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Working paper submitted by the Republic of Croatia

EVALUTION OF BIOLOGICAL AGENTS AND TOXINS

A few delegations submitted working papers during previous sessions for evaluation and selection of some agents and toxins according to existing criteria. Some changes to the list of agents and toxins were also proposed.

Document BWC/AD HOC GROUP/WP.356 was prepared by our delegation with the intention to show all three lists of human pathogens and toxins as well as animal and plant pathogens which are current at the moment by the existing criteria, for including pathogens and toxins to the list of bacteriological (biological) agents and toxins.

As the human, animal and plant pathogens and toxin lists will be hard to define, we proposed several tables of enlisted pathogens and toxins with important criteria, on the basis of which a decision could be made to include in, or exclude from, a list of bacteriological (biological) agents and toxins. These tables are preliminary and serve as the basis for discussion and as an aid to defining the final list of bacteriological (biological) agents and toxins.

The additional list of criteria for toxins and list of toxins, were prepared to assist the discussions when the time comes for the final list to be made. These additional criteria for toxins are actually a combination of existing and additional criteria and are not recommended as new criteria. They should be used for more detailed risk assessment and comparison of the toxins on the list, in which the lower the total number, the more dangerous the toxin as a toxin warfare agent, and for the purposes of making a final decision on the list of toxins easier. In the additional list of criteria for toxins, we can see at a glance an unimportant criterion: ease of decontamination. For toxins, decontamination would be relatively unimportant but fungal toxins are extremely difficult to decontaminate and once an area is contaminated (infected), it can take years of hard cleaning to get rid of these toxins, especially if delivered with fungal spores.

We wish to state that it is very hard to find in available literature, data for the most important criterion under number 1; for all pathogens and toxins the criterion is: [Vectors, Pests or] Agents known to have been developed, produced, stockpiled or used as weapons (in the tables - Weaponized). Therefore, we cannot be 100 per cent sure that data for this criterion are correct.

For all other data we can state that it is correct in 95 per cent of cases. This means that the list of pathogens and toxins can be a great help in the comparison of some pathogens and toxins, enabling easier decision-making on whether to include or exclude pathogens and toxins in the lists. In the tables, the plus sign (+) signifies that a pathogen or toxin satisfies the particular criterion for inclusion in the list. At the same time the minus sign (-) signifies that a pathogen or toxin does not satisfy the criterion for inclusion in the list. In the column: Totals, you can see a number of positive and negative answers.

For example, for criterion: No effective prophylaxis or therapy, the positive answer signifies the absence of an effective prophylaxis and medical treatment. The existence of immunization and appropriate treatment against a particular agent is in inverse proportion to the likelihood that the agent will be used.

Our opinion is that if a certain pathogen or toxin satisfies the bulk of the criteria, it should be recommended for inclusion in the list. But, we must know what the bulk of the criteria is, or the principal criteria for including pathogens and toxins to the list of bacteriological (biological) agents and toxins.

On the tables of human pathogens and toxins you can see some biological agents and toxins which were not listed in the previous list. These additional agents and toxins are not recommended as new agents for inclusion in the list. They should be used for more detailed risk assessment and for comparison with pathogens and toxins.

The evaluation of agents and toxins according to existing criteria is valid only under the assumption that all criteria have equal status. We have to agree and make a final decision to see if all the criteria are valid and have the same value in evaluating a particular pathogen or toxin. We are not sure that all criteria are equal for the final evaluation. Perhaps we should consider it, and request an opinion from the scientists and experts who will use their knowledge to assess the validity of certain criteria and maybe even sort them by value or points. We think that the criteria we have used are still valid for the diseases in the "natural form". Genetically engineered bacteria and viruses present a difficult problem. What looks unlikely now, may be technically feasible tomorrow.

All of this shows that it is very hard to make a final decision on the criteria and the final list of agents and toxins for the needs of the future Protocol to the BWC, based on these criteria.

Following the above we propose the lists and criteria for agents and toxins be well

studied, and that an opinion by scientists and experts be obtained, as the lists of agents and toxins should be scientifically based.

The Croatian delegation suggests the inclusion of one animal pathogen in the list. Our suggestion is the *Nipah virus*. Nipah virus is the so-called hendra-like virus that has disrupted Malaysia and caused tremendous agricultural disruption and financial problems.

CRITERIA FOR HUMAN PATHOGENS AND TOXINS

(see tables 1, 2 and 3)

1. [Vectors or] Agents known to have been developed, produced, stockpiled or used as weapons.
2. Likely methods and high level of dissemination or cover a large area as aerosol, spores in aerosol, sabotage (food and water supply) and infected vector.
3. Low infection dose or high toxicity [or potency].
4. High level of morbidity [and short incubation or latent period].
5. High level of contagiousness in population (transmissibility man to man especially through contact).
6. Infection or intoxication [by variety of route, especially] by respiratory route.
7. High level of incapacity or mortality.
8. Stability in the environment.
9. No effective prophylaxis (i.e. immune sera, vaccines or antibiotics) and/or therapy commonly available and widely in use.
10. Difficulty of detection or identification [at the early stage].
11. Ease of production [and transportation].

ADDITIONAL CRITERIA FOR TOXINS

The following additional criteria can be discussed by the Group and may be used in combination for selection of toxins to be included in/excluded from a list of toxins (see table 4):

Toxicity:

1 = Lethal dose (LD₅₀) in the 10⁻⁹g/kg range.

10 = Lethal dose (LD₅₀) in the 10⁻³g/kg range.

Onset:

The time from exposure to onset of clinical signs (latency) varies greatly among toxins. In this table, immediate (battlefield relevant) onset rather than delayed (terrorist relevant) onset is considered desirable.

1 = Minutes to hours onset.

10 = Multiple hours or days to onset.

Level of incapacity or mortality:

The number assigned in the table depends on whether the goal is to incapacitate or to kill.

1 = Severely incapacitating.

10 = Invariably lethal.

Likely methods of dissemination:

1 = Toxin could be aerosolised and delivered to cover large areas for aerosol contamination (large-scale dissemination). Toxin could be used in sabotage for contamination food and water.

10 = Toxin could not be aerosolised and delivered to cover

large areas for aerosol contamination. Toxin could be difficult used in sabotage.

Stability in environment/storage:

This factor refers to stability in storage or weapons and environment.

1 = Extremely stable in storage and environment.

10 = Unstable in environment or requires special storage conditions.

Ease of decontamination:

1 = Extremely difficult to decontaminate after a toxin aerosol attack.

10 = Decontamination would be relatively unimportant and general decontamination procedures effectively destroy toxin.

Production (Ease of production):

1 = Toxin can be ease produced in large quantities (low technology, low cost, widely available e.g. fermentation).

10 = Toxin that is very difficult to produce in weaponizable quantities (cutting edge, high cost, only available to specialised teams (e.g., solid phase synthesis of >100 amino acid polypeptides, advanced genetic manipulation).

The following criteria were discussed by the Group and may be used in combination for selection of animal pathogens to be included in a list of bacteriological (biological) agents and toxins (see table 5):

1. [Vectors or] Agents known to have been developed, produced or used as weapons;

2. Agents which have severe socio-economic and/or significant adverse human health impacts to be evaluated against a combination of the following criteria:

(a) High morbidity and/or mortality rates;

(b) Short incubation period and/or difficult to diagnose/identify at an early stage;

(c) High transmissibility and/or contagiousness;

(d) Lack of availability of cost effective protection/treatment;

(e) Low infective/toxic dose;

(f) Stability in the environment;

- (g) Ease of production.

CRITERIA FOR PLANT PATHOGENS

The following criteria were discussed by the Group and may be used in combination for selection of animal pathogens to be included in a list of bacteriological (biological) agents and toxins (see table 6):

1. [Pests or] Agents known to have been developed, produced or used as weapons;

2. Agents which have severe socio-economic and/or significant adverse human health impacts, due to their effect on staple crops, to be evaluated against a combination of the following criteria:

- (a) Ease of dissemination (wind, insects, water, etc.);

- (b) Short incubation period and/or difficult to diagnose/identify at an early stage;

- (c) Ease of production;

- (d) Stability in the environment;

- (e) Lack of availability of cost effective

protection/treatment;

(f) Low infective dose;

(g) High infectivity;

(h) Short life cycle.

Table 1. Human pathogens (viruses) assessment according to criteria for selecting pathogens as BW

Viruses	o-nized	dissemi-nation	ion dose	morbi-dity	gh con-transmissibility man to man)	variety of route (respiratory route)	apacity/ty	bility viron-ment	detection/i den-tificati on	pro-phylaxis and/or therapy	uc-tion	Totals +/-
o HF virus	+				-	+		+				9/2
	+				-	-		-				7/4
	+				+	+		-				10/1
rus	-				-	+		-				7/4
	+				-	+		+				8/3
	-				-	+		-				7/4
us	+				-	+		+				9/2
	-				+	+		-				8/3
	+				+	-		-				8/3
er virus	+				-	-		+				6/5
eph. virus	+				-	-		+				7/4
virus	+				+	+		+				10/1
	+				-	+		-				7/4
	+				-	+		-				7/4
irus	+				-	+		-				8/3

Viruses	o-nized	dissemination	ion dose	morbi-dity	gh con-transmissibility man to man)	variety of route (respiratory route)	capacity/ty	bility viron-ment	detection/i den-tificati on	pro-phylaxis and/or therapy	uc-tion	Totals +/-
rus	-				+	+		+				8/3
fever v. (CHIK)	-				-	+		-				5/6
irus	+				-	-		-				5/6
s	-				-	-		-				4/7

Table 2. Human pathogens (bacteria, rickettsiae, protozoa and fungi) assessment according to criteria for selecting pathogens as BW

Bacteria					Contagiousness (transmissibility man to man)	Variety of route (respi-ratory route)	Incubation period (days)	Availability in environment	Methods of detec- tion/iden- tification	Prophylaxis (vaccina- tion)	Available therapy (antimi- crobial)		
BACTERIA													
Cis					-	+							
is					-	+							
ensis					-	+							
					-	+							
Pseudomonas) mallei					-	+							
Pseudomonas) pseudomallei					-	+							
taci					-	+							
rensis					-	+							
					+	+							
RICKETTSIAE													
tti					-	+							
vazekii					-	+							
ettsii					-	+							

Bacteria					Contagiousness	Variety of route	Incapacity		Time of detec-	Prophylaxis	Pre therapy		
Rickettsiae					(transmissibility	(respi-ratory	or	ty	tion/iden-	(vaccina-	(antimi-		s
Protozoa	zed	nation	on dose	morbi-dity	man to man)	route)	lity	on-ment	tification	tion)	crobial)	uc-tion	
Fungi													
PROTOZOA													
Leishmania					+	-							
Trypanosoma					+	-							
FUNGI													
Candida					-	-							
Aspergillus					-	-							
Trichosporon					-	-							

Table 3. Toxin assessment according to criteria for selecting toxins as TW

Toxin/ Bioregulator	Size	Toxicity	Stability	Wide variety of route - respiratory route	High incapacity/ mortality	Prevention of prophylaxis/ therapy	Persistence in the envi- ronment	Ease of detection/ identification	Production	Costs
				+	+	+		+		
				+	+	+		+		
				+	+	+		+		
				+	+	+		+		
Exotoxins				+	+	-		+		
				+	+	+		+		
				+	+	-		+		
Microcystins				+	+	+		+		
Enterotoxins				+	+	-		+		
				+	+	+		+		
				+	+	+		+		
				+	+	+		+		
				+	+	+		+		
Enterotoxins (SEB)				+	+	+		+		
				+	+	+		+		

Toxin/ Bioregulator	ized	icity	gh idity	y variety of route - respiratory route	of incapacity/ tality	prophylaxis/ rapy	n the envi- ronment	of detection/ fication	duc-tion	s
				+	+	-		+		
				+	+	+		+		
erfrigens				+	+	+		+		
mycotoxins (T2,DON,HT2)				+	+	+		+		
				+	+	+		+		
				+	+	+		+		
				+	+	+		+		
afotoxin				+	+	+		+		

Table 4. Toxin risk assessment (the lower the total number means the more dangerous the toxin as TW)

Toxin/ Bioregulator	Toxicity	Onset	Incubation/ Mortality	Methods of dissemination	In the environment/ Storage	Contamination	Mode of action	Totals
	2	6	5	5	5	5	1	29
	7	8	5	5	5	1	3	34
	5	1	6	7	6	8	3	36
	3	2	3	4	9	8	3	37
Ins	1	3	7	3	2	6	1	23
	6	6	2	4	2	3	3	31
	3	4	6	5	8	7	3	41
Toxins	3	4	6	5	2	5	3	33
	3	7	6	6	8	5	9	44
Microcystins	5	2	5	3	7	7	3	37
In	2	3	6	5	5	7	5	34
	3	6	5	4	5	5	1	29
	2	4	8	3	5	3	9	34
	3	6	8	3	2	5	1	28
	3	2	8	3	3	7	5	31
enterotoxins (SEB)	4	6	2	2	3	5	2	24

Toxin/ Bioregulator	Toxicity	Onset	Incubation/ Mortality	Methods of dissemination	Survival in environment/ Storage	Contamination	Mode of action	Totals
	1	4	2	3	3	7	2	22
	1	9	8	4	3	7	2	34
	3	4	5	3	5	5	9	34
perfringens	3	6	8	3	3	7	8	33
Mycotoxins (T2,DON,HT2)	7	2	7	2	1	2	2	23
	3	7	6	5	6	6	8	36
	3	6	5	5	6	6	1	32
	4	5	7	6	7	5	4	38
aflatoxin	6	1	7	2	3	5	4	28

Table 5. Animal pathogens assessment according to criteria for selecting pathogens as BW

Animal pathogens	ized	o-economic/ alth impacts	ty/mortality rates	ion period	missibility/ agi- ess	ective/ lose	agnose/ identify at an early stage	ity on-ment	bility of cost- effective protection/ ment	uc-tion	s
VIRUSES											
fever virus		-					+				
a virus		-					+				
is		-					+				
e fever virus		+					+				
h virus		+					-				
ase virus		+					+				
ruminants virus		+					+				
is		+					+				
virus type 1		-					+				
atitis virus		-					+				
sickness virus		-					+				
sease virus		-					+				

Animal pathogens	ized	o-economic/ alth impacts	ty/mortality rates	ion period	missibility/ agi- less	ective/ lose	agnose/ identify at an early stage	ity on-ment	bility of cost- effective protection/ ment	uc-tion	s
<i>encephalitis virus</i>		+					+				
MYCOPLASMAS											
vine (pleuropneum.) (M. mycoides var. mycoides type SC) (CBPP)		-					+				
rine (pleuropneum.) n var. capri pneumoniae type F38) (CCPP)		-					+				

Table 6. Plant pathogens assessment according to criteria for selecting pathogens as BW

Plant pathogens	Localized	Pro-economic/ human health impacts	Incubation period	Transmission (wind, insects, water, etc.)	Life cycle	Survival dose and infectivity	Ability to diagnose/ in early stage	Stability in environment	Availability of cost- effective protection/ treatment	Control measures	Other
FUNGI											
Coffea coffeanum var. virulans		-		+			+				
Scirrhia pini (Scirrhia pini)		-		+			+				
Uromyces coffeae (Uromyces coffeae)		+		+			+				
Uromyces coffeae (Uromyces coffeae)		-		+			+				
Uromyces coffeae (Uromyces coffeae)		+		+			+				
Uromyces coffeae (Uromyces coffeae)		+		+			+				
Uromyces coffeae (Uromyces coffeae)		+		+			+				
Uromyces coffeae (Uromyces coffeae)		+		+			+				
Uromyces coffeae (Uromyces coffeae)		+		+			+				
BACTERIA											
Xanthomonas coffea (Xanthomonas coffea)		+		+			+				
Xanthomonas coffea (Xanthomonas coffea)		-		+			+				

Plant pathogens	Localized	Pro-economic/ human health impacts	Incubation period	Transmission (wind, insects, water, etc.)	Latency cycle	Relative dose and infectivity	Time to diagnose/ in early stage	Stability in environment	Availability of cost- effective protection/ treatment	Control measures	Prevention
albilineans		+		+			+				
campestris pv. citri		+		+			+				
campestris pv. oryzae		+		+			+				
VIRUSES											
disease virus		+		-			+				
