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ew with President Ford
August 25, 1975 [1]

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ue, Mr. President, the continuation of dministration has been criticized that How do you look at that?

y deny that. Détente as it has proceed- nswer every question that arises in the has been very helpful in easing and viet Union and ourselves.

been a balanced give-and-take by the I can assure you that in the process of imitation agreement number two, there ed by either side.

ir and equitable reduction in strategic lso important to understand that if we , it means that the arms race continues, ll have to spend roughly $2 billion to $3 n with the Soviet Union in their planned

oth sides, the Soviet Union and ourselves ms race, as Mr. Brezhnev and I did on a k in December of last year.[2]

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imistic, but I recognize there are some yet e technical matters that will satisfy both ave a high degree of capability of verifica-

tial Documents, Sept. 1, 1975, pp. 905-906.
974, pp. 746-750.

tion as to whether or not the Soviet Union is living up to the promises made if and when a SALT II agreement is made.

We have a tremendous technical capability in this regard, through a variety of means. I am sure they feel the same way.

But if the technical problems of verification, if other matters of balance are worked out—and I think it is possible—I think we will have a SALT II agreement.

. . . .

Canadian Working Paper Submitted to the Conference of the Committee on Disarmament: Use of Measurements of Lethality for Definition of Agents of Chemical Warfare, August 26, 1975 [1]

SUMMARY

To arrive at a Treaty limiting or prohibiting chemical weapons it may be necessary to define what chemical agents shall fall within the terms of the Treaty in which case it will also be necessary to agree to a measure of lethality. The specific problems associated with determination of lethality of chemical warfare agents are discussed and the general concept of the LD_{50} as a measure of lethality is explained.

It is recommended that separate standards of lethality should be adopted for three groups of agents, according to their routes of entry into the human body, i.e., inhaled gases or vapours, percutaneously lethal materials, and supertoxic solids. It is also recommended that a reference toxic material be adopted by agreement for each of these three groups of agents; and that the reference toxic material should be a readily available substance chosen to have a lethality equal or slightly less than what is agreed to be the least lethal of chemical agents to be restricted or prohibited in each class.

A specific proposal based on the above general principles is submitted for discussion.

DEFENCE RESEARCH ESTABLISHMENT SUFFIELD
RALSTON, ALBERTA

MEASUREMENT OF LETHALITY OF TOXIC MATERIALS: GENERAL DESCRIPTION OF THE LD_{50}

The lethality of a toxic material is usually determined by administering the material to several groups of uniform animals of a single species. The groups usually contain from 5 to 30 individuals, the number depending on the degree of accuracy required, and on the availability

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[1] CCD/473, August 26, 1975.

of suitable animals. An accurate measurement of LD_{50} requires the use of from 30 to 100 animals; tests using groups of animals smaller than 5 individuals yield only approximate results. Within each group, the animals are equally exposed to the same toxic material: in the case of injected toxic substances, each animal receives an amount proportional to his body weight: in the case of inhaled gases, each animal is exposed to the same concentration of the gas diluted in air for the same length of time. At a selected time after the end of the exposure (from a few hours to several days, depending on the nature of the effects of the poison) the number of dead animals in the group is counted.

Each of the several groups of animals is given a different dosage level, beginning with a dosage which kills few or none of the animals in the group, and increasing for each group until a dosage is reached which kills all or nearly all the animals in the group. The stepwise increases in dosage are chosen to be sufficiently small to result in two or three of the groups having killing ratios between 20% and 80%.

A set of data obtained in this way is then subjected to a mathematical process which estimates the dose which would be expected to kill 50% of a large population of similar animals. The resulting figure is the dose for 50% kill or LD_{50} and is usually expressed as milligrams of toxic material per kilogram of body weight.

LD_{50} values for a given toxic material vary considerably, depending on a number of factors, some of which are:—

Concentration of the dosage;
Rate of administration;
Route of application;
Animal (species
(age
(sex
(genetic strain
Time of determination of death

Estimates of lethality for man are usually based on LD_{50} figures from more than one species of mammals extrapolated to a body weight of 70 Kg. When results with different species are in wide disagreement, results obtained with primate species are given disproportionate weight in making the human estimate.

Measurement of Lethality of Inhaled Toxic Materials

When the toxic material is a vapour or aerosol which is inhaled into the lungs, practical difficulties arise in determining the amount of toxic material actually inhaled by each individual animal exposed. This determination would be required in order to calculate the LD_{50} in mg. toxic material inhaled per Kilogram of body weight.

These difficulties are normally avoided by using the LCt_{50} as the measure of toxicity. The concentration of the toxic material in the air (in mgm. per cubic metre) is multiplied by the time of exposure (in minutes). The resulting product or Ct, is a measure of the dosage breathed by each animal which allows for variations in size. The amount of air an animal breathes per minute is approximated proportional to body weight; and therefore Ct values are proportional to inhaled dosage per Kilogram.

$$LD_{50}\,(\text{inhaled}) = LCt_{50} \times \frac{\text{liters of air inhaled per minute}}{\text{Kilograms body weight}}$$

Either LD_{50} (inhaled) or LCt_{50} can be used as indices of vapour toxicity, however, the LCt_{50} has obvious practical and theoretical advantages over the LD_{50} (inhaled) for comparison of lethality of inhaled materials.

Measurement of Lethality of Toxic Material Absorbed Through the Skin

For toxic materials (usually liquids of low volatility) which cause death when absorbed through the skin, the LD_{50} (percutaneous) may be estimated by applying measured amounts of liquid droplets to the bare shaved skin of suitable animals, while at the same time preventing the inhalation of vapours. For extremely toxic materials, difficulties in measuring and applying the very small amounts of liquid may be encountered; in these cases, the toxic material may be suitably diluted in a non-toxic volatile solvent. The calculation of the LD_{50} is the same as that previously described, and is expressed proportionally to the body weight, i.e., mg. per Kgm.

Possible Approaches to Standards of Lethality for Treaty Purposes

A standard of lethality which would be suitable for international agreement should as far as possible define materials which would be attractive as chemical weapons, but exclude a number of materials in common use which, although lethal at low doses, are unattractive as weapons and have important economic and utilitarian values (or the use of the latter materials as CW agents could be banned, but their manufacture for civil purposes might be permitted).

Toxic materials which would be effective as weapons may be classified in three categories as follows:—

I. *Vapour Group*

This group of possible CW agents are toxic materials which are volatile liquids, which can be loaded into munitions as liquids but which readily vapourize on release, either because of the heat of explosion or by evaporation in air, releasing large clouds of highly concentrated toxic vapour. Examples of agents of this type are Phosgene, Hydrogen Cyanide and non-persistent nerve gases. They produce their effects by inhalation over short periods of time (seconds to minutes), either by effects on the lung itself (e.g., phosgene), or through absorption through the lungs into the blood stream to cause subsequent systemic poisoning (e.g., hydrogen cyanide, non-persistent nerve gas).

II. *Percutaneous Group*

This group of dangerous materials are toxic substances which are absorbed through the intact skin. They are generally liquids of low volatility, which on release remain as slowly evaporating droplets. The vapours are also toxic (by inhalation), but present at low concentrations. These agents may attack the skin itself (e.g., mustard), or may be absorbed through the skin into the blood stream (e.g., persistent nerve gas), thus causing general systemic poisoning, or may be absorbed by inhalation of low concentrations of vapour over comparatively long periods of time (minutes to hours).

III. *Supertoxic Solids*

Solid toxic materials are generally not dangerous as possible agents of warfare, because they are not readily absorbed through the skin, and are not sufficiently volatile to form inhalable vapour clouds, or sufficiently heat resistant to be disseminated as toxic smoke from pyrotechnic devices. However, development of munitions for producing large clouds of inhalable aerosol of solid materials would allow these substances to become available as weapons. Solid materials would have to be considerably more toxic than persistent nerve gases to offer any military advantage. Examples of such supertoxic solid materials are found among naturally-occurring toxins; examples are snake venom, ricin, staphylococcus enterotoxin, botulinus toxin.

The approximate lethal levels of toxic materials, including agents of chemical warfare, are indicated in Table I.

In considering possible criteria for materials to be defined by treaty as potential weapons, it would appear to be impractical to use only the injected LD_{50}s as such a criterion because:—

(a) Injected LD_{50}s only very approximately reflect the toxicity of materials by inhalation or percutaneous absorption.

(b) A limiting LD_{50} high enough to include phosgene and hydrogen cyanide (e.g., about 1 mg/Kg) would also include a large number of toxic solids which need not be considered as likely weapons.

(c) LD_{50} figures by any route vary widely depending on test conditions, particularly on species and sex of animals used. In order to specify a limiting injected LD_{50}, it would probably be necessary to specify test conditions quite exactly, and these test conditions would be difficult to standardize, particularly as to the specifications of the animals to be used.

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Because of the difficulties enumerated above, it would seem more practical to set up three standards of lethality, one for inhaled gases and vapours, a second for percutaneously toxic substances, and a third for supertoxic solids. If these levels were chosen to just include the least toxic of present chemical agents of chemical warfare, the degree of overlap with toxic materials necessary for use in industry, agriculture, and medicine, would be minimized.

The difficulties of standardizing animal test conditions are encountered with any toxic material. However, it may be argued that accurate LD_{50} figures are unnecessary for treaty purposes, since it is only necessary to decide whether a given material is more or less lethal than a set limit. Considerable savings in test costs could be realized and less uncertainty would exist if certain easily available chemicals were named as agreed standards of lethality.

Based on the foregoing considerations, the following scheme is proposed as a basis for discussion:

Proposed Criteria of Lethality

Materials fulfilling any of the following criteria of lethality would be considered as potential agents of chemical warfare to be subject to a general prohibition (or, more particularly, to be considered as agents sufficiently lethal and militarily useful to be made subject of a ban on their manufacture):

1. Vapour-forming materials having lethality equal to or greater than that of reference substance (suggested standard: Phosgene) when administered by inhalation to animals of any of the common laboratory species (mouse, rat, rabbit, guinea pig, cat or dog).
2. Percutaneously toxic materials having lethality equal to or greater than that of the reference substance (suggested standard: Nicotine (alkaloidal base)) when administered percutaneously to any of the common laboratory species (mouse, rat, rabbit, guinea pig, cat, dog or swine).
3. Materials having lethality equal to or greater than that of the reference substance (suggested standard: Neostigmine) when administered by subcutaneous injection to any of the common laboratory species (mouse, rat, rabbit, guinea pig, cat or dog).

The reasons for proposing these particular substances as reference materials are (a) that they are materials readily available commercially in many countries, (b) that they have levels of toxicity such as to minimize inclusion in a prohibition of less toxic materials which have legitimate uses (see Table I). It may be possible to establish a ban on manufacture, without interference in commercial uses, on all those agents having a lethality greater than these standards.

General Description of Testing Procedures for Proposed Criteria of Lethality

The principle of comparative testing would be to subject one small group of uniform animals (mammals) to a dosage of the reference substance, by the appropriate route (inhalation, percutaneous or injected subcutaneously), and to subject a second group to an equal dosage of the chemical to be tested. The dosage used would be one known to be close to the LD_{50} for the reference substance. In most cases, all the animals in the group receiving the test chemical would either live or die, and a clear-cut decision on the lethality of the chemical could be made. In the minority of cases, some of the animals in the test group would survive and some die; this would indicate that the material was of approximately equal lethality to the reference substance, and would be considered as a possible chemical warfare agent. These borderline cases would be of minor importance, since they would not offer attractive alternatives to recognized agents of chemical warfare.

The advantages of this proposal over more accurate methods for determining LD_{50} values are that it is a much simpler and more economical test which need not be tied to any particular species or strain of animal, or to any agreed mathematical calculation.

Limitations of the Proposal

The most important limitation on the above proposal, or on others which adopt a sole criterion of lethality, is that they would not include materials which are less lethal, but which could still have military utility against forces or civilians poorly protected. (For this reason, it may be necessary to allow a category of chemical agents of lesser lethality the use of which as agents of weapons of war would be prohibited, but whose manufacture for legitimate civil uses would be permitted.)

This shortcoming could be avoided if the treaty also prohibited materials which caused disability lasting more than a few days. However, the means of verifying this property of chemicals would be much more difficult than simple lethality, and at the present time non-lethal but permanent disabling chemical weapons are only a possibility.

The treatment of chemical weapons which cause temporary disability (incapacitating agents and irritant agents) is outside the scope of this paper; however, similar principles might be applicable in defining levels of incapacitating potency as have been proposed above for defining lethality, i.e., use of known incapacitating or irritant compounds as standards of comparison for tests with experimental animals or human subjects.

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TABLE I. *Approximate lethal dosages of CW agents and other toxic materials*

GROUP I—Toxic Vapours and Gases

Name of Lethal Material	Approximate Lethal Dose Inhaled	
	LCt_{50} mg min/m³	LD_{50} mg/Kg.
Carbon Monoxide	150,000	21
Ammonia	70,000	10
Sulfur Dioxide	40,000	5.6
Chlorine	36,000	5.1
Hydrogen sulfide	22,000	3.1
Hydrogen cyanide	5,500	0.790
Phosgene [1]	3,000	0.43
Ozone	2,000	0.28
Non-Persistent nerve gas	100	0.014

GROUP II—Percutaneously Toxic Liquids

Name of Lethal Material	Approximate Lethal Doses Percutaneous		
	Percutaneous mg/Kg.	Inhaled Vapour LCt_{50} mg min/m³	Injected mg/Kg.
Parathion	500		5
Diisopropyl fluorophosphate	100	5,000	4
Allyl alcohol	50	140,000	—
Nicotine (base) [1]			
Mustard Gas	20 (?)	2,000	10
Paraoxon	10		—
Persistent nerve gas	0.2	50	0.02

GROUP III—Supertoxic Solids

Name of Lethal Material	Approximate Lethal Dose Injected mg/Kg. (subcutaneous)
Strychnine	1.0
Physostigmine	0.5
Curarine	0.5
Neostigmine [1]	0.4
Digitoxin	0.3
Carbachol	0.3
Snake Venoms	0.5 → 50
Ricin	0.02
Carbamates	0.01
Bacterial Toxins	
—staphylococcus	0.00001
—tetanus	0.00000003
—botulin	0.00000002

[1] Proposed reference substance.