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Exposure of Drugs to Nuclear Explosions, Project 22.4

Food and Drug Administration
Department of Health, Education, and Welfare

Nevada Proving Grounds
March—June 1953

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A representative selection of 42 common drug preparations was exposed to the action of nuclear radiation and blast at two shots in the Upshot-Knothole series in Nevada in the spring of 1953. The drugs were packaged in the form in which they would be found on drugstore shelves and were exposed to various levels of neutron and gamma radiation ranging up to 50,000 r. Insulin and vitamin B_{12} were reduced in potency by about 10 and 50 per cent, respectively, but no other preparation tested showed any deterioration. Some of the drugs showed a moderate level of induced radioacitivity. This activity was traced either to an actual mineral constituent of the drug itself,

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20. Abstract (Continued)

as in the case of thiopental sodium, or to an excipient, such as calcium phosphate used in aureomycin. However, the level of activity was so low that little or no radiological health hazard would be involved in the normal use of the exposed drugs, although those with a high sodium content should be allowed to "cool" for several days before using them. Any drugs in containers remaining physically undamaged at a distance of 1000 yd from the explosion of a nominal atomic bomb are considered entirely safe for immdiate use. Under heavy exposure the glass containers in which the drugs were packaged displayed strong but short-lived activity due to their sodium content. Clear glass also showed a marked "darkening." None of the closures failed, and none of the closure materials deteriorated chemically or biologically under the conditions of the tests.

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FOREWORD

This report has had classified material removed in order to make the information available on an unclassified, open publication basis, to any interested parties. This effort to declassify this report has been accomplished specifically to support the Department of Defense Nuclear Test Personnel Review (NTPR) Program. The objective is to facilitate studies of the low levels of radiation received by some individuals during the atmospheric nuclear test program by making as much information as possible available to all interested parties.

The material which has been deleted is all currently classified as Restricted Data or Formerly Restricted Data under the provision of the Atomic Energy Act of 1954, (as amended) or is National Security Information.

This report has been reproduced directly from available copies of the original material. The locations from which material has been deleted is generally obvious by the spacings and "holes" in the text. Thus the context of the material deleted is identified to assist the reader in the determination of whether the deleted information is germane to his study.

It is the belief of the individuals who have participated in preparing this report by deleting the classified material and of the Defense Nuclear Agency that the report accurately portrays the contents of the original and that the deleted material is of little or no significance to studies into the amounts or types of radiation received by any individuals during the atmospheric nuclear test program.

ABSTRACT

A representative selection of 42 common drug preparations was exposed to the action of nuclear radiation and blast at two shots in the Upshot-Knothole series in Nevada in the spring of 1953. The drugs were packaged in the form in which they would be found on drugstore shelves and were exposed to various levels of neutron and gamma radiation ranging up to 50,000 r. Insulin and vitamin B_{12} were reduced in potency by about 10 and 50 per cent, respectively, but no other preparation tested showed any deterioration. Some of the drugs showed a moderate level of induced radioactivity. This activity was traced either to an actual mineral constituent of the drug itself, as in the case of thiopental sodium, or to an excipient, such as calcium phosphate used in aureomycin. However, the level of activity was so low that little or no radiological health hazard would be involved in the normal use of the exposed drugs, although those with a high sodium content should be allowed to "cool" for several days before using them. Any drugs in containers remaining physically undamaged at a distance of 1000 yd from the explosion of a nominal atomic bomb are considered entirely safe for immediate use. Under heavy exposure the glass containers in which the drugs were packaged displayed strong but short-lived activity due to their sodium content. Clear glass also showed a marked "darkening." None of the closures failed, and none of the closure materials deteriorated chemically or biologically under the conditions of the tests.

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EXPOSURE OF DRUGS TO NUCLEAR EXPLOSIONS

1 OBJECTIVE

After an atomic-bomb attack on any community, there will be an urgent and immediate need for drugs and standard medical preparations to treat the large numbers of casualties expected, as well as to continue the treatment of persons whose health depends on such substances as insulin. The questions arise whether the drugs and supplies salvaged from drugstores and pharmacies in the zone exposed to the bomb will be affected by the radiations and lose their potency or become poisonous or whether the containers will be damaged by some unexpected shock or blast effect and cause the contents to become unsterile. With a view to answering these questions, the Food and Drug Administration participated with the Federal Civil Defense Administration in two of the nuclear tests at Operation Upshot-Knothole in the spring of 1953 and exposed a representative group of drugs and medical preparations to a wide range of intensity of nuclear radiations and blast.

2 OPERATIONS AND INSTRUMENTATION

Forty-two drug preparations, listed in Table 1, were exposed to two shots in the Upshot-Knothole series as part of the Civil Effects Tests. Those drugs which were considered essential in the critical situations likely to arise after an atomic bombing were selected by the Food and Drug Administration. A complete list was not attempted; it was the purpose rather to study the effects of radiation and blast on a limited representative group of drugs in the field in order to delineate the problems involved and to give guidance for further experimentation if it proved to be needed.

With few exceptions all drugs were contained in glass bottles or ampuls and in the original commercial package units. The size selected was the common one that might be found on the drugstore shelf or moving in commerce. It is believed that in most situations the findings on small drug units will be applicable also to bulk units.

Exposures were made at high levels of shock and radiation by placing the samples as close as 400 yd to Ground Zero. Exposures were also made at lower levels at greater distances from Ground Zero and through the use of simple earth shielding. The drug samples were tested in four ways after exposure: (1) for chemical composition, (2) for induced radioactivity, (3) for potency, and (4) for acquired toxicity. The closures were examined for physical intactness, as measured by standard sterility or pyrogenicity tests, and for chemical deterioration, as evidenced by changes in the drug through contact with the closure material.

Table 1—DRUGS EXPOSED TO NUCLEAR DETONATIONS

Drug preparation	Form	Unit	Quantity per package
(1) Vitamin D	Gelatin capsule	50,000 units	500 per bottle
(2) Vitamin B_{12}	Glass ampul	10 ml	1 ampul
(3) Vitamin K	Glass ampul	1 ml	6 per package
(4) Folic acid	Tablet	5 mg	100 per bottle
(5) Meperidine hydrochloride	Tablet	50 mg	25 per bottle
(6) Morphine sulfate	Tablet	15 mg	20 per vial
(7) Pantopon*	Tablet	50 mg	20 per vial
(8) Methadone hydrochloride	Glass vial	10 ml	1 vial
(9) Amyl nitrite perles	Glass capsules	0.3 ml	12 per metal box
(10) Nitroglycerin	Tablet	0.6 mg	100 per bottle
(11) Methanthelin bromide	Tablet	50 mg	100 per bottle
(12) Phenobarbital	Tablet	30 mg	100 per bottle
(13) Thiopental sodium	Sterile powder	1 g	6 ampuls per box
(14) Prantal methyl sulfate*	Tablet	100 mg	100 per bottle
(15) Aspirin	Tablet	300 mg	24 per bottle
(16) Atropine sulfate	Tablet	0.4 mg	100 per bottle
(17) Digifolin*	Glass ampul	2 ml	20 per box
(18) Epinephrine hydrochloride	Glass ampul	1 ml	12 per box
(19) Sulfadiazine	Tablet	500 mg	100 per bottle
(20) Insulin	Ampul	40 units	10 ml per ampul
(21) Protamine zinc insulin	Ampul	40 units	10 ml per ampul
(22) Cortisone acetate	Powder	50 mg	1 vial
(23) Ethyl ether	Metal cannister	¼ lb	1 cannister
(24) Aureomycin	Capsule	250 mg	16 per vial
(25) Aureomycin	Crystalline powder	2 g	1 vial
(26) Chloramphenicol	Capsule	250 mg	16 per vial
(27) Chloramphenicol	Crystalline powder	2 g	1 vial
(28) Terramycin	Crystalline powder	200 mg	1 vial
(29) Penicillin, potassium G	Crystalline powder	500,000 units	1 vial
(30) Penicillin, procaine in oil	Glass vial	300,000 units	1 vial
(31) Penicillin, dibenzyl aq. susp.	Glass bottle	2 fl. oz	1 bottle
(32) Bacitracin	Powder	1 g	1 vial
(33) Streptomycin	Powder	1 g	1 vial
(34) Isotonic sodium chloride	Glass ampul	100 ml	1 ampul
(35) Dextrose, 10 per cent in water	Glass bottle	250 ml	1 bottle
(36) Dextran	Glass bottle	500 ml	1 bottle
(37) Polyvinyl pyrrolidine (PVP)	Glass bottle	500 ml	1 bottle
(38) Benzalkonium chloride	Glass bottle	4 fl. oz	1 bottle
(39) Thioglycollate medium USP	Glass bottle	250 ml	1 bottle
(40) Tygon intravenous tubing	Finely divided	7 g/250 ml†	1 bottle
(41) Latex (gum rubber) tubing	Finely divided	9 g/250 ml†	1 bottle
(42) Rubber stoppers‡	Finely divided	20 g/250 ml†	1 bottle

* Trade name.
† Dextrose saline.
‡ Natural rubber, black, lacquered.

2.1 Protective Packaging

The drugs were arranged for exposure by packing them in heavy wooden boxes. These boxes were 4 in. deep, 18 in. wide, and 25 in. long. The frames were of $\frac{7}{8}$-in. stock with $\frac{3}{4}$-in. plywood tops and bottoms, and all parts were secured with 2-in. iron screws. The space in each box was divided into compartments with $\frac{1}{2}$-in. plywood slats extending in the longest dimension. The slats served to restrict possible movement of the contents in the event of violent shock. The drug units, in addition to being individually wrapped in paper, were packed in a single layer between liberal amounts of excelsior. Single-layer packing was used to reduce shadowing effects. All the heavy bottles containing from 250 to 500 ml of perfusion solutions were packed in one compartment and tightly wedged between wrappers of corrugated paper. The arrangement of the drug units was identical in all boxes.

Twenty drug boxes, each weighing 40 lb packed, were prepared in the Food and Drug Administration laboratories, Washington, D. C., and shipped to the Nevada site. Three units were never exposed but were used as controls against possible deterioration or damage to the contents during transit.

2.2 Indicating and Detecting Elements

Before exposure each box was opened, and the following indicating and detecting elements were installed: (1) neutron detectors consisting of sulfur for fast neutrons and gold for thermal neutrons; (2) gamma-ray detectors containing Eastman and Du Pont film covering the range up to 20,000 r and chemical dosimeters of the chlorinated hydrocarbon type; and (3) heat-test papers in the 54 to 305°C range.

2.3 Drug Form

Wherever possible the form of the drug selected for exposure was the form commonly administered. About half the preparations were therefore in powder or tablet form. Theoretically the dry form might be expected to be less sensitive to ionizing radiation than the liquid form. Furthermore many of the tablets contained therapeutically inert additions, such as excipients and stabilizers, which are known to complicate analytical methods. Consequently, in the case of the important antibiotics, pure crystalline forms were also exposed together with the therapeutic forms. The thioglycollate medium was prepared in the laboratory and then sterilized and sealed with standard commercial equipment. This test was intended to detect contamination in case the seal failed momentarily during violent pressure changes.

In order to study possible chemical deterioration of common closure materials, such as gum rubber, tygon plastic, and natural black rubber, these materials were reduced to small pieces and enough of each was suspended in dextrose-saline medium in order to increase the ratio of exposed closure-material area to solution about 20-fold. The resultant preparations were then sterilized and sealed with standard commercial equipment.

2.4 Method of Exposure

An attempt was made to place the boxes in as high a radiation flux as possible and still avoid gross physical destruction. No man-made shielding, such as bunkers or test buildings, was used. The drug boxes were simply placed at varying distances from Ground Zero directly on or in the desert terrain surrounding the shot tower. Because of the uncertainty as to what constituted adequate protection from violent displacement or crushing, it was decided to bury some of the boxes at varying depths in the soil. Where a minimum of shielding was desired, the boxes were let into the soil a distance of 4 in. so that the flat tops were flush with the surface, and the exposed wooden surface was protected from charring by covering with a layer of sand about $\frac{1}{2}$ in. thick. In both tests the boxes were located along surveyed lines that had been established by the Rad-Safe organization parallel to the existing access roads. It was thus possible to recover them quickly and easily. Because of intense residual radiation no attempt was made to recover the boxes before D + 1.

2.5 Methods of Measurements

2.5.1 Radioactivity

The radioactivity of the drug preparations after exposure was measured with standard portable beta-gamma survey meters. Early measurements were made and completed at Mercury. Additional measurements were made in the Food and Drug laboratories in Washington with a Geiger counter scaler, standardized against a National Bureau of Standards beta source. Most of the drug preparations in the latter tests were ashed to reduce self-absorption. Measurements were repeated at intervals over a 4-month period to measure the apparent half life of the induced activities. Efforts were also made to identify the elements in the drug samples chemically and to correlate these findings with the observed composite half lives.

2.5.2 Chemical Tests

Eighteen of the drug preparations were examined in an infrared spectrophotometer. This technique was used as a screening test to decide whether more extensive biological methods would be worth while. It is estimated that this instrument was sensitive enough to record changes of ±10 per cent in composition. A qualitative spectroscopic examination was made on 20 ashed drug preparations in order to establish the presence of the main elemental components as well as to trace elements of possible significance.

2.5.3 Biological Tests

Seven standard bio-assay techniques were applied to 13 different drug preparations to establish potency. In addition, a number of other biological tests, such as blood pressure, electrocardiogram, guinea-pig intestine, and mortality, were applied to a variety of different drugs.

2.5.4 Sterility

Standard sterility tests were run, as well as bio-assays, to determine the presence or the absence of pyrogens.

3 RESULTS

3.1 Shot 7 (April 25)

Table 2 shows the arrangement of the drug boxes for exposure and the radiation flux measured in each box. Drug boxes at 600 yd from Ground Zero were recovered at D + 2; how-

Table 2—LOCATION* OF AND RECORDED NEUTRON AND GAMMA FLUX IN DRUG BOXES, SHOT 7

Box No.	Distance from Ground Zero, yd	Depth of soil shielding, ft	Radiation flux: Neutrons/cm² Sulfur	Radiation flux: Neutrons/cm² Gold	Radiation flux: Gamma, measured on film, r
17	400	1†		4.47×10^{12}	>20,000
12	400	1			>20,000
16	400	2		5.18×10^{11}	6,000
11	600	0‡		5.58×10^{12}	>20,000
18	600	1		1.29×10^{12}	3,000
8	600	2		8.31×10^{10}	<760

* Location: East quadrant. On a line 100 ft south of the access road and paralleling the rad-safe line.

† Box 17 was also protected by overlayering with 4-in. planking.

‡ Box 11 was set 4 in. into the soil with the lid flush with the surface.

ever, because of high residual activity at 400 yd, recovery of boxes at this distance was delayed until D+4. All boxes were intact and undisturbed. There was no breakage of any glass containers. A preliminary examination for radioactivity with portable survey instruments showed marked beta-gamma activity in the range of 20 to 40 mr/hr. This was most marked

Table 3—RADIOACTIVITY OF GLASS BOTTLES AND DRUG CONTENTS EXPOSED AT 600 YD, SHOT 7

Box No.	Depth of soil shielding, ft	Beta-gamma activity at D+2, mr/hr	
		PVP perfusion bottle, 500-ml capacity	Dextrose bottle, 250-ml capacity
8	2	1.75	1.5
18	1	11.5	9.7
11	0	20	20

Fig. 1—Darkening of glass from exposure to nuclear explosion. A glass container from heavily exposed box 11 is compared with a control.

in box 11, which had not been shielded. All readings on the boxes located at 400 yd, shielded with soil, and recovered at D+4 were 7 mr/hr. The removal of dust from the surface of the boxes, even wiping with a moist cloth, did not materially reduce the activity. When the contents of the boxes were opened and examined, it was found that most of the activity came from the glass.

Table 3 shows the comparative readings in milliroentgens per hour on two heavy glass containers taken from each of three boxes situated at 600 yd. The activity of the glass changes rapidly, declining to 0.2 to 0.4 mr/hr by D+7. Rough measurements indicate that the half life of the observed activity is of the order of 0.5 day. This is approximately the half life of Na^{24}, and, since sodium is present in most types of commercial glasses, the induced activity is thus accounted for.

In this connection the interesting observation was made that all the clear glass from box 11, which had received the largest amount of radiation, exhibited a marked "darkening" without a notable loss in transparency (see Fig. 1). In fact, the degree of darkening was directly

proportional to the amount of exposure, as was shown when the glass from other boxes that had been partially shielded was compared. After nearly 7 months there is no visible change in the glass, although it was stored out of contact with direct sunlight. In practice this darkening of glass could serve as a warning of heavy exposure to ionizing radiation.

Table 4—RADIOACTIVITY OF DRUG CONTAINERS AND DRUG CONTENTS FROM BOX 11 EXPOSED AT 600 YD, SHOT 7

Drug preparation	Beta-gamma activity at D+2, mr/hr		
	Container and contents	Container	Contents
(1) Vitamin D	25–30	25–30	0.5
(4) Folic acid	15	16	0.0
(5) Meperidine hydrochloride	22	22	0.13
(10) Nitroglycerin	13.5	14	0.0
(11) Methanthelin bromide	20	18	17
(12) Phenobarbital	17.5	19.5	3.0
(13) Thiopental sodium	16.5		5.5
(14) Prantal methyl sulfate	16	17	0.9
(15) Aspirin	25–30	25–30	0.13
(19) Sulfadiazine	22	22	0.9
(22) Cortisone acetate	17.5	19	0.0
(24) Aureomycin capsules	22	22	5.0
(26) Chloramphenicol capsules	19.5	20	0.1
(29) Potassium penicillin G	18	17	0.2
(32) Bacitracin powder	6.5	6.5	0.15
(33) Streptomycin	21	20	0.0

Table 5– DECLINE IN RADIOACTIVITY OF DRUGS FROM BOX 11, SHOT 7

Drug preparation, approx. 0.5 g	Beta-gamma activity, mr/hr		Half life, days
	D+2	D+7	
(11) Methanthelin bromide	17	0.5	1.0
(12) Phenobarbital	3.0	1.2	3.8
(13) Thiopental sodium	5.5	0.5	1.5
(14) Prantal methyl sulfate	0.9	0.8	29
(19) Sulfadiazine	0.9	0.5	5.8
(24) Aureomycin	5.0	2.0	3.8

In many of the smaller drug packages where it was possible to empty the container without spoiling the contents, readings were made on the container and contents, the empty container, and the contents alone. The results are shown in Table 4. It is clear that most of the activity comes from the glass container with variations accounted for mainly by the size and thickness of the glass. However, in the case of (11) methanthelin bromide, (12) phenobarbital, (13) thiopental sodium, (14) prantal methyl sulfate, (19) sulfadiazine, or (24) aureomycin, there is no question that significant activity has also been acquired by the drug itself.

The change in activity of these drugs was followed by measuring again at D+7. The results are shown in Table 5. Calculations show that the average half lives, with the exception

of (14) prantal methyl sulfate, range between 1 and 6 days. Analytical results to be discussed later indicate that the sodium content of (11) methanthelin bromide and (13) thiopental sodium is sufficient to account for the relatively short half lives of these two drug preparations. It is possible that trace elements account for the short half lives of the other drug preparations since the presence of liberal amounts of calcium, phosphorus, and sulfur as found would tend, at least in the case of (12) phenobarbital, (19) sulfadiazine, and (24) aureomycin, to produce longer apparent half lives.

With regard to the possible health hazards of ingesting such radioactive drugs within the first week, definite criteria are available. By conversion of the observed activities at D+2 to microcuries per gram, assuming a 10 per cent geometry of the detecting instrument with no allowance for self-absorption, the following values were obtained: (11) methanthelin bromide, 0.2; (12) phenobarbital, 0.04; (13) thiopental sodium, 0.08; (14) prantal methyl sulfate, 0.01; (19) sulfadiazine, 0.008; and (24) aureomycin, 0.1. The National Committee on Radioactive Protection has set limits* for occupational exposure to Ca^{45}, Na^{24}, and P^{32} permitting the daily deposition in the body of 1, 20, and 0.5 μc of these isotopes, respectively. These limits were set on the assumption that intake would occur through water consumed at a daily rate of 2.5 liters and that absorption would be complete. However, it is doubtful whether complete absorption would occur from ingesting any of these drugs. Even if absorption were complete and all the activity were due to Ca^{45} or P^{32}, the consumption of 1 g of (11) methanthelin bromide, to take the worst example, would only approach ¼ or ½ the respective permissible occupational limits of these two isotopes.

3.2 Shot 8 (May 19)

Eleven drug boxes were exposed by setting them 4 in. into the ground with the lids flush with the surface. A thin layer of sand was sprinkled on the lids to avoid charring of the wood. Distances from Ground Zero, as well as the radiation exposure recorded in the boxes, are shown in Table 6. The recovery of all boxes was made at H+29. None of the boxes were displaced from their setting, and they were all intact and undamaged, except for box 3 at 1000 yd which was slightly charred because some of the protective sand layer had washed off during a rainstorm that preceded the test. The boxes recovered at the 400-yd distance were immediately tested for radioactivity. Readings in excess of 400 mr/hr were recorded. Since this was considered a dangerous level of activity, the boxes were set apart to "cool" before opening. Observations on the other boxes were as listed below.

2500 yd: Contents intact; at H + 32, no radioactivity.

1000 yd: Contents intact; at H + 34, radioactivity of entire box, 1.5 mr/hr; contents, chiefly the larger heavier glass containers, 4 to 5 mr/hr.

600 yd: Contents intact; at H+36, radioactivity of entire box, 18 mr/hr; contents, chiefly the larger heavier glass containers, 25 to 30 mr/hr.

At D+2 the boxes from the 400-yd location were examined again. At this time the activity had declined to approximately 15 mr/hr, with the probe held at a distance of 60 cm from the section of the box containing the heavy perfusion bottles. When the boxes were opened, it was noted that those containing the PVP solutions had been broken in boxes 15 and 20. All the clear glass showed strong darkening such as that observed in box 11, shot 7.

In Table 7 are listed some of the activities of the full containers, as well as the drug contents, of boxes 9 and 15 exposed at 600 and 400 yd, respectively. It is evident that the exposure at 400 yd produced greater activity. This is further emphasized when it is noted that box 15 had cooled nearly twice as long as box 9 and also that, in order to make comparable measurements on the bottles from box 15, it was necessary to keep the probe at least a distance of 10 cm. By way of interest it can also be seen that the "active" drugs are again (11) meth-

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*The maximum permissible amounts of radioisotopes in the human body and the maximum permissible concentrations in air and water, National Bureau of Standards Handbook 52, Mar. 20, 1953.

Table 6—LOCATION* OF AND RECORDED NEUTRON AND GAMMA FLUX IN DRUG BOXES,† SHOT 8

Box No.	Distance from Ground Zero, yd	Radiation flux: Neutrons/cm²		Radiation flux: Gamma, r	
		Sulfur	Gold	Film	Chemical
19	400		2.69×10^{13}	>20,000	44,000
20	400		2.74×10^{13}	>20,000	44,000
15	400		2.20×10^{13}	>20,000	44,000
7	600		1.41×10^{12}	15,000	19,700
9	600		1.76×10^{12}	19,000	
13	600		1.53×10^{12}	14,000	19,700
5	1,000		6.51×10^{10}	1,000	
10	1,000		6.27×10^{10}	1,100	
3	1,000		5.39×10^{10}	1,100	
6	2,500			4.8	
1	2,500			4.8	

* Location: Southwest quadrant. On a line 15 ft northwest of the access road and paralleling the rad-safe line.

† The boxes were not shielded; they were set 4 in. into the soil with the lids flush with the surface.

Table 7—EFFECT OF DISTANCE ON INDUCED RADIOACTIVITY OF DRUGS, SHOT 8

Drug preparation	Beta-gamma activity, mr/hr: Box 9 exposed at 600 yd*		Box 15 exposed at 400 yd‡	
	Drug bottle and contents†	Contents†	Drug bottle and contents§	Contents†
(4) Folic acid	15	0.0	6.0	
(5) Meperidine hydrochloride	14	0.0	15	0.3
(10) Nitroglycerin			4.0	0.3
(11) Methanthelin bromide	11	7.5	9.0	>20
(12) Phenobarbital	8.5	0.6	5.5	10
(13) Thiopental sodium	9.5	4.0	9.0	20
(14) Prantal methyl sulfate	10	0.5	4.0	4.0
(15) Aspirin	12	0.0	11	0.3
(16) Atropine sulfate	10.5	0.0	4.5	0.3
(19) Sulfadiazine	18	0.25	20	1.2
(24) Aureomycin capsule	16		6.0	7.0
(25) Aureomycin crystalline powder			7.0	0.3
(26) Chloramphenicol capsule	11	0.1	7.0	0.3
(28) Terramycin			7.0	0.3
(29) Potassium penicillin G	11	0.4	8.0	2.0
(32) Bacitracin	10	0.2	9.0	0.3
(33) Streptomycin	10.5		9.5	

* Readings made at H + 36.

† Readings made with probe in contact with sample.

‡ Readings made at H + 58.

§ Readings made with probe held 10 cm from sample.

anthelin bromide, (12) phenobarbital, (13) thiopental sodium, (14) prantal methyl sulfate, (19) sulfadiazine, (24) aureomycin, and (29) potassium penicillin G (see Table 5).

3.3 Heat-test Papers

Although the radiant heat flash from the nuclear detonation was sufficient to char exposed wood at a distance of 1000 yd, none of the test papers showed any evidence of heat, even the one sensitive to 54°C. The test papers were mounted inside each box on the lid which faced exposure, and there was therefore ¾ in. of wood plus a thin layer of sand insulating the test paper from the heat flash. It is evident that only insignificant amounts of heat from the explosions reached the samples.

Table 8—INDUCED RADIOACTIVITY OF DRUGS READ AT D + 5 FROM BOX 20 EXPOSED AT 400 YD, SHOT 8

Drug preparation	Induced radioactivity, μc	
	Per gram of drug preparation	Per daily intake of drug preparation
(1) Vitamin D	1.0×10^{-4}	6.8×10^{-5}
(4) Folic acid	2.0×10^{-5}	3.2×10^{-6}
(5) Meperidine hydrochloride	1.4×10^{-4}	7.6×10^{-4}
(10) Nitroglycerin	4.1×10^{-4}	
(11) Methanthelin bromide	2.0×10^{-2}	2.2×10^{-2}
(12) Phenobarbital	3.6×10^{-2}	1.8×10^{-2}
(13) Thiopental sodium	2.2×10^{-2}	4.6×10^{-2}
(14) Prantal methyl sulfate	1.9×10^{-2}	2.8×10^{-2}
(15) Aspirin	4.9×10^{-5}	1.4×10^{-4}
(16) Atropine sulfate	0	0
(19) Sulfadiazine	2.8×10^{-3}	2.2×10^{-2}
(24) Aureomycin capsule	8.0×10^{-2}	2.0×10^{-1}
(27) Chloramphenicol crystalline powder	1.1×10^{-3}	1.1×10^{-3}
(28) Terramycin	4.9×10^{-4}	4.9×10^{-4}
(29) Potassium penicillin G	1.4×10^{-3}	8.8×10^{-4}
(32) Bacitracin	1.7×10^{-3}	1.7×10^{-3}
(33) Streptomycin	1.9×10^{-4}	1.9×10^{-4}

3.4 Radioactivity Measurements

When the drug boxes were returned to the Food and Drug laboratories in Washington, additional measurements were made with a thin end-window Geiger counter connected to a standard scaler. To this end the solid drugs were finely ground, and the solutions evaporated to dryness. Some samples were read in the dry powdered form, but most of them were further processed by ashing in a muffle furnace at 500°C in order to reduce self-absorption. Table 8 shows a selected list of dry drugs measured at D + 5. These samples were not ashed but were ground finely and spread thinly on planchettes. No correction was made for self-absorption since it was shown that, under the conditions of these measurements, self-absorption did not introduce an error greater than 10 per cent. Activities have been expressed in microcuries per gram of drug preparation and also as microcuries per daily intake of drug preparation. The factors involved in this calculation will be discussed further in connection with Table 9.

Samples of nearly all the drugs exposed in box 20 at 400 yd (shot 8) were processed by ashing. The ashed samples were thinly spread on aluminum planchettes and measured repeatedly for radioactivity during a 4-month period in order to determine the rate of decay.

Table 9--INDUCED RADIOACTIVITY OF DRUGS READ AT D + 3(
FROM BOX 20, SHOT 8

Drug preparation	Ash ratio*	Microcuries per milliliter or gram of drug preparation	Av. 24-hr intake of pure drug	Excipient ratio†	Microcuries per av. 24-hr intake
(1) Vitamin D	5.7×10^{-3}	4.1×10^{-5}	31 mg	210	2.7×10^{-5}
(2) Vitamin B_{12}		6.3×10^{-5}	3 ml	1	1.9×10^{-4}
(3) Vitamin K		1.5×10^{-4}	0.5 ml	1	7.5×10^{-5}
(4) Folic acid	3.1×10^{-2}	5.7×10^{-5}	10 mg	16.3	9.3×10^{-4}
(5) Meperidine hydrochloride	5.5×10^{-2}	5.1×10^{-5}	750 mg	7	2.7×10^{-4}
(6) Morphine sulfate	6.9×10^{-4}	2.5×10^{-5}	20 mg	1.4	1.0×10^{-4}
(8) Methadone hydrochloride		1.1×10^{-5}	5 ml	1	5.3×10^{-5}
(11) Methanthelin bromide	4.5×10^{-1}	8.7×10^{-5}	300 mg	5.29	1.4×10^{-4}
(12) Phenobarbital	5.0×10^{-1}	1.7×10^{-2}	150 mg	3.27	6.8×10^{-3}
(13) Thiopental sodium	3.3×10^{-1}	1.5×10^{-4}	2 g	1.06	3.2×10^{-4}
(14) Prantal methyl sulfate	3.0×10^{-1}	7.4×10^{-3}	600 mg	2.55	1.1×10^{-2}
(15) Aspirin	2.4×10^{-4}	9.3×10^{-6}	2 g	1.4	2.6×10^{-5}
(16) Atropine sulfate	5.8×10^{-4}	4.1×10^{-5}	6 mg	830	2.0×10^{-4}
(17) Digifolin		3.5×10^{-6}	2 ml	1	6.7×10^{-6}
(18) Epinephrine hydrochloride		8.7×10^{-6}	1 ml	1	8.7×10^{-6}
(19) Sulfadiazine	1.1×10^{-1}	1.5×10^{-3}	6 g	1.32	1.2×10^{-2}
(20) Insulin		3.7×10^{-7}			
(21) Protamine zinc insulin		6.2×10^{-5}	0.5 ml	1	3.1×10^{-5}
(24) Aureomycin capsule	4.9×10^{-1}	3.8×10^{-2}	1 g	2.45	9.1×10^{-2}
(25) Aureomycin crystalline powder	2.0×10^{-4}	1.4×10^{-3}	1 g	1	1.3×10^{-3}
(26) Chloramphenicol capsule	3.2×10^{-4}	1.3×10^{-3}	1 g	1.21	1.6×10^{-3}
(27) Chloramphenicol crystalline powder	1.2×10^{-4}	5.1×10^{-5}	1 g	1	5.1×10^{-5}
(28) Terramycin	1.0×10^{-4}	7.9×10^{-5}	1 g	1	7.9×10^{-4}
(29) Penicillin, potassium G	2.0×10^{-1}	8.1×10^{-4}	620 mg	1	1.4×10^{-4}
(30) Penicillin, procaine in oil		4.7×10^{-6}	1 ml	1	4.7×10^{-6}
(31) Penicillin, dibenzyl aq. susp.		1.3×10^{-3}	40 ml	1	1.4×10^{-3}
(32) Bacitracin	2.1×10^{-2}	3.1×10^{-4}	1.2 g	1	3.8×10^{-4}
(33) Streptomycin	4.7×10^{-3}	4.4×10^{-5}	1 g	1	4.4×10^{-5}
(34) Isotonic sodium chloride		5.4×10^{-5}	2000 ml	1	1.1×10^{-1}
(35) Dextrose, 10 per cent in water		4.5×10^{-7}	500 ml	1	2.3×10^{-4}
(36) Dextran		7.8×10^{-5}	500 ml	1	3.9×10^{-2}
(37) Polyvinyl pyrrolidine (PVP)		3.3×10^{-5}	1000 ml	1	3.3×10^{-2}
(38) Benzalkonium chloride		2.6×10^{-4}			
(39) Thioglycollate medium USP		2.8×10^{-5}			
(40) Dextrose saline (tygon)		2.5×10^{-5}	2000 ml	1	5.0×10^{-2}
(41) Dextrose saline (latex)		2.8×10^{-5}	2000 ml	1	5.6×10^{-2}
(42) Dextrose saline (rubber stoppers)		3.0×10^{-5}	2000 ml	1	6.0×10^{-2}

* Ash ratio = milligrams of ash per milligram of the drug preparation.

† Excipient ratio = milligrams of the dry-drug preparation per milligram of the pure drug.

When the logarithm of activity was plotted against time, it soon became apparent that some of these plots were not straight lines. This indicated the presence of several radioactive species having different rates of decay. Spectroscopic analyses and standard macrochemical analyses, as well as the reported formulation of the drug preparation, confirmed this finding.

In Tables 9 and 10 data are assembled on the drugs exposed in box 20. Although the activity of the drug preparations was observed over a considerable period, only the D + 30 observations are listed. In Table 9 activities expressed as microcuries per gram of drug preparation and microcuries per average daily intake are given in columns 3 and 6, respectively. Collateral information upon which the calculated values in column 6 are based is given in columns 4 and 5. The values given in column 4 have been derived from a number of authoritative sources and represent the average amount of drug that would normally be ingested in 24 hr. These values do not represent extreme situations such as might be met in the case of atropine applied in massive amounts to combat the effects of "nerve gas" or of perfusion liquids often applied in heroic proportions.

Column 5 gives the ratio of the dry-drug preparation to the pure drug. It shows that in some cases the proportion of inert excipient is very large, e.g., for (1) vitamin D and (16) atropine, or moderately large for (4) folic acid, (6) morphine, (11) methanthelin bromide, (12) phenobarbital, etc.

By reference to column 2 it is possible to gain some insight as to the nature of the excipient. This column gives the ratio of ashed to unashed drug. For example, an organic excipient, such as lactose [(16) atropine], gives a very low ratio, whereas a mineral excipient, such as calcium phosphate [(24) aureomycin], gives a much larger ratio.

The presence of mineral ash always results in increased radioactivity in the drug preparation. This is well shown in the case of the two antibiotics (24) aureomycin and (26) chloramphenicol, exposed in pure crystalline as well as capsular form. It is shown in column 2 that the crystalline forms have a very low ash content as compared with the capsular forms, and column 5 shows that the capsular forms are diluted with mineral excipients. By reference to column 6, which shows the respective microcuries of activity on a daily intake basis, it can be seen that (24) aureomycin in capsular form supplies nearly 100 times the radioactivity of the crystalline, whereas (26) chloramphenicol supplies approximately 30 times. The activity of (11) methanthelin bromide, (12) phenobarbital, (14) prantal methyl sulfate, and (19) sulfadiazine undoubtedly can be traced largely to the excipients, although the sulfur of constitution in (14) prantal methyl sulfate and (19) sulfadiazine may be also a contributing factor.

In Table 10 are listed the apparent half lives of the drug preparations measured over a period of about 4 months, during which readings were made at monthly intervals. If a semilog plot of the measurements was a reasonably straight line, the activity was presumably due to a single radioactive species, and the half life was read from the graph. If, on the other hand, the plot showed a curvature, the activity was due to at least two radioactive species. Two half lives were then calculated, one for the initial period of approximately 30 days beginning at D+30 and one for the final 30 days of the observation period beginning either at D+90 or D+120, depending on whether the sample was active enough to obtain a dependable reading after that length of time.

The marked activity of many of the drug samples at D+2 was evidently due to Na^{24}; however, a simple calculation shows that this particular atomic species with a half life of 0.62 day has all disappeared by D+30. It is probable that the activity at D+30 is largely contributed by phosphorus and calcium. The analytical data appended to the table show that phosphorus is present in (3) vitamin K, (12) phenobarbital, (14) prantal methyl sulfate, (19) sulfadiazine, (21) protamine zinc insulin, and (24) aureomycin. For all these drugs the "initial half lives" range between 13.6 and 18.7 days, which is surprisingly close to the 14.8-day half life of phosphorus. (2) Vitamin B_{12} and (39) thioglycollate medium, however, are exceptions because, in spite of their phosphorus content, they do not show much activity. The four preparations containing considerable amounts of calcium show the highest activity at D+30. These are (12) phenobarbital, (14) prantal methyl sulfate, (19) sulfadiazine, and (24) aureomycin. The apparent half life of all the activities, of course, lengthens with time.

Table 10—APPARENT RADIOACTIVE HALF LIVES OF DRUGS AND SIGNIFICANT ELEMENTS FOUND IN BOX 20, SHOT 8

Drug No.	Calculated half life, days			Significant elements and half lives, days							
	Initial*	Final†	Entire‡	Ca, 180	P, 14.3	Sn, 105	Zn, 250	Fe, 46	Na, 0.62	Cl ——→	S, 87
(1)	28	410									
(2)			72	tr	+§	0	0	+	+++¶	++¶	(?)
(3)	19	41		+	+§	+	0	++	++		(?)
(4)			58								
(5)			55							++§	
(6)											+§
(8)	56	86		+	0	+	0	++	++	++§	
(11)	22	93		tr	0	0	0	++	+++¶		+++¶
(12)	14	18		++++¶	++¶	tr	0	++	tr		+
(13)	37	137		0	0	+	0	+	+++§		+§
(14)	15	26		++¶	+¶	tr	0	++	tr		+§
(15)											
(16)											+§
(17)	50	59		+	0	++	tr	++	+		(?)
(18)	68	146		0	0	0	0	+	++§	++§	
(19)	14	21		++¶	+¶	tr	0	++	tr		+§
(20)											+§
(21)	17	47		tr	+§¶	+	+§	+	+		+§
(24)	15	35		++++¶	+¶	tr	0	++	tr		+
(25)			87	0	0	0	0	(?)	tr		
(26)	7	373									
(27)	30	373									
(28)	62	375									
(29)	46	180									
(30)	18	36									
(31)	25	95							++§		
(32)			101								
(33)	37	285									
(34)			109	tr	0	0	tr	+	++++§	++++§	
(35)											
(36)			85						++§	+++§	
(37)			115	++§	0	+	0	++	+++§	+++§	(?)
(38)	66	145		+	0	+	0	+	++	+++§	(?)
(39)	42	95		0	+§	+	0	+	++§		+§
(40)			85						++§	+++§	
(41)			109						++§	+++§	
(42)			71						+++§	+++§	

* Initial = half life calculated for the period from D+30 to D+60.

† Final = half life calculated for the period from D+90 to D+120 or D+120 to D+150.

‡ Entire = half life calculated for the entire period from D+30 to D+120, or D+150.

§ Element present as a constituent of the drug.

¶ Element present as a constituent of the excipient or vehicle.

Other elements also contribute to the observed radioactivity. For example, tygon tubing, which was part of the transfusion kit exposed with the dextran bottle, had an activity of 2×10^{-3} μc/g at D + 30 (box 20) with an estimated half life of the order of 100 days. Spectroscopic analysis revealed the presence of tin from which a radioactive isotope, Sn^{113} with a half life of 105 days, can be produced. Although tin occurs in more than traces in tygon tubing (it is added in the curing process), trace quantities of this element were found in many of the drugs (see Table 10) presumably due to the fact that some pharmaceutical equipment is lined with tin.

In the case of iron, which was found in trace amounts in all drugs examined, the possibility of the production of the radioactive Fe^{59} species with a half life of 46 days could be entertained. However, on the basis of calculations which assume that if all the activity in a sample (100 dis/min) were caused by iron, it can be shown that the entire sample would have to be composed of iron (approximately 2 g). This is obviously impossible. It may be also noted parenthetically that the iron screws used in the boxes showed a barely measurable activity.

In seeking to explain the radioactivity of the isotonic saline, at D + 30 neither the short-lived Na^{24} (0.62 day) nor the long-lived Cl^{36} (2×10^{-6} years) can account for the observed half life of 109 days. However, the transmutation of the stable Cl^{35} isotope to the radioactive S^{35} isotope by an n,p reaction is a distinct possibility. It may be assumed therefore that all the drugs containing chlorine will be radioactive by virtue of S^{35} with a half life of 87 days. It should be emphasized that the other perfusion fluids, such as dextran, PVP, and the dextrose salines, all have activities of the same order; they all contain chlorine, and the calculated half lives are within a range that is attributable to S^{35}.

In the light of the observations made on the possible hazards of ingesting drugs at D + 2 (see Table 5), it is apparent that those systematically examined at D + 30 (see Table 9) would constitute even less hazard. There is no question but that the ingestion of radioactivity is undesirable, in general, and should be avoided, particularly if exposure is to extend over many years. However, in cases of major disaster, such as envisaged here, the risk involved in the widespread use of drugs having no more activity than levels found in these experiments is quite negligible. In addition, the tolerance level for radioactivity is much higher under emergency conditions and for a short time than it is for long-continued exposure.

3.5 Chemical Tests

Drugs from box 20, heavily exposed at 400 yd to 44,000 r (chemical dosimeter) gamma rays, 7.18×10^{10} fast neutrons per square centimeter, and 2.74×10^{13} thermal neutrons per square centimeter, were examined on a recording infrared spectrophotometer, and the tracings were compared against those developed from the "transit control drugs." It will be recalled that the transit controls consisted of three drug boxes which were shipped to Mercury, Nev., and returned to Washington without having been exposed to ionizing radiation. The following drugs were studied: (5) meperidine hydrochloride, (6) morphine sulfate, (7) pantopon, (8) methadone hydrochloride, (9) amyl nitrite, (10) nitroglycerin, (11) methanthelin bromide, (12) phenobarbital, (13) thiopental sodium, (14) prantal methyl sulfate, (15) aspirin, (19) sulfadiazine, (22) cortisone acetate, (23) ethyl ether, (25) crystalline aureomycin, (27) crystalline chloramphenicol, (29) potassium penicillin G, and (35) 10 per cent dextrose solution. The over-all sensitivity of these tests was such that a 10 per cent deviation from normal could be detected. In no instance could any abnormality be detected, and it may be concluded therefore that gamma and neutron fluxes of the above intensity produced no measurable change in chemical constitution. In view of the negative results from a heavy exposure, drugs from less exposed boxes were not examined.

3.6 Biological Tests

3.6.1 Toxicity

(a) Closure Materials. The question as to whether certain standard closure materials could, upon exposure to ionizing radiation, impart toxins or impurities to a standard per-

fusion medium consisting of dextrose saline was studied in the following way: The solutions of dextrose saline that had been in contact with finely divided tygon plastic, gum rubber, and lacquered black-rubber stoppers while being exposed in box 20 were injected into rabbits. This is a standard pyrogen test capable of detecting less than 0.05 μg of a pyrogen or physiological equivalent. Under these conditions the animals would also respond to toxins that might have been elaborated in the test materials. All tests proved to be negative. Furthermore these experiments demonstrated that the dextrose saline contained no pyrogen of bacterial origin which might have developed had the standard commercial closures failed under the impact of pressure changes. Other tests conducted with the dextrose saline also proved to be uniformly negative. They were: blood-pressure response, dog; electrocardiogram, dog; and guinea-pig intestine.

(b) Other Drugs. (19) Sulfadiazine, (11) methanthelin bromide, and (6) morphine sulfate were tested by the guinea-pig intestine method. All tests were negative.

(c) Antibiotics. From the most heavily exposed boxes, 11, 15, and 19 and control box 2. (25) Crystalline aureomycin, (27) crystalline chloramphenicol, (29) potassium penicillin G, and (32) bacitracin were tested for toxicity by the standard mouse test used in the Division of Antibiotics in its certification operations. All tests were negative. Fiducial limits of the test were ±20 per cent.

3.6.2 Potency

(a) Antibiotics. From the most heavily exposed boxes, 11, 15, and 19 and control box 2. (24) Aureomycin capsules, (25) aureomycin crystals, (26) chloramphenicol capsules, (27) chloramphenicol crystals, (29) potassium penicillin G, (30) procaine penicillin, (31) dibenzyl penicillin, and (32) bacitracin were assayed by the standard methods used by the Division of Antibiotics in its certification operations. All antibiotics were up to normal potency. Fiducial limits of the assay were ±5 per cent.

(b) Epinephrine. From the most heavily exposed boxes, 11, 15, and 19 and control box 2. According to the standard pharmacopoeial test, all samples were within the range of acceptable potency. Fiducial limits of the assay were ±20 per cent.

(c) Digifolin. From the most heavily exposed boxes, 11, 15, and 19. According to the standard pharmacopoeial test, all samples were within the range of acceptable potency. Fiducial limits of the assay were ±20 per cent.

(d) Vitamin D. From the most heavily exposed box 11, "intermediate" box 7, and control box 2. According to the standard pharmacopoeial test, all samples were within the range of acceptable potency. Fiducial limits of the assay were ±15 per cent.

(e) Folic Acid. From the most heavily exposed boxes 11, 15, and 20; intermediate box 7; and control boxes 2 and 14. By an alternate chemical test for this vitamin, all samples were within the range of acceptable potency. Fiducial limits of the assay were ±5 per cent.

(f) Vitamin B_{12}. Visual observation showed that heavily exposed samples had changed color. Microbiological tests showed that the potency was also considerably reduced. Table 11 shows the results. It can be seen that there is a good inverse relation between potency and the amount of radiation flux. Independent tests under laboratory conditions conducted with an exposure of 150,000 *r* confirmed this finding. For the present therefore it may be assumed that vitamin B_{12} is sensitive to both neutron and gamma radiation.

(g) Insulin. Examination of heavily exposed insulin solution showed it to be darker than the standards. Bio-assay by means of the standard rabbit blood-sugar test showed that the potency was also reduced. The results of the test are shown in Table 12. It can be seen that there is a good inverse relation between potency and the amount of radiation flux.

(h) Protamine Zinc Insulin. Bio-assay by means of the standard rabbit blood-sugar test showed no reduction in potency of heavily exposed samples.

3.7 Bacteriological Tests

Eighteen bottles containing the USP thioglycollate medium were incubated at 35°C for 2 weeks. All were sterile, thus showing that the closures had resisted pressure changes during

exposure and remained bacteriologically intact. Portions from bottles heavily exposed in boxes 7, 9, and 11 and control 2 were inoculated with viable microorganisms. Normal growth was obtained in all cases within 24 hr. It was concluded that exposure to ionizing radiation did not change the nutrient properties of the medium.

Table 11—EFFECT OF RADIATION ON THE POTENCY OF VITAMIN B_{12}

Box No.	Radiation flux: Neutrons/cm² Sulfur	Neutrons/cm² Gold	Gamma, r	Vitamin B_{12} concentration, μg/ml*
2		Control		15.0
14		Control		15.2
3		5.39×10^{10}	11,000	13.9
7		1.41×10^{12}	15,000†	13.7
8		8.31×10^{10}	760	14.0
11		5.58×10^{12}	20,000	8.1
15		2.20×10^{13}	20,000‡	8.0
20		2.74×10^{13}	20,000	8.0

* Fiducial limits of the assay were ±5.0 per cent.
† Chemical dosimeter, 19,700 r.
‡ Chemical dosimeter, 44,000 r.

Table 12—EFFECT OF RADIATION ON THE POTENCY OF INSULIN

Box No.	Radiation flux: Neutrons/cm² Sulfur	Neutrons/cm² Gold	Gamma, r	Potency, %	Fiducial limits, P = 0.95
11		5.58×10^{12}	20,000	86.6 of control 14	76–99
18		1.29×10^{12}	3,000	90.8 of control 2	79–104
19		2.69×10^{13}	20,000*	92.7 of control 4	90–96

* Chemical dosimeter, 44,000 r.

Two samples of benzalkonium chloride were tested for their bacteriostatic potency. No difference was found between the exposed sample and the control.

3.8 Uncompleted Tests

Because of a lack of sensitive definitive tests, examinations of PVP and dextran were incomplete at the time this report was ready for submission.

4 SUMMARY AND CONCLUSIONS

A selected list of drugs has been exposed to nuclear explosions in order to subject them to high levels of ionizing radiation and shock. The results are as follows:

1. Insulin was reduced in potency by about 10 per cent.
2. Vitamin B_{12} was reduced in potency by about 50 per cent.
3. No deterioration was observed in any of the other drug preparations.

4. Glass containers exhibited marked induced radioactivity which decayed rapidly. Heavily exposed clear glass showed a marked darkening.

5. Many drugs exhibited induced radioactivity which was measurable several months after exposure.

6. A significant amount of the induced radioactivity in the drugs was traced to the presence of certain mineral excipients, such as calcium phosphate.

7. Little or no radiological health hazard is involved in the normal use of the exposed drugs, although those with a high sodium content should be allowed to cool several days before they are used.

8. The tests used in this series of experiments show that any drugs in containers remaining physically undamaged at a distance of 1000 yd from a nominal type nuclear detonation are entirely safe for use.