus CEB is working on. Research on airborne influenza infections was published as early as 1974 by scientists from the French military health service.¹³² More recently,

¹²⁶ Breton P, Delamanche I, Buee J, Goudey-Perrere F, Perriere C (1999) Anomalies électroencéphalographiques chez le rat après administration de venin de poisson-pierre (*Synanceia verrucosa*). Abstract of a poster at the Colloque SFET 1999. <http://www.sfet.asso.fr/resumbreton.htm>.

¹²⁷ Deschaux O, Bizot JC (1997) Effects of penitrem A on rat’s performances in passive avoidance and Morris water maze test. *Mycopathologia* 138:99-104.

Breton P, Bizot JC, Buee J, DeLaManche I (1998) Brain neurotoxicity of penitrem A: electrophysiological, behavioural and histopathological study. *Toxicon* 36:645-655.

¹²⁸ Dorandeu F, Pernot-Marino I, Veyret J, Perrichon C, Lallement G (1998) Secreted phospholipase A2-induced neurotoxicity and epileptic seizures after intracerebral administration: an unexplained heterogeneity as emphasized with paradoxin and crotoxin. *J Neurosci Res* 54:848-862.

¹²⁹ Vidal DR (1990) Immunosuppressive activity of trichothecene mycotoxins. *Bull Inst Pasteur* 88:159-192
Vidal D, Mavet S (1989) In vitro and in vivo toxicity of T-2 toxin, a Fusarium mycotoxin, to mouse peritoneal macrophages. *Infect Immun* 57:2260-2264

¹³⁰ Goyffon M (1994) Facts on venomous animals. *Ann Pharm Fr* 52:99-109.

¹³¹ The *Laboratoire de Chimie et d’Immunologie des Protéines* (head : Dr. André Ménez) of the *Département d’Ingénierie et d’Etudes des Protéines* in Gif-sur-Yvette published abundantly on snake, sea anemone, and scorpion toxins.

¹³² Lemercier G, Schmitt D, Quenin P, Jayne A, Fontanges R (1974) Local immune response in experimental airborne influenza of Balb/c mice infected with myxovirus influenza A/Hong-Kong/1/68 (H3N2). *Arch Gesam Virusforsch.* 45:113-121.

CEB and the army hospital HIA Bégin in cooperation with academic scientists were involved in several projects focusing on the development of possible treatments for airborne influenza infections.¹³³ One aspect of this work is the superinfection of influenza infected animals with other pathogens.¹³⁴ According to a recent publication, a “*mouse model of lethal influenza A virus infection*” was established for these experiments.¹³⁵

This kind of research is not exceptional, and military personnel are subject to influenza infections as much as the general public. A military research program on influenza treatment or prophylaxis can easily be explained. It should be noted, however, that CEB is a dedicated biodefense facility and that the army hospital HIA Bégin is one of the three major military biodefense research institutions. Hence it is safe to assume that this influenza research has a special focus on biological defense. While influenza virus may indeed be an effective biological weapon – especially if genetically engineered strains bearing genes from the deadly 1918 strain are considered¹³⁶ – it is, from a military perspective, not the prime viral BW agent. Most experts consider other viruses such as Ebola, Lassa or smallpox as major BW threats.¹³⁷ It is an open question why the French military biodefense community has maintained a special focus on influenza, from at least 1974 until today.

Bottex C, Bienvenu P, Fontanges R (1977) Affinity chromatography purification of surface antigens from Myxovirus influenzae. C R Hebd. Seances Acad Sci Ser D 284:2059-2062.

¹³³ Ramisse F, Deramoudt FX, Szatanik M, Bianchi A, Binder P, Hannoun C, Alonso JM (1998) Effective prophylaxis of influenza A virus pneumonia in mice by topical passive immunotherapy with polyvalent human immunoglobulins or F(ab')₂ fragments. Clin Exp Immunol 111:583-587.

Dreffier C, Ramisse F, Dubernet C (2003) Pulmonary administration of IgG loaded liposomes for passive immunoprophylaxy. Int J Pharm 254:43-47.

¹³⁴ Hernandez E, Ramisse F, Gros P, Cavallo JD (2000) Super-infection by Bacillus thuringiensis H34 or 3a3b can lead to death in mice infected with the influenza A virus. FEMS Immunol Med Microbiol 29:177-181. Alonso JM, Guiyole A, Zarantonelli ML, Ramisse F, Pires R, Antignac A, Deghmane AE, Huerre M, van der Werf S, Taha MK (2003) A model of meningococcal bacteremia after respiratory superinfection in influenza A virus-infected mice. FEMS Microbiol Let 222:99-106.

¹³⁵ See footnote 74.

¹³⁶ For a discussion of the genetic resurrection of the Spanish flu virus from 1918, see our homepage www.sunshine-project.org.

¹³⁷ See, for example, the CDC lists for bioterrorism agents, which lists in category A only filoviruses (Ebola, Marburg) and arenaviruses (such as Lassa).

3. A short overview of French biological capabilities

Microbiology and the production of biological agents are technology areas with a pronounced dual-use character. Nearly all knowledge and nearly every item that is needed to produce large volumes of biological agents for BW purposes is also relevant for civilian – e.g. medical – purposes. Thus, many countries in the world have the technological basis to engage in an offensive biowarfare program, because they maintain research, development and/or production activities for legitimate purposes. Hence the capability of a country to produce biological agents does not indicate any malign intent, but the absence of any such capability is an indication that a given country may be less likely to engage in illicit activities or may be confronted with major technological difficulties if it starts a BW program.

In the following, we give a short overview on France's capabilities in the biological area. This overview is based on a standardized methodology that is followed in all Sunshine Project Country Reports. It allows for a comparative assessment (or ranking) of the capabilities of different countries in the area of research, development and production.

In order to compare countries, we used parameters where global data is available. This is particularly difficult in the area of biotechnology. As no universal and agreed definition of the term 'biotechnology' exists, hardly any global assessments or rankings on biotechnological capabilities are available. The parameters that are used in the following were selected for the simple reason that comparative data was available. They have limitations, but in combination they give an indication of a country's biological capabilities. For the areas of production and development, only quantitative data was available, while the PubMed database¹³⁸ allows also for a qualitative assessment of research capabilities.

3.1.1. *Production*

France has a very strong biotechnology research, development and production capability. The capability to produce biological agents may be assessed on the basis of two parameters: the number of biotechnology companies and vaccine production capacity.

Biotechnology Companies: The international consultancy company Ernst & Young publishes regular overviews of the global biotechnology industry. For some countries, Ernst & Young determines the number of public and private biotechnology companies based on a coherent definition. Although the sheer number of companies does not indicate their technology potential or size, the number of companies may be taken as an indication of modern biotechnology capability within a country. According to the 2004 Ernst & Young Report, France has 246 biotechnology companies, ranking fifth globally.¹³⁹

Vaccine Production: The WHO maintains a database of most producers of human vaccines worldwide. While some of this information – particularly the production quantities – is confidential and not disclosed, the list of the manufacturers and the types of vaccines they produce is available from WHO. The number of different vaccine types produced in a country is an indication of biological production capability. It should be noted though that several countries with a highly developed modern biotechnology do not have a significant production of vaccines. Hence the absence of a vaccine production does not necessarily indicate a limited biological production capability. It should also be noted that some countries may not produce vaccines for human use, but for animal use. France has one manufacturer that produces a total of 16 different human vaccines, the second highest number worldwide.

3.1.2. *Development*

The number of patents in a particular technology area may be taken as an approximate value for the capabilities of a given country in the area of development. As national patent databases are likely to be regionally biased and as key-word based searches may reflect variations in terminology rather than

¹³⁸ See <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>.

¹³⁹ Ernst & Young Global Biotechnology Report 2004.

differences in patenting, we choose an international patent search using a globally harmonized system of technology codes.

The EspaceNet database of the European Patent Office allows for global searches using the International Patent Classification (IPC) system. We counted all IPC class C12 patents, which include all inventions related to “*Biochemistry; Beer; Spirits; Wine; Vinegar; Microbiology; Enzymology; Mutation or Genetic Engineering*”.¹⁴⁰

With a total number of 23,302 priority patents in IPC class C12, France holds a global rank of 5.

3.1.3. *Research*

The relative strength of French research in areas relevant to BW is indicated by the number of scientific publications on issues pertinent to BW agents. For the purpose of this study, anti-personnel agents that have been stockpiled or otherwise weaponized by state armed forces since 1946,¹⁴¹ according to their possessor states, were used as examples of typical BW agents (see figure 1).

A search in the PubMed database was conducted, using the term ‘France’ in the affiliation of the corresponding author, combined with the scientific names of the agents (bacteria and viruses) or the name of the toxin in case of the four toxins. The search was restricted to the five-year period 1999-2003 to get a more recent account of research activities.¹⁴²

For each biological agent, the total number of scientific papers was determined and expressed as percent of the global number¹⁴³ of papers in this category. As a control, a general microbiology-related query¹⁴⁴ was used to determine the overall share of French papers in the relevant field.

Figure 1 below shows the result: 6.3% of all publications on microbiological issues were published by a French corresponding author. For some of the analysed typical BW agents, a lower percentage of France-based papers was determined, but five agents showed an above average percentage of the global total.

As a specific research focus in one country may be attributable to specific environmental or other regional conditions, a similar analysis was performed on three neighbouring countries (Germany, Italy, Spain). As shown in figure 2, no above average research focus could be determined for the five agents in these countries, excepting Spain’s modestly stronger research focus on Q-fever and brucellosis.

Based on publications, the following agents are a French speciality. To elucidate the general direction of French research in these specific areas, a rough analysis of the publications retrieved with our query in PubMed was performed:

¹⁴⁰ The search on the Advanced Search site of EspaceNet (at http://ep.espacenet.com/search97cgi/s97_cgi.exe?Action=FormGen&Template=ep/en/advanced.hts&REF=y) was performed on 8 September 2004. The exact query was: IPC = C12 and Priority Number = Two-digit country code (FR for France). This query searches for patents that were first filed (the so called priority patent) in France. Random checks indicated that more than 95% priority patents filed in France were developed and/or applied for by French citizens or institutions. EspaceNet does not allow to search for specific time frames.

¹⁴¹ As listed in the 2004 WHO report ‘Public health response to biological and chemical weapons’, Table 3.1, page 33. Two agents from this list were not used in our analysis: *Rickettsia prowazeki*, because the PubMed database contains only one single scientific publication on this agent for the years 1999-2003. And aflatoxin, which is considered to be an unlikely BW agent candidate, despite the fact that the former Iraqi government claimed that it produced and weaponized aflatoxin in its former BW program.

¹⁴² The exact query for the PubMed search was: France[Affiliation] AND *name of agent*. Limits: Publication Date 1.1.1999 – 31.12.2003. The search was conducted on 20 September 2004.

¹⁴³ As a ‘global’ reference, all global papers minus those with first/corresponding authors from the USA was used. This was deemed necessary as the USA alone accounts for more than 30% of all microbiology papers listed in PubMed. Any under- or overrepresentation of a given research subject in the US would lead to a corresponding over- or underrepresentation of this subject in any other country. Hence the US-papers were omitted from the global reference.

¹⁴⁴ The general microbiology query was ‘microbiology OR bacteria OR virus OR toxin’.

Brucellosis: The bacterium *Brucella suis* typically causes flu-like symptoms in humans and was weaponized by the USA in the 1950s as a “non-lethal” biological weapon. France has a high focus on brucellosis research: From a total of 75 publications on *Brucella suis* in 1999-2003, the corresponding author of 30 papers was based in France (40%). 29 of these are from the INSERM unit 431 *Microbiologie et pathologie cellulaire infectieuse* at the University of Montpellier (head: Jean-Pierre Liautard). This unit is entirely devoted to *Brucella* research and aims to understand the course of infection as well as to develop treatments and vaccines against brucellosis.¹⁴⁵

Q-fever: Of a total of 66 French publications related to *Coxiella burnetii*, the causative agent of Q-fever, 47 were co-authored by Didier Raoult, head of the *Unité des Rickettsies* at the Université Méditerranéenne in Marseille (see section 2.5.7). Another 8 publications are co-authored by A. Rodolakis from the *Unité de Pathologie Infectieuse et Immunologie*, INRA, in Nouzilly. A major focus of the *Unité des Rickettsies* appears to be the development of rapid diagnostic tools for *C. burnetii* as well as potential treatments.

Anthrax: From a total of 44 French publications related to *Bacillus anthracis*, the causative agent of anthrax, 31 were co-authored by Michelle Mock, head of the *Unité Toxines et Pathogénie Bactériennes* at the Institute Pasteur in Paris (see above chapter 2.5.2). As outlined above, some of this work is directly linked to biological defense and financed by the Ministry of Defense. Many different aspects of anthrax including its way of infection, its toxins, possible vaccine developments, antibiotic susceptibilities etc. are studied in France.

Plague: No specific research focus on *Yersinia pestis*, the causative agent of plague, could be identified. A few studies focusing on diagnostics or treatment were published in France, as well as several publications addressing genetic parameters that influence the virulence of *Yersinia pestis*.

¹⁴⁵ See this unit’s homepage at <http://www.montp.inserm.fr/unit431/U431.html>.

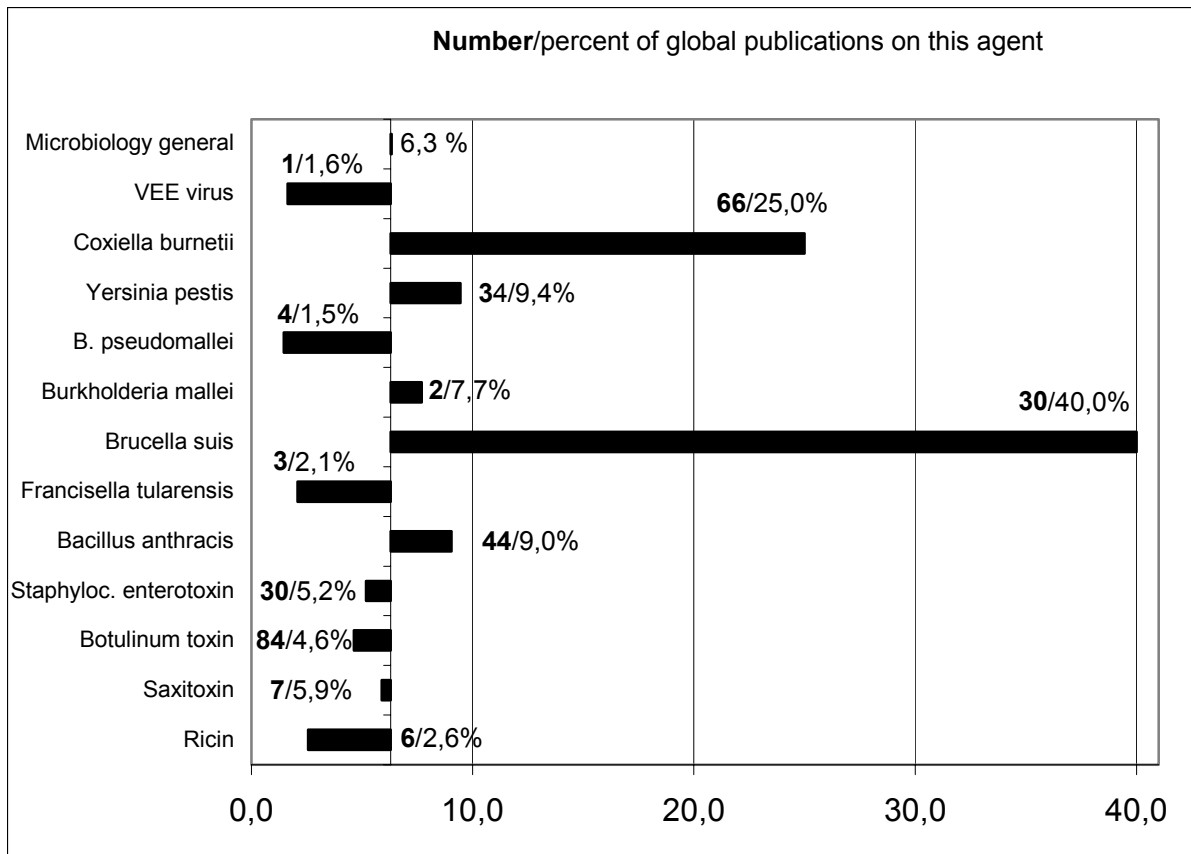


Figure 1: PubMed-listed research articles on selected agents published in 1999-2003 with the corresponding author based in France.

The bold figure indicates the absolute number of papers for each agent, the second number indicates its significance in relation to global research on this agent (expressed as percent of all global publications per agent).

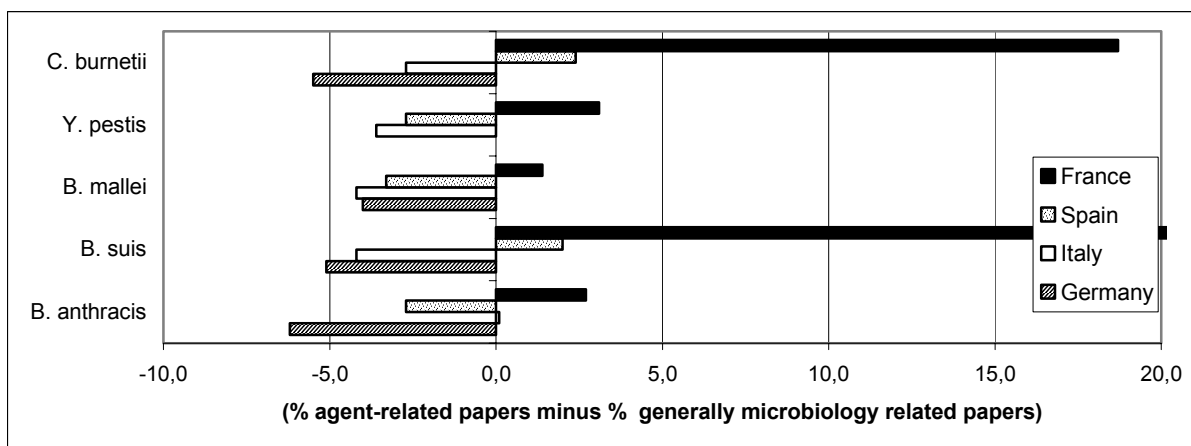


Figure 2: Above average research activities on selected agents in France compared with three neighbouring countries.

As shown in figure 1, an above average research focus in France was determined for five agents. For these, the same analysis was performed for papers corresponding authors based in Spain, Italy and Germany, to elucidate any potential regional conditions that may contribute to this effect. In a first step, the share of each country of the global number of papers in the general field of microbiology was determined. It was 7.8% for Germany, 4.2% for Italy and 3.3% for Spain. In a second step, each country's share of papers on each toxin was determined and subtracted from the general share.

4. French 'Non-lethal' chemical weapons

A variety of indirect evidence suggests that France may be developing so-called 'non-lethal' chemical weapons and thus may be in violation of the Chemical Weapons Convention. French military scientists have investigated a broad range of incapacitating agents – from tear gas to neurotoxins and psychoactive drugs. A variety of delivery devices for 'non-lethal' chemical weapons have been developed, patented, and marketed by French companies.

The French program on 'non-lethal' chemical weapons may be comparable in scope and magnitude to the US program, but – absent an effective Freedom of Information Law in France – only circumstantial evidence and isolated information is available, leaving some latitude for speculation. It should be noted, however, that based on the information available it can not be concluded with certainty that France has indeed a coordinated military R & D program on these prohibited weapons.

The French army is equipped with tear gas and uses it, including use abroad. During recent French Army operations in Cote d'Ivoire, for example, French soldiers used tear gas several times. In October 2002, January 2003 and December 2003, French troops were confronted with demonstrations and blockades outside their military base and – according to official sources – used tear gas.¹⁴⁶

'Non-lethal' chemical weapons – a major threat to biological and chemical arms control

The Chemical Weapons Convention (CWC) prohibits any kind of chemical weapon – deadly nerve gases as well as less lethal chemical agents. This includes the use of tear gas as a method of warfare.¹⁴⁷ This comprehensive and unambiguous ban is currently threatened by the increasing interest of several countries in so-called 'non-lethal' chemical agents such as the opium-like 'knockout gas' that was used by Russian special forces during the Moscow theatre siege in October 2002.

The interest in incapacitating chemical agents is not new. Even during the Cold War chemical arms race, 'non-lethal' chemical weapons were developed and stockpiled by NATO countries. But as the revolution in biotechnology leads to an increased understanding of molecular processes in the brain, targeted neuroactive substances are becoming available that may be used as fast acting weapons to incapacitate or "calm" an enemy. Several countries are developing and/or stockpiling this kind of weapons including Russia – as was tragically demonstrated in the hostage crisis – and the USA.¹⁴⁸

This technical development and renewed military interest is accompanied by attempts to poke loopholes into the broad prohibitions of the CWC. The USA advocates an interpretation of the CWC that would allow the use of tear gas, opium-like substances and other neuroactive compounds in combat. Considering the rate of biotechnological discoveries and the manifold possibilities to manipulate human behaviour with chemical substances, this development is a major threat to arms control. A recent editorial in the CBWC Bulletin summarised: *"It is hard to think of any issue having as much potential for jeopardizing the long-term future of the Chemical and Biological Weapons Conventions as does the interest in creating special exemptions for so-called 'non-lethal' chemical weapons. (...) Exemption blurs the simple line, no poisons in war. (...) The importance of averting the hostile exploitation of biotechnology (...) is immeasurably more important than the marginal utility of 'non-lethal' chemical weapons in military and paramilitary operations."*¹⁴⁹

¹⁴⁶ See website of the French Ministry of Defense at www.defense.gouv.fr/gendarmerie/actualite/archives/licorne.html

¹⁴⁷ The use of tear gas and other 'riot control agents' is, however, permitted under the CWC for "law enforcement including domestic riot control purposes". e.g. tear gas used by police against demonstrations or rioting inmates.

¹⁴⁸ Sunshine Project research in the past three years revealed a huge 'non-lethal' chemical weapons program in the USA. More at www.sunshine-project.org/incapacitants/.

¹⁴⁹ The CBW Conventions Bulletin – Quarterly Journal of the Harvard Sussex Program on CBW Armament and Arms Limitation. No. 61:1-2, September 2003. <http://www.sussex.ac.uk/spru/hsp/cbwcb61.pdf>.

4.1. Delivery devices

French companies have a great interest in markets for “non-lethal” chemical weapons. Several companies from the French defense sector are actively developing and manufacturing delivery devices for tear gas and – potentially – other “non-lethal” chemicals. According to *Jane’s Defence Industry* database, several French companies are manufacturing and selling tear gas grenades, including SAE Alsetex and NobelSecurité.¹⁵⁰ But the major player in France appears to be *Etienne Lacroix Tous Artifices SA* in the south of France. Etienne Lacroix is mainly known for its fireworks products; but it has been long known to also have an interest in chemical weapons. In a directory of the French Defence Industries from 1988, Etienne Lacroix is the only company listed in category 1040: *Chemical weapons and equipment*.¹⁵¹ It is unclear whether the chemical weapons offered by Etienne Lacroix at that time were of a more or less lethal design.

One of the current bestsellers in Etienne Lacroix’s portfolio is the GALIX system to protect combat vehicles. Developed jointly with the French weapons manufacturer Giat Industries, the Galix system is mounted on tanks and can fire smoke grenades, infrared decoys, and tear gas grenades. According to Etienne Lacroix’s catalogue, the GALIX system can be equipped with *law enforcement ammunition* (which explicitly includes tear gas) as well as with *peacekeeping ammunition*, which is not further defined in the catalogue. It should be noted that French Leclerc tanks are routinely equipped with the GALIX system. It would be an outright violation of the Chemical Weapons Convention if the GALIX system on a combat tank were loaded with tear gas, or other chemical ammunition.



The GALIX system¹⁵²

Another French development in this area is the little-known SIMULTITOX (see picture below). Said to be developed for NBC training, this system appears to be designed to disperse aerosols in combat like situations. While SIMULTITOX is indicated as a training system, marketing managers from Etienne Lacroix are eager to sell it for actual weapons use.

At a June 2004 weapons exposition outside Paris, we presented ourselves as a foreign aid organization interested in purchasing ‘non-lethal’ weapons for use in refugee camps. We were told by a salesperson from Etienne Lacroix that, if we are interested, the SIMULTITOX could easily be provided with a payload of “non-lethal” chemical agents such as malodorants.

¹⁵⁰ According to Jane’s Defence Industry database in Sub-Category anti-riot CS grenades, <http://fasttrack.janes.com/janesdata/ft/2358/2435/2436/2438/index.html> (as of 18 August 2004)

¹⁵¹ See facsimile reprinted in *La Politique*, 27 October 1988 in the article *The Chemical Connection* by Jean-Pierre Ravery.

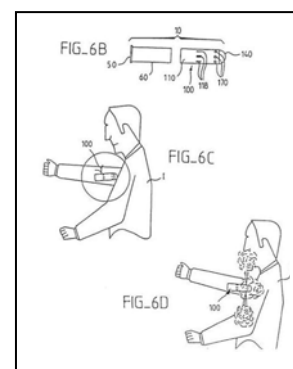
¹⁵² Picture taken from <http://www.pyrotronics.com/military.html>. Pyrotronics is a member of the Lacroix group.



SIMULTITOX: Etienne Lacroix offers malodorants for this grenade, a model said to be for NBC training.¹⁵³

Etienne Lacroix appears to be the French company with the strongest research and development effort in the area of delivery devices for ‘non-lethal’ chemical weapons. This is indicated by several French and US patents from the past 15 years for devices to deliver tear gas or “*incapacitating*” fluids of un-defined composition:

- A recent US patent (# 6,250,226) from June 2001 is titled “*Non-lethal ammunition with incapacitating effect*”. This ammunition is designed to disperse any kind of “active agent”, which, according to the patent text, is preferably an “*incapacitating agent*”. The nature of such an incapacitant is not further specified in the patent. The active agent “*can take numerous forms, including powders, in particular powders in a solvent, smoke producers, and aerosols.*” No definite size or range of this ammunition is given in the patent. While some diagrams in the patent suggest rather small calibres (see diagram on the right), the ammunition is designed to be fired from a launching tube.



- US patent 6,209,461,¹⁵⁴ granted in April 2001, claims a “*non-lethal projectile (...) to disperse a pressurized fluid in a controlled manner by impact*”. The kind of fluid is again indicated in the patent: “*in particular an incapacitating fluid or a marking fluid*”.
- US patent 5,501,153, assigned to Etienne Lacroix in March 1996, describes a warhead for dispersing pyrotechnical and/or ‘*lacrimatory substances*’ and ‘*incapacitating compositions*’. The warhead was explicitly developed ‘*in order to increase the range of incendiary and/or incapacitating weapons*’. As the patent is not about a complete delivery device but only a warhead design, no specific size or range is given in the patent.
- French patent # 94 03852 from 1994 describes a “*Non-lethal bullet*” releasing an “*active fluid on living target’s organism*”. Said fluid is characterised as an “*irritating fluid*” in the patent. The assignee is Ruggieri, a French ammunition and fireworks manufacturer now owned by Etienne Lacroix.
- Other French patents (# 87 17661, #89 03457, # 92 02036) describe ammunition that are all designed to disperse substances of an unspecified nature.

¹⁵³ Picture taken from <https://naveodtechdiv.navsea.navy.mil/IraqOIG/PDF-low/10-MiscExplosiveDevice.pdf> as of 18 August 2004.

¹⁵⁴ This patent was registered in France as patent # 96 07780 in June 1996.

While all these patents are assigned to Etienne Lacroix, indicating that this company is most active in this area, other companies were also developing devices that may be capable to disseminate chemical agents.

Next in line is Giat Industries, the largest French state-owned arms manufacturer, producing mostly tanks and guns and co-producing the GALIX system with Etienne Lacroix. Giat owns two patents for a non-lethal projectile able to disperse a solid or liquid payload during flight and a launcher for such a projectile.¹⁵⁵

Thales, one of the biggest privately owned arms companies in France, owns a patent on “*Ammunition for the distribution of an incendiary mix*”, describing an aerial bomb to spread incendiary gels (e.g. napalm) as well as other products of undefined nature.¹⁵⁶ Two other Thales patents cover aerosol dispensing devices, although these are primarily intended to release electric and/or acoustic energy to disperse a hostile crowd¹⁵⁷ and to disperse concentrated hydrofluoric acid to disable optic systems.¹⁵⁸

Of special interest is SNPE (*Société Nationale des Poudres et Explosifs*), a large chemical and explosives manufacturer which has an R & D facility in Vert-Le-Petit right next to CEB. SNPE owns a patent on anaesthetic compounds and another for a propulsion mechanism for long range tear gas grenades.¹⁵⁹ SNPE seems to have an interest in riot control chemicals: In 1989, it was granted a US patent on a new method to disseminate lachrymatory (tear) agents, using a paper that burns at very low temperatures, thereby disseminating an active compound with which the paper is impregnated.¹⁶⁰

Located near Nice, the company SMA (*Société Méditerranéenne d'Aérosols in Plan-de-Grasse*) also appears to work on incapacitating chemical weapons. According to its website, SMA is an approved supplier for NATO and the French Interior Ministry,¹⁶¹ SMA owns a patent from 1998 on ‘*incapacitating composition and a device for its use*’ which covers a mixture of piperine and capsaicinoids.¹⁶² According to a 1999 scientific article, SMA provided OC sprays to the French police.¹⁶³

4.2. French military research on incapacitating agents

There is no doubt that CEB is interested, to a certain extent, in tear gas. Two publications from CEB’s *Laboratoire de Toxicologie Respiratoire*, conducted with the French police research center, cover experiments on the toxicity of tear gas (CS) and pepper spray.¹⁶⁵

In addition CEB maintains two departments tasked with research that may be relevant to ‘non-lethal’ chemical agents: The *Laboratoire de Toxicologie Respiratoire* and the *Laboratoire de Pharmacologie*

¹⁵⁵ French patent 95 13632 “*Device to launch a non-lethal projectile*” and 95 13634 “*Projectile allowing the dispersion of a product on its trajectory*”.

¹⁵⁶ European patent EP 0 399 907 A1 from May 1990.

¹⁵⁷ French patent 96 08390.

¹⁵⁸ French patent 86 07987.

¹⁵⁹ French patent 93 13615 from November 1993: “*Ignition-propulsion set adaptable to tear gas grenades*”, providing for a longer range than rifle shots.

¹⁶⁰ US patent # 4,859,454.

¹⁶¹ www.sma.fr (as of 14 May 2004).

¹⁶² US Patent 5,821,450, French patent 95 09856.

¹⁶³ Debarre S, Karinthi L, Delamanche S, Fuché C, Desforges P, Calvet JH (1999) Comparative acute toxicity of o-chlorobenzylidene malonitrile (CS) and oleoresin capsicum (OC) in awake rats. *Human Exp Toxic* 18:724-730.

¹⁶⁵ Debarre S, Karinthi L, Delamanche S, Fuché C, Desforges P, Calvet JH (1999) Comparative acute toxicity of o-chlorobenzylidene malonitrile (CS) and oleoresin capsicum (OC) in awake rats. *Human Exp Toxic* 18:724-730.

Delamanche S, Desforges P, Morio S, Fuche C, Calvet JH (2001) Effect of oleoresin capsicum (OC) and ortho-chlorobenzylidene malonitrile (CS) on ciliary beat frequency. *Toxicology* 165:79-85

du Comportement. The latter, which translates as *Behavioural Pharmacology Laboratory*, is particularly interesting.

Researchers from both laboratories publish abundantly on classical chemical weapons agents such as sulphur mustard and sarin, their effects and possible medical countermeasures. In addition to these straightforward chemical defense efforts, a variety of experiments have been published that indicate interest in other neurotoxic or psychoactive compounds.

Jean-Charles Bizot from the *Behavioural Pharmacology Laboratory* at CEB has (co-) authored several scientific publications on a broad range of psychoactive substances (including atropine, scopolamine, haloperidol, diazepam, amphetamine and many others) which were used in behavioural studies in animals. Anaesthetics or other compounds that sedate or reduce an enemy's capacity for aggression are potential 'non-lethal' weapons. A study co-authored by Bizot investigated the effect of several drugs on impulsive and/or aggressive behaviour. As pointed out in this paper, this research is related to "a variety of disorders whose clinical features include impulsive and/or aggressive conducts (impulsive arsonists, violent offenders, personality-disordered subjects, fire setters, pathological gamblers...").¹⁶⁶

In one publication, the effects of various compounds, including organophosphate nerve gases at sub-toxic levels and drugs to counter their effects, were tested for psychotropic effects.¹⁶⁷

Apart from these behavioural or memory-related studies some neuropharmacological research was conducted at CEB¹⁶⁸ One publication describes a new method for the analysis of enkephalins¹⁶⁹ – the body's morphin-like substances to alleviate pain or sedate. The only explanation for the interest of CEB in enkephalin analysis are ongoing experiments involving enkephalins, similar opiates or opiate receptors at CEB. While this is a legitimate subject of biomedical research, it does raise questions if it is pursued secretly at a dedicated chemical/biological defense research unit of the French Armed Forces.

A variety of other experiments at CEB investigated the effect of drugs on memory and learning in animals. Drugs tested include the honey-bee toxin apamin,¹⁷⁰ diazepam (trade name Valium), physostigmine and scopolamine¹⁷¹, the NMDA receptor antagonist AP5¹⁷² and the fungal toxin penitrem

¹⁶⁶ Bizot JC, LeBihan C, Puech AJ, Hamon M, Thiebot MH (1999) Serotonin and tolerance to delay of reward in rats. *Psychopharmacology* 146:400-412.

¹⁶⁷ Bizot JC (1998) Effects of various drugs including organophosphorus compounds (OPC) and therapeutic compounds against OPC and DRL responding. *Pharmacol Biochem Behav* 59:1069-1080.

¹⁶⁸ Deurveilher S, Delamanche IS, Hars B, Breton P, Hennevin E (1999) Chronic, low-level exposure to the cholinesterase inhibitor DFP. I. Time course of neurochemical changes in the rat pontomesencephalic tegmentum. *Pharmacol Biochem Behav* 64:95-103.

Zimmer L, Vancassel S, Cantagrel S, Breton P, Delamanche S, Guilloteau D, Durand G, Chalon S (2002) The dopamine mesocorticolimbic pathway is affected by deficiency in n-3 polyunsaturated fatty acids. *Am J Clin Nutr* 75:662-667.

Nio J, Besson MJ, Breton P (1993) Ontogenic distribution of muscarinic receptors and acetylcholinesterase in the rabbit hippocampus. *Brain Res Bull* 31:723-732.

¹⁶⁹ Bossee A, Fournier F, Tasseau O, Bellier B, Tabet JC (2003) Electrospray mass spectrometric study of anionic complexes of enkephalins with Cu(II): regioselective distinction of Leu/Ile at the C-terminus induced by metal reduction. *Rapid Commun Mass Spectrom* 17:1229-1239.

¹⁷⁰ Deschaux O, Bizot JC (1997) Effect of apamin, a selective blocker of CA2+-activated K+-channel, on habituation and passive avoidance responses in rats. *Neuroscience Letters* 227:57-60

¹⁷¹ Anglade F, Chapouthier G, Dodd RH, Baudoin C (1999) Olfactory memory in rats, cholinergic agents and benzodiazepine receptor ligands. *J Physiol* 93:225-232.

Anglade F, Galey D, Chapouthier G (1996) Septal scopolamine-systemic diazepam interaction in passive avoidance learning in rats. *Behav Pharmacol* 7:827-829.

Anglade F, Bizot JC, Dodd RH, Baudoin C, Chapouthier G (1994) Opposite effects of cholinergic agents and benzodiazepine receptor ligands in a passive avoidance task in rats. *Neuroscience Letters* 182:247-250

¹⁷² Puma C, Bizot JC (1998) Intraseptal infusions of a low dose of AP5, a NMDA receptor antagonist, improves memory in an object recognition task in rats. *Neuroscience Letters* 248:183-186.

A¹⁷³ The latter toxin is known to cause tremors and, at high concentration, convulsions and death. The US armed forces have also shown interest in convulsants as "non-lethal" weapons.

Like the elements of the US chemical-biological defense program that are also pursuing "non-lethal" chemical weapons, CEB has the capacity to produce its own psychoactive compounds. According to one publication, d-amphetamine was synthesized at the CEB's chemical department¹⁷⁴ (most other compounds were usually purchased from retailers or pharmaceutical companies).

In the late 1990s, CEB staff co-published with the research group of Marie-Hélène Thiébot from INSERM U.288 at the *Hospital Salpêtrière* in Paris. This group has a very broad expertise in psychoactive drugs. Whether or not it is still cooperating with CEB or receiving research money from the Ministry of Defense is unclear.

CEB is not the only French military institution involved in such studies. The chemical defense group at CRSSA published at least one study on behavioural drug effects¹⁷⁵ and investigated a broad range of drugs.¹⁷⁶ The medical research center of the French Navy in Toulon maintains a 'behavioural pharmacology laboratory' (The *Laboratoire de pharmacologie comportementale* at IMNSSA, the *Institut de Médecine Navale du Service de Santé des Armées*, Toulon Naval). Here, research on behavioural/memory effects (on human volunteers as well as animals) of a variety of anaesthetic drugs including ketamine,¹⁷⁷ dopamine antagonists¹⁷⁸ and nitrous oxide¹⁷⁹ is conducted.

The interest of the French military in opiates is not new. According to the 1992 French CBM, a report published in 1988 in Paris outlined in 25 pages the "*Molecular pharmacology of opiate receptors*".¹⁸⁰ The fact that this paper was listed in a CBM indicates that this research is related to biological or chemical weapons research.

The overall objective of the (publicly known) experiments at the *Behavioural Pharmacology Laboratory* at CEB is difficult to understand. Some of these studies may well be related to chemical defense work, for example, study of the side effects of drugs commonly used to treat nerve gas poisoning. But the major effort that has been undertaken to establish a broad range of behavioural animal tests can hardly be justified for side effect studies. Establishment of the animal methods requires experience and

¹⁷³ Deschaux O, Bizot JC (1997) Effects of penitrem A on rat's performances in passive avoidance and Morris water maze test. *Mycopathologia* 138:99-104.

Breton P, Bizot JC, Buee J, DeLaManche I (1998) Brain neurotoxicity of penitrem A: electrophysiological, behavioural and histopathological study. *Toxicol* 36:645-655.

¹⁷⁴ Bizot JC (1998) Effects of various drugs including organophosphorus compounds (OPC) and therapeutic compounds against OPC and DRL responding. *Pharmacol Biochem Behav* 59:1069-1080.

¹⁷⁵ Filliat P, Pernot-Marino I, Baubichon D, Lallement G (1998) Behavioral effects of NBQX, a competitive antagonist of the AMPA receptors. *Pharmacol Biochem Behav* 59:1087-1092.

¹⁷⁶ Lejoyeux M, Daveloose D, Maziere JC, Ades J, Viret J (1993) A spin label study of the membrane effect of various psychoactive drugs in human erythrocytes. *Life Sci* 52:PL7-PL11.

¹⁷⁷ Micallef J, Guillermain Y, Tardieu S, Hasbroucq T, Possamai C, Jouve E, Blin O (2002) Effects of subanaesthetic doses of ketamine on sensorimotor information processing in healthy subjects. *Clin Neuropharmacol* 25:101-106.

Guillermain Y, Micallef J, Possamai CA, Blin O, Hasbroucq T (2001) NMDA receptors and information processing: human choice reaction time under a subanaesthetic dose of ketamine. *Neuroscience Letters* 303:29-32.

¹⁷⁸ Courtiere A, Hardouin J, Goujon A, Vidal F, Hasbroucq T (2003) Selective effects of low-dose dopamine D1 and D2 receptor antagonists on rat information processing. *Behav Pharmacol* 14:589-598.

¹⁷⁹ Rabat A, Hardouin J, Courtiere A (2004) Nitrous oxide impairs selective stages of working memory in rats. *Neuroscience Letters* 364:22-26.

Courtier A, Hardouin J, Vidal F, Possamai CA, Hasbroucq T (2003) An additive factor analysis of the effect of sub-anaesthetic doses of nitrous oxide on information processing: evidence for an impairment of the motor adjustment stage. *Psychopharmacology* 165:321-328.

Coutiere A, Hardouin J (1997) Behavioural effects induced by nitrous oxide in rats performing vigilance task. *Behav Pharmacol* 8:408-415.

¹⁸⁰ According to CBM 1992, page 78, this is Report Nr. D8REP4, 88 of the Cent. Documentation Armement, order no. PB88-2193332.

infrastructure, suggesting a long-term and systematic commitment at CEB to conduct psychopharmacological studies on a range of psychoactive compounds and their effect on behaviour and/or memory. There are several possible explanations for CEB's motivation in this program. One may be the development of 'non-lethal' chemical agents, another one may be the development of performance or memory enhancing compounds for the French soldier. Some of this research may be related to performance studies that are unrelated to 'non-lethal' chemical agents. It must be emphasized that we could not find a single document by French researchers that explicitly indicates an official objective to develop calmatives, convulsants or other incapacitants as 'non-lethal' chemical weapons. But absent a clarification from the French government, CEB's research could be interpreted as including illegal 'non-lethal' chemical weapons development activities.

5. French Confidence Building Measures and Transparency

5.1.1. *BWC ratification*

France is party to all major biological and chemical arms control agreements. On 10 May 1926, it ratified the Geneva Protocol, albeit with two reservations that essentially made the commitment of the French Government one of ‘no first use’¹⁸⁶. France withdrew these reservations 70 years later, on 25 November 1996.

France did not formally accede to the Biological Weapons Convention until 27 September 1984¹⁸⁷, although a national law implementing the basic BWC provisions was passed much earlier, on 9 June 1972 (Law No. 72-467). Detailed information on national BW-related legislation may be obtained from the VERTIC collection of national implementation legislation.¹⁸⁸ The Chemical Weapons Convention was ratified by France on 2 March 1995.¹⁸⁹

5.1.2. *Confidence building measures – a culture of non-compliance*

In every year from 1992 through 2002, France submitted confidence building measures (CBMs) under the BWC. Some, but not all, of the French CBMs included information on biodefense programs (Measure A2) and/or on biological research centers (Measure A1). See table 1 for an overview.

¹⁸⁶ <http://projects.sipri.se/cbw/docs/cbw-hist-geneva-parties.html>. The reservations were: 1) The said Protocol is only binding on the government of the French Republic as regards States which have signed or ratified it or which may accede to it. (2) The said Protocol shall ipso facto cease to be binding on the government of the French Republic in regard to any enemy State whose armed forces or whose allies fail to respect the prohibitions laid down in the Protocol.

¹⁸⁷ Décret No. 84-1014 of 16 November 1984, published in the Official Journal on 18 November 1984, page 3562, according to French CBM 1992, Measure F.

¹⁸⁸ For French legislation, see <http://www.vertic.org/datasets/F.htm>

¹⁸⁹ <http://projects.sipri.se/cbw/docs/cw-cwc-rat.html>

Year	A1 research centers	A2 biodefense program
1992	Nothing new to declare	Declaration submitted
1993	Declaration submitted	Nothing new to declare
1994	Declaration submitted	Nothing new to declare
1995	Nothing new to declare	Nothing new to declare
1996	Nothing new to declare	Nothing new to declare
1997	Nothing new to declare	Nothing new to declare
1998	Declaration submitted	Nothing new to declare
1999	Nothing new to declare	Nothing new to declare
2000	Declaration submitted	Declaration submitted
2001	Nothing new to declare	Declaration submitted
2002	No information submitted	Declaration submitted

Table 1: CBMs submitted by France under the BWC.

Not all French CBMs contained information on biodefense programs or research centers. In some, France indicated that it had ‘nothing new to declare’.¹⁹⁰

A detailed analysis of the contents of all CBMs submitted by France reveals that they contain very limited information and thus do not adequately serve their confidence-building purpose. A variety of issues severely limit the usefulness of the French CBMs in terms of building confidence and promoting biological weapons control:

- They are incomplete. Major information on the nature, scope and location of the French biodefense program has been omitted. The omissions are constant. Only CEB is consistently listed as a biodefense facility, while another facility that is strongly engaged in the French biodefense program (CRSSA with its *département de biologie des agents transmissibles*) has only once been declared as a biodefense facility. France has never declared the CEB facility in Cazaux or HIA-Bégin.

It has been argued that the current CBM format requires declaration only for a facility “*which has a substantial proportion of its resources devoted to the national biological defence research and development programme*”¹⁹¹, and not for all facilities involved in a biodefense program. Considering that the term ‘facility’ is not clearly defined, probably every biodefense institution in the world could be excluded from the declaration requirement if the term ‘facility’ is creatively interpreted by the declaring country. CRSSA, for example, is tasked with many activities, and biodefense is a minor part of CRSSA’s overall work. But most of the work in the *département de biologie des agents transmissibles* appears to be biodefense. It should therefore be declared. Considering that the purpose of CBMs is to create confidence, countries should abstain from dubious manipulations of the term “facility” to justify omitting significant biodefense institutions from their declarations. The more elements of a national biodefense program that are excluded from a CBM submission intended to build confidence, the more paradoxical the CBM’s effect will be.

- They are inconsistent. The French government does not appear to take the CBMs seriously and its preparation of them has been rather sloppy. While most CBMs mention CEB as France’s only biodefense facility, the CBM 2000 declares only the *département de biologie des agents transmissibles* at CRSSA –and not CEB. CBM 1992 declares only CEB under Measure A2; but under

¹⁹⁰ Documents from BWC Review Conferences BWC/CONF.V/2, BWC/CONF.V/2/Add.1, BWC/CONF.IV/2.

¹⁹¹ According to the ‘Annex to Final Declaration on Confidence-building measures’, Third BWC Review Conference, document BWC/CONF.III/23, Part II, Form A, part (ii) number 7: “Provide a declaration in accordance with Form A, part 2 (iii) for each facility, both governmental and non-governmental, which has a substantial proportion of its resources devoted to the national biological defence research and development programme.”

Measure F it declares CEB, CRSSA and the *Centre de Recherches de Médecine Tropicale du Service de Santé des Armées* as biodefense facilities.

- They provide inadequate information about contractors. As a significant part of the French biodefense program is contracted to civilian entities, more information on outsourced research and contractors should be provided. Only CBM 2000 provides a list of all outsourced research including the names of the civilian biodefense contractors. This should be standard procedure for future CBM submission from the French and all other governments.
- They are unavailable to the public. The French government does not make its CBMs available to the general public. Other governments (Australia, USA) have placed their CBMs on the internet. France has not. The Sunshine Project posted the most recent French CBM available to us on its website at www.sunshine-project.org.

Many of the questions in this report could and should have been addressed in the CBMs submitted by France to the United Nations. According to the final document of the Third Review Conference of the Biological Weapons Convention, France has the obligation to annually submit a complete declaration on its biodefense program to the United Nations. To date, France has not complied with this obligation.

If the French government is supportive of the international ban on biological weapons, and if it supports a strengthening of the Biological Weapons Convention, it should contribute to building confidence by submitting future CBMs that are complete, consistent and unambiguous.

It is noteworthy that the French government and the relevant institutions did not reply to the written requests that we sent for clarification of the many questions outlined in this report.

Glossary of French Names

Bulletin Officiel des Annonces de Marchés Publics (BOAMP)	Official Bulletin on Public Tenders
Centre d'études du Bouchet (CEB)	Le Bouchet Research Center
Centre de recherches du service de santé des armées (CRSSA)	Research Center of the Armed Forces' Health Service
Département de biologie des agents transmissibles	Department for the Biology of Transmissible Diseases
Département d'Ingénierie et d'Etudes des Protéines	Department for Protein Engineering and Research
DGA – Délégation Générale de l'Armement	General Armament Authority
Hôpital d'instruction des armées Bégin (HIA Bégin)	Bégin Military Teaching Hospital
Institut de médecine tropicale du service de santé des armées (IMTSSA)	Institute for Tropical Medicine of the Army's Health Service
Service Evaluation des Effets Biologiques	Unit for the Evaluation of Biological Effects (at CEB)
Unité Bactéries Anaérobies et Toxines	Anaerob Bacteria and Toxin Unit

¹⁹⁴ The term "biodefense program" includes all government and private activities related to defense against biological weapons, regardless of the names of the programs or the agencies that conduct the activities.

Government Undertaking on Biodefense Programs

The Biological and Toxin Weapons Convention (BTWC) prohibits the development, production and stockpiling of biological agents intended to harm humans, animals, plants, materials or the environment. The BTWC allows for defensive research; but contains no exemption for law enforcement, riot control or similar purposes. While biodefense programs¹⁹⁴ are necessary for protection against biological warfare, they can also blur the distinction between offensive and defensive activities and an offensive capability may be generated in the course of defensive work.

There is an urgent need to ensure that governments restrict themselves in biodefense programs and guarantee full transparency in all aspects of biodefense research, to prevent a race for offensive capabilities under cover of defense. We call on all governments to adopt this Undertaking and to make it binding upon their biodefense programs.

Ensuring Transparency

No biodefense research shall be conducted with legal secrecy (classification). All aspects of biodefense activities shall be made available to the public and to other countries, including details on the type, costs, budget, location, duration, intent and, in most cases, results of all projects. In a limited number of cases the detailed results (but no other aspects) of biodefense activities may need to be kept confidential, however, these shall be limited to results that are more than likely to generate a demonstrable threat.

Prohibitions on Certain Activities

Delivery Devices: Delivery mechanisms having a design that is appropriate for hostile use with biological agents shall not, for any purpose, be developed or constructed.

Genetic engineering: Biodefense programs will not, for any purpose, utilize or construct, including single-gene changes, novel biological agents with an enhanced offensive potential.¹⁹⁵

Weaponization: Active biological agents that could be used to cause harm shall not be weaponized.¹⁹⁶

Aerosolization: Aerosolization of active biological agents in biodefense programs shall be prohibited except for bench-scale testing of passive defenses.

About the Sunshine Project

Many biological weapons are rapidly destroyed by bright sunlight. The Sunshine Project works to bring facts about biological weapons to light!

We are an international non-profit organization with offices in Hamburg, Germany and Austin, Texas, USA. We work against the hostile use of biotechnology in the post-Cold War era. We research and publish to strengthen the global consensus against biological warfare and to ensure that international treaties effectively prevent development and use of biological weapons.

More about the Sunshine Project at www.sunshine-project.org.

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¹⁹⁵ (e.g. treatment resistance, environmental stability, and enhanced pathogenicity)

¹⁹⁶ The term "weaponization" is defined as preparing and treating a biological agent to enhance its effectiveness as a weapon, and/or inserting a biological agent into a delivery system suitable for hostile use.