INSTITUTE FOR DEFENSE ANALYSES

Combined Nuclear Effects Feasibility Study

Robert A. Zirkle
Janet C. Marroquin Pineda

October 2022

IDA Paper P-33233

Log: H 22-000377

INSTITUTE FOR DEFENSE ANALYSES
730 E.Glebe Rd
Alexandria, VA 22305

The Institute for Defense Analyses is a nonprofit corporation that operates three Federally Funded Research and Development Centers. Its mission is to answer the most challenging U.S. security and science policy questions with objective analysis, leveraging extraordinary scientific, technical, and analytic expertise.

About This Publication
This work was conducted by the Institute for Defense Analyses under contract HQ0034-14-D-0001, project FN-6-4947, "Medical CBRN Defense Analyses" for the U.S. Army Office of The Surgeon General (OTSG) Executive Agent. The views, opinions, and findings should not be construed as representing the official position of either the Department of Defense or the sponsoring organization.

Acknowledgments:
The authors thank Kristen A. Bishop and Douglas Schultz for their thoughtful reviews of this paper.

For More Information:
Dr. Robert A. Zirkle, Project Leader
rzirkle@ida.org, 703-845-2038
Ms. Jessica L. Stewart, Director, SFRD
jstewart@ida.org, 703-575-4530

INSTITUTE FOR DEFENSE ANALYSES

IDA Paper P-33233

Combined Nuclear Effects Feasibility Study

Robert A. Zirkle
Janet C. Marroquin Pineda

This page is intentionally blank.

Executive Summary

Experience derived from the nuclear explosions in Hiroshima and Nagasaki, as well as modeling results, indicate that victims of a nuclear weapons event are likely to suffer injuries due to absorbing some combination of prompt radiation, blast, and thermal fluence insults. Moreover, evidence suggests that combinations of radiation, blast, and thermal insult are likely to have synergistic effects (i.e., the injuries sustained by a combination of two or all three insults are likely to be more severe than those produced by each insult separately).

The North Atlantic Treaty Organization (NATO) current methodology for estimating casualties due to nuclear effects, Allied Medical Publication (AMedP)-7.5, does not account for such synergistic effects (nor did its predecessors in the AMedP-8 series). The issue of adding synergistic effects to the AMedP casualty estimation methodology has not been considered since the late 2000s, but research into these effects has been active as of late. The Office of the Surgeon General of the U.S. Army asked IDA to re-examine past work and review the latest research and tools to assess the feasibility of incorporating synergistic effects into the next iteration of AMedP-7.5.

In the current AMedP-7.5 methodology, the effects of each insult are initially considered separately, with sign/symptom severity progressions over time drawn for the relevant physiological systems of each insult class. Four representative systems were chosen for radiation, three for thermal, and one was chosen for primary blast effects (the only blast effect considered in this manner). Five different range bands were chosen for each insult class based on their expected level of injury, starting with no observable effect.

Overall injury profiles were then developed for each insult range by overlaying the individual physiological system progressions onto a single plot and then tracing out the maximum exhibited physiological symptom severity at each point in time. The process was repeated for combined effects: the appropriate radiation, blast, and thermal injury profiles were overlaid and the maximum severity chosen at each point in time.

The IDA research team considered three alternative approaches for developing a synergistic combined methodology: output and/or products from the 1990s Combined Methodology Study; applying data from human clinical or animal experimental studies; and employing output and/or products from various mechanistic models (in particular the Health Effects from Nuclear and Radiological Environments (HENRE) model developed by Applied Research Associates).

The Combined Methodology Study took input from subject matter experts to develop a set of combined sign/symptom severity progressions across relevant physiological symptom categories (much like the AMedP-7.5 methodology for individual insults) across all combinations of radiation, blast, and thermal insult bands. These progressions were then used to develop performance degradation curves, all of which subsequently went into the Consolidated Human Response Nuclear Effects Model (CHRNEM). Unfortunately, the original combined progressions have been lost and the CHRNEM code is only available in a compiled format (i.e., the human-readable source code has been converted to a machine-readable language). The progressions have never been recovered.

The IDA research team determined that insufficient reliable human data existed from previous nuclear explosions or accidents to develop a combined methodology, though blast and thermal data from recent terrorist or insurgent-related events might be worth examining further. The research team found multiple issues with using data from animal experiments to develop a model of human response to combined effects. Among these issues were the paucity of data from large animal models (generally considered the best models for extrapolating to human response); significant differences between the small animal models generally employed in most recent experimental work and human response; difficulty of finding appropriate animal models that reflected to human response across combined insults; and the general lack of understanding of the mechanisms underlying many of these responses.

Many of the issues with animal models carried over into mechanistic modeling, which largely relies on small animal models for development and validation. The HENRE modeling includes a number of mechanistic models for representing the effects of radiation, thermal and combined radiation/thermal. HENRE does treat combined radiation and thermal in a synergistic manner, largely through these mechanistic models. Blast effects, however, are treated separately and not combined synergistically with the other two insults.

The mechanistic model outputs do not readily lend themselves to something like sign/symptom severity progressions, though this correlation is done for radiation alone as part of an estimation of performance degradation following radiation exposure. To do so, modified versions of the radiation sign/symptom severity progressions developed under the earlier Intermediate Dose Program (IDP) are required. As mentioned above, similar combined progressions developed during the Combined Methodology Study have been lost, so a similar approach with radiation and thermal is not possible.

Although the IDA research team determined that none of the three alternative approaches could currently be used to develop a synergistic methodology, there may be an opportunity to characterize synergistic effects from combined nuclear injuries through additional efforts.

First, the development process used during the Combined Methodology Study—developing the required sign/symptom progressions through meetings with subject matter experts—might be used to develop a new set of combined progression curves that incorporate synergistic effects. Such an approach, however, would be difficult and potentially time-consuming.

In addition, novel research in regenerative medicine and synthetic biological environments—such as body-on-a-chip technology developed by Wake Forest Institute of Regenerative Medicine and funded by the Defense Threat Reduction Agency—may provide a platform for generating new human-comparable data. This technology is being explored to characterize injuries from chemical agents and has been used to study drug toxicity in lieu of animal models.

However, studying synergistic effects from combined radiation, blast, and thermal injuries would require significant financial and labor resources for a tailored line of effort with uncertain success, and would likely be limited in the physiological responses that could be examined. Otherwise, the best approach for now would be to continue using the non-synergistic methodology currently employed in the AMedP methodology.

This page is intentionally blank.

Contents

This page is intentionally blank.

1. Background

Victims of nuclear weapon events are likely to suffer from injuries due to exposure from some combination of prompt radiation, blast,[1] and thermal fluence. Researchers found that of those injured during the nuclear attacks against Hiroshima and Nagasaki who survived for at least 20 days, 60.5 percent in Hiroshima and 57.7 percent in Nagasaki suffered injuries from exposure to either blast, thermal fluence, or irradiation; 34.5 percent in Hiroshima and 37.1 percent in Nagasaki suffered injuries from exposure to two of these insults, and 5.0 percent in Hiroshima and 5.2 percent in Nagasaki suffered injuries from exposure to all three insults.[2]

Conservative estimates indicate that as many as half the dead and injured in the two cities may have suffered from combined injuries.[3] An oft-cited East German estimate from the 1960s suggested that, based on the experience in Hiroshima and Nagasaki, 65-70 percent of the injured following a nuclear war would suffer from combined injuries, with the following distribution:[4]

- Radiation injury + burns: up to 40 percent;
- Radiation injury + blast-related trauma: up to 5 percent;
- Burns + blast-related trauma: up to 5 percent; and
- Radiation injury + burns + blast-related trauma: up to 20 percent.

---

1 Three types of blast effects will be examined in this paper: primary (the direct effect on the body from peak overpressure), secondary (due primarily to missiling or debris striking the body), and tertiary (due to whole-body translation through the air). A fourth set of blast effects, known as quaternary (due to the indirect effects of blast such as building collapse, fires, etc.) will be largely ignored.

2 Otfried Messerschmidt, "Results of Animal Experiments as a Basis for Recommendations on Therapy of Combined Injuries (Radiation Injury Plus Wounds)," *Pathophysiology of Combined Injury and Trauma*, ed. Richard I. Walker, Dale F. Gruber, Thomas J. MacVittie, and James J. Conklin (Bethesda, MD: Armed Forces Radiobiology Research Institute, 1983), 36-37.

3 Messerschmidt, "Results of Animal Experiments," 37.

4 K. Geiger, *Grundlagen der Militaermedizin* (*Foundations of Military Medicine*) (Berlin: Berliner Deutscher Militaer Verlag , 1964) quoted in Messerschmidt, "Results of Animal Experiments," 37. These values are usually assumed to pertain to a nuclear war with multiple nuclear detonations; see Messerschmidt, "Results of Animal Experiments," 37; and Donis R. Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*, Joint DNA-USANCA Study (Washington DC: Defense Nuclear Agency, 1979), 1-2. One study, however, suggests that it is relevant to a single detonation; see James J. Conklin, Richard I. Walker, and Dennis L. Kelleher, "Evaluation and Treatment of Nuclear Casualties: Part III – Management of Combined Injuries," *Medical Bulletin of the US Army, Europe*, 40, no. 12 (December 1983): 17. It is unclear from the available sources what yields or heights of burst were assumed in this estimate, though one author talks about the use of "rocket weapons;" see O. Messerschmidt et al., *Investigations Concerning the Pathogenesis and Therapy of Combined Injuries* (Munich: Federal Republic of Germany Ministry of Defense, 1974), 1.

A more recent estimate of a low-yield nuclear detonation indicated again that up to 70 percent of the casualties would suffer from combined injuries, with 30-40 percent suffering radiation injury and burns, 5-10 percent suffering trauma and burns, and 20-30 percent suffering from all three types of injury (no "radiation plus trauma" effects were shown).[5] Note that trauma in these studies refers to injury due to blast effects.

Evidence suggests that there are synergistic effects across blast, initial radiation, and thermal fluence challenges arising from a nuclear detonation (i.e., the injuries sustained by a combination of two or all three insults are likely to be more severe than those produced by each insult separately). Observations from mortality and injury severity among victims of Hiroshima and Nagasaki suggested to researchers early on the presence of synergistic effects between radiation, thermal fluence, and blast.[6]

Experimental data have also indicated synergistic effects. For example, the likelihood of death associated with thermal injuries has been shown to increase when radiation injuries are also present.[7] In general, exposure to radiation increases the severity and recovery time for other types of injuries.[8] Similarly, statistical analyses examining burn and trauma patient cases indicate that combined blast and thermal injuries produce synergistic effects that impact mortality.[9]

The current NATO-approved casualty estimation methodology, as documented in Allied Medical Publication (AMedP)-7.5, does not take the synergistic effect of these combined challenges into account when estimating casualties from nuclear weapons

---

5 Ronald E. Goans, *Medical Management of Radiological Casualties*, 4th ed. (Bethesda, MD: Armed Forces Radiobiology Research Institute, July 2013), 40.

6 Messerschmidt, "Results of Animal Experiments," 38; James W. Brooks et al., "The Influence of External Body Radiation on Mortality from Thermal Burns," *Annals of Surgery* 136, no. 3 (September 1952): 533; Hamilton Baxter et al., "Reduction of Mortality in Swine from Combined Total Body Radiation and Thermal Burns by Streptomycin," *Annals of Surgery* 137, no. 4 (April 1953): 450; and Siegmund J. Baum, *The Pathophysiology of Combined Radiation Injuries: A Review and Analysis of the Literature on Non-Human Research*, DNA-TR-90-211 (Los Alamos, NM: Technico Southwest, Inc., July 1991), 3.

7 Brooks, et al., "The Influence of External Body Radiation on Mortality from Thermal Burns," 541; Baxter, et al. "Reduction of Mortality in Swine," 451; Edward L. Alpen and Glenn E. Sheline, "The Combined Effects of Thermal Burns and Whole Body X Irradiation on Survival Time and Mortality," *Annals of Surgery* 140, no. 1 (July 1954): 114-115.

8 Baum, *The Pathophysiology of Combined Radiation Injuries*; Andrea L. DiCarlo, Narayani Ramakrishnan, and Richard J. Hatchett, "Radiation Combined Injury: Overview of NIAID Research," *Health Physics* 98, no. 6, (June 2010): 864.

9 John M. Santaniello, Fred Luchette, Thomas J. Esposito, Henry Gunawan, R. Lawrence Reed, Kimberly A. Davis, and Richard L. Gamelli, "Ten Year Experience of Burn, Trauma, and Combined Burn/Trauma Injuries Comparing Outcomes," *The Journal of TRAUMA injury, Infection, and Critical Care* 47 (2004): 696-701.

events. This means that the estimation methodology likely under-estimates one or more results: the severity of injuries, the duration of injury, and/or the number of fatalities.

The lack of a true combined injury profile—one which considered the synergistic effects across injury types—was attributed in the AMedP-7.5 documentation to the lack of available data on these synergistic effects.[10] It has now been over 10 years since IDA performed a thorough search of available combined effects data. As additional research has been done since then, the Office of the Surgeon General of the U.S. Army asked IDA to revisit this issue to determine the feasibility of adding these effects in the next iteration of the methodology.

[10] Sean M. Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5) NATO Planning Guide for the Estimation of CBRN Casualties*, IDA Document D-8122 (Alexandria, VA: Institute for Defense Analyses, October 2016), 14-1.

This page is intentionally blank.

2. Current AMedP-7.5 Nuclear Methodology

To begin, there are four different types of blast effects: primary, secondary, tertiary, and quaternary. The static overpressure produced by a nuclear explosion causes trauma to the body known as primary blast injuries. For most expected yields and conditions, the degree of injury will be a function of peak static overpressure and the speed of its rise. Dynamic pressures produced by the explosion can lead to secondary, tertiary, and quaternary blast injuries.

Secondary effects are due to the impact of debris on the body (missiling), to include glass fragments, wood, and stones, for example. Tertiary blast injuries are due to translation of the body through the air and subsequent deceleration, either sudden (e.g., hitting a solid object) or gradual (decelerative tumbling). Quaternary blast effects are due mainly to events such as building collapse.[11]

The current AMedP methodology mainly models primary blast effects, with the addition of a partial accounting for fatalities due to tertiary effects (whole-body translation and decelerative tumbling) based on a calculation indexed to static overpressure.[12] To fully model the other blast effects, far more detail would be needed than currently required by the methodology.[13] Moreover, the methodology is only currently applied outside of urban or built-up areas, limiting the applicability of quaternary effects.

It should be acknowledged that, for troops in the open, detonation of expected battlefield size nuclear weapons (100kt or less) will result in even the lowest primary blast injuries to occur at ranges where radiation and/or thermal effects will exceed lethal levels.[14] Nonetheless, combinations of primary blast with radiation and/or thermal effects should be relevant in cases where troops have some protection against radiation and thermal, such as armored vehicles or foxholes (where the effects of blast may be enhanced due to reflections of blast wave).

---

[11] Oxford et al., *Technical Reference Manual to AMedP-7.5*, 16-1 to 16-6.

[12] Oxford et al., *Technical Reference Manual to AMedP-7.5*, 16-1.

[13] Oxford et al., *Technical Reference Manual to AMedP-7.5*, 16-5 to 16-6.

[14] See, for example, Igor Cherniavskiy and Volodymyr Vinnikov, "Prognostic Assessment of the Zone of Occurrence of Radiation Combined Injuries within a Nuclear Blast Area," *International Journal of Radiation Biology* 98, no. 5 (2022): 883, https://doi.org/10.1080/09553002.2021.1998707.

In the current AMedP methodology, individual sign/symptom progressions have been drawn for the relevant affected physiological systems for radiation, primary blast, and thermal.[15] Four representative systems were chosen for radiation: cardiovascular, immune, lower gastrointestinal, and upper gastrointestinal. Three representative systems were chosen for thermal: cardiovascular, immune, and skin. Only one representative system—respiratory—was chosen for primary blast effects. Overall injury profiles were then developed for each insult range by overlaying the individual physiological system sign/symptom progressions onto in a single plot and then tracing out the maximum exhibited physiological symptom severity at each point in time.

To represent combined injuries, a similar approach was applied.[16] Specifically, the appropriate injury profile for each relevant insult range was overlaid onto a single plot and again the maximum severity at each point in time was chosen to construct a composite injury profile. The process is shown below for a nuclear environment of 4 Gray (Gy) radiation, 200 kilopascals (kPa) static blast overpressure, and 25 "%BSA," or percent body surface area burned. Figures 1 to 3 show the injury profile maps for each insult.

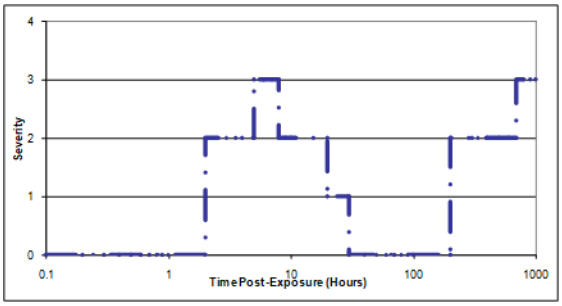


Figure 1. Whole-Body Radiation Injury Profile Map for Dose of 4 Gy

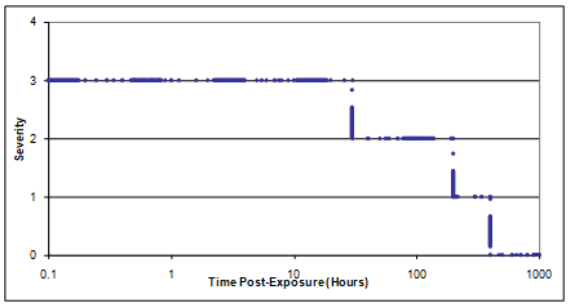


Figure 2. Blast Injury Profile Map for Overpressure of 200 kPa

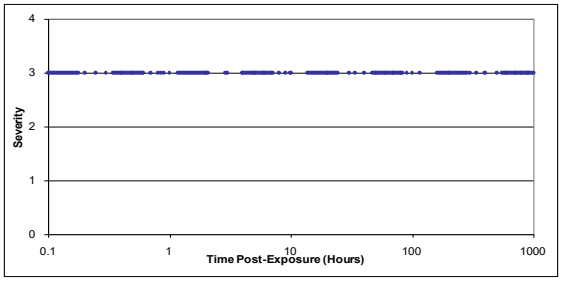


Figure 3. Thermal Injury Profile Map for 25 %BSA

---

[15] Oxford et al., *Technical Reference Manual to AMedP-7.5*, 15-8 to 15-14, 16-8 to 16-10, and 17-6 to 17-9.

[16] Carl A. Curling et al., *Technical Reference Manual: NATO Planning Guide for the Estimation of Chemical, Biological, Radiological, and Nuclear (CBRN) Casualties, Allied Medical Publication-8(C)*, IDA Document D-4082 (Alexandria, VA: Institute for Defense Analyses, August 2010), 172.

These three profiles are then overlaid onto the same plot as shown in Figure 4.

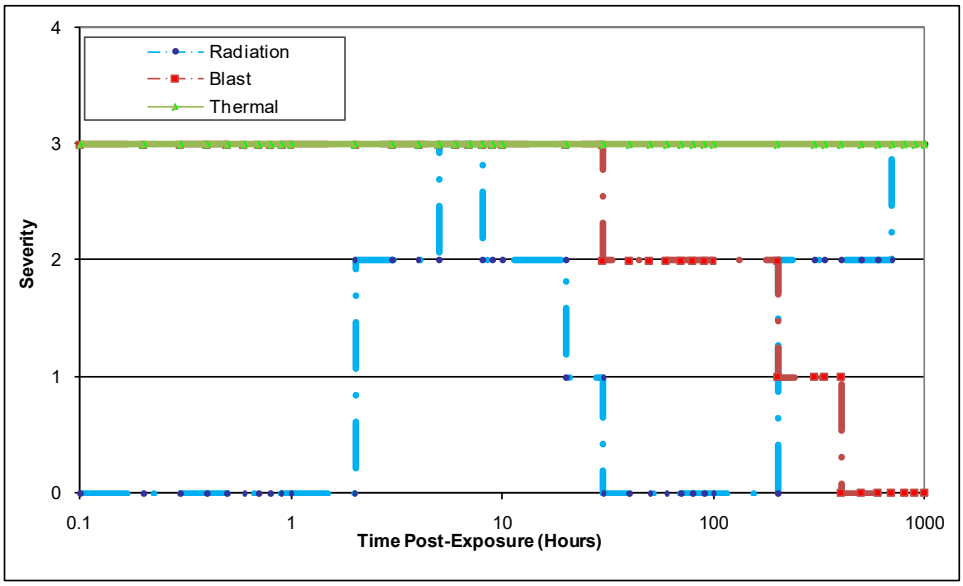


Figure 4. Composite Nuclear Injury Profile Maps for 4 Gy, 200 kPa, and 25 %BSA

The composite nuclear injury profile is obtained by drawing the maximum values of the overlaid radiation, blast, and thermal injury profile maps shown in Figure 4. This set of maximum values becomes the overall composite nuclear injury profile map for 4 Gy, 200 kPa, and 25 %BSA, shown in Figure 5.

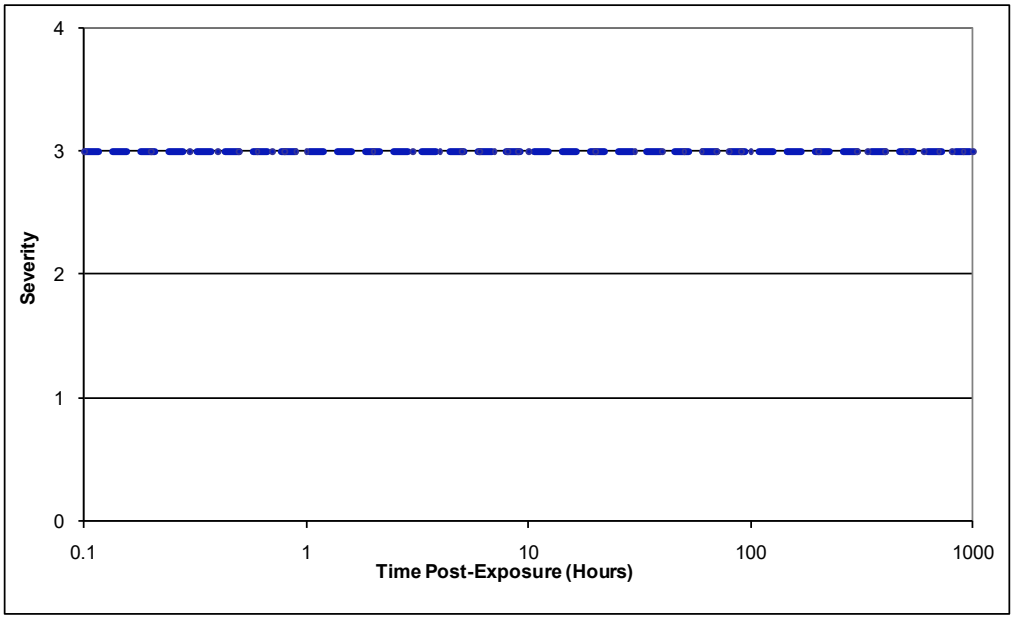


Figure 5. Composite Nuclear Injury Profile for 4 Gy, 200 kPa, and 25 %BSA

As can be seen, this approach does not take into account synergistic effects. The resulting composite injury severity for the combined effects never exceeds the highest severity level of the individual injury profiles.

3. Approaches to Incorporating Synergistic Combined Effects

Three alternative approaches to developing synergistic effects will be explored: modification of the "Combined Injury Methodology" developed by Technico Southwest in the 1990s; use of empirical results from animal and human test programs, especially those conducted since 2008; and adaption of output from more recently developed mechanistic models.

A. Combined Injury Methodology

One approach to developing a methodology designed to model human response from exposure to various combinations of radiation, blast, and thermal is to look at a previous effort to model such effects, the Combined Injury Methodology.

1. Description

The Combined Injury Methodology was developed by Technico Southwest in the early 1990s for the Defense Nuclear Agency (DNA).[17] The methodology was incorporated into the Consolidated Human Response Nuclear Effects Model (CHRNEM).[18] The final output of the methodology was a measure of soldier performance following exposure to some combination of prompt radiation, primary blast, and thermal fluence.

An intermediate step in the methodology was the mapping of signs/symptoms severity levels over time for relevant symptom categories (essentially the sign/symptom progression found in the AMedP methodology) following exposure to combinations of these insults. This effort was a follow-on from DNA's Intermediate Dose Program (IDP), which was designed to output soldier performance following exposure to prompt radiation alone.[19]

---

[17] Sheldon G. Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, DNA-TR-92-134 (Espanola, NM: Technico Southwest, Inc., June 1993).

[18] Sheldon G. Levin and James W. Fulton, *Consolidated Human Response Nuclear Effects Model (CHRNEM)*, DNA-TR-93-45 (Espanola, NM: Technico Southwest, Inc., September 1993).

[19] G. H. Anno, D.B. Wilson, and M.A. Dore, *Acute Radiation Effects on Individual Crewmember Performance*, DNA-TR-85-52 (Los Angeles, CA: Pacific-Sierra Research Corporation, August 31, 1984); Siegmund J. Baum et al., *Symptomatology of Acute Radiation Effects in Humans After Exposure*

The IDP assembled a panel of subject matter experts (SMEs), consisting of radiologists and other physicians, to develop sign/symptom severity levels over time manifested in six symptom categories that were considered to constitute acute radiation sickness:[20]

- Upper gastrointestinal distress
- Lower gastrointestinal distress
- Fatigability and weakness
- Hypotension
- Infection, bleeding, and fever
- Fluid loss and electrolyte imbalance

Signs/symptom severity progressions were generated for each of these symptom categories across eight dose ranges: 75-150, 150-300, 300-530, 530-830, 830-1,100, 1,100-1,500, 1,500-3,000, and 3,000-4,500 centigray, or cGy (free-in-air).[21] For the Combined Injury Methodology, the developers considered five radiation doses (50, 150, 300, 500, and 1,000 (free-in-air)) based on their estimated effects, ranging from "no effect" to "very severe (see Table 1). As a result, the developers made some minor modifications to the six sets of sign/symptom severity progressions developed during the IDP.[22]

Table 1. Insult Dose Ranges and Effects Categories

	Dose Level				
Insult	None (0)	Minor (1)	Moderate (2)	Severe (3)	Very Severe (4)
Prompt Radiation (cGy)	50	150	300	500	1,000
Thermal Fluence (cal/cm^2)	3	7	10	15	43
Blast Overpressure (psi)	10	20	30	35	42

In a similar fashion to the IDP, the Combined Injury Methodology developers initially assembled SME panels to develop sign/symptom severity progressions following exposure to thermal fluence and primary blast for their respective symptom categories. For thermal

to Doses of 75 to 4500 Rads (cGy) Free-in-Air, DNA-TR-85-50 (Los Angeles, CA: Pacific-Sierra Research Corporation, August 31, 1984); and G.H. Anno, D. B. Wilson, and S. J. Baum, *Severity Levels and Symptom Complexes for Acute Radiation Sickness: Description and Quantification*, DNA-TR-86-94 (Los Angeles, CA: Pacific-Sierra Research Corporation, November 30, 1985).

[20] Anno, *Severity Levels and Symptom Complexes for Acute Radiation Sickness*, 2-3.

[21] Anno, *Severity Levels and Symptom Complexes for Acute Radiation Sickness*, 18.

[22] Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, 19-20.

fluence, the same set of symptom categories were used as with radiation, with the exception of the removal of lower gastrointestinal and the addition of pain.[23]

The insult dose values for thermal, again based on their estimated effect, were 3, 7, 10, 15, and 43 cal/cm^2 (see Table 1). These values, in turn, were converted to percent of total body area burned (1-10 percent, 11-20 percent, 21-30 percent, 31-40 percent, and 41-50 percent) before presentation to the SMEs.[24] Soldiers were assumed to be wearing battle dress uniform (BDU) over a T-shirt, with their hands and head uncovered.

For primary blast, only four symptom categories were considered:[25]

- Upper gastrointestinal distress
- Lower gastrointestinal distress
- Fatigability and weakness
- Hypotension

Five insult doses also were selected for primary blast based on their estimated effect: 10, 20, 30, 35, and 42 psi (see Table 1).[26] Only primary blast effects were considered in the methodology; secondary and tertiary effects were ignored largely due to their unpredictability and because "overpressures required to accelerate a man to velocities that would cause injury would not occur in a foxhole."[27]

The Combined Injury developers then presented this collection of sign/symptom severity progressions to a panel of medical SMEs as a starting point in developing sign/symptom progressions for various combinations of insults by symptom category. To limit the time involved, the developers only presented progressions corresponding to the middle three dose levels (minor through severe) to the SME panel, resulting in 27 dose insult combinations (3x3x3).

In this manner, expected synergistic effects were included in the sign/symptom severity progressions. The progressions for the combinations including "none" and "very

---

[23] Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, 23.

[24] Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, 14 and 27.

[25] A common symptom category for primary blast is upper respiratory distress (the only physiological system represented in primary blast in the AMed methodology), which was not one of the categories in the IDP effort. SMEs incorporated the effects of this symptom category into "fatigability and weakness;" see Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, 33.

[26] Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, 14.

[27] Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, 37.

severe" dose levels were then generated by extrapolating the panel's responses to the original 27 combinations using a simple set of algorithms.[28]

The resulting set of progressions was presented to a panel of Army SMEs to determine, in a manner similar to that used in the IDP effort, subsequent soldier performance in a variety of tasks. Based on algorithms developed during the IDP effort, the Combined Injury developers generated sign/symptom severity (by symptom category) to performance decrement equations, summing the individual performance decrement equations to obtain an overall performance value. All of these results—the mapping of insult dose combinations to sign/symptom severity progressions to performance decrement—were incorporated into the CHRNEM model, which input combinations of dose values and output expected soldier performance. The CHRNEM model was subsequently included in the methodology used to generate the first version of the AMedP-8 nuclear document.

2. Problem with Approach

Unfortunately, the combined sign/symptom progressions that resulted from the Combined Injury process are unavailable. The document describing the development process does not include the symptom category progressions generated by the SMEs, though it does describe the algorithms used to generate the progressions at the extreme dose values based on this SME panel input.[29] Moreover, while the CHRNEM code includes these algorithms, neither the CHRNEM source code nor the original algorithms are available.[30] Indeed, the original methodology cannot be reconstructed due to loss of the

---

[28] If one insult were at the "none" level, then the highest severity of the other two insults was chosen at each time point, but the severity always had to be less than or equal the combination selected by the SMEs of those two insults and the "mild" level of the third. If two insults were at the "none" level, then the severity level of the third was chosen. If one insult was at the "very severe" level, then the highest severity of the three insults was chosen at each time point, with the caveat that the resulting severity had to be greater than or equal to the combination selected by the SMEs when this (the "very severe") insult was set to the "severe" level; see Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, 37. The authors provided no justification for these algorithms other than noting that injuries resulting from "very severe" levels of any of the three insults would result in soldier performance falling below 25 percent, making them combat ineffective; see Levin, Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, 37 and 52.

[29] Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, 37. The document does contain the individual radiation, burn, and blast sign/symptom severity progressions or the resulting combined injury performance graphs, but it does not include the intermediate step of the combined sign/symptom severity progressions; see Levin, *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*, A-2 to A-13 and C-2 to C-10.

[30] According to ARA, the "[o]riginal algorithms used to describe the increase in symptom severity due to combinations of insults were not adequately documented" and "[s]ource code for CHRNEM is also not available;" see Kyle Millage et al., *Overview of the Implementation of NucModel*, (Arlington, VA: Applied Research Associates, November 20, 2007), 9.

sole hard drive on which it was stored.[31] Other models that used the Combined Injury methodology—specifically, a modified version of the Janus combat model used to generate data for AMedP-8(nuclear) and the NBC CREST model—also only contained tables/algorithms mapping decrement in soldier performance as function of dose and time.[32]

Modifications would have been required owing to differences in the dose ranges employed between the two methodologies, but the Combined Injury combined sign/symptom progressions would have been an excellent starting point for developing similar progressions in the current AMedP methodology. That said, the process for developing these progressions in the Combined Injury Study, though laborious, might be worth re-creating.

B. Clinical/Experimental Studies

A second approach to developing a synergistic combined injury methodology involves the use of empirical data derived either from clinical studies of human response or controlled experiments using animals as test subjects.

1. Human Data

One potential source for human data on combined injury comes from victims of the Hiroshima and Nagasaki atomic bombings; however, little scientific observation was conducted on combined effects and insult doses often are highly uncertain. Moreover, as one author has pointed out, both Japanese and American observers "paid attention only to the individual injuries, especially those subjects with acute radiation diseases that had not been observed until then."[33]

Another potential source for human data on combined injury involving radiation are nuclear accidents during research or nuclear plant operations. However, it is difficult to draw useful conclusions due, in part, to uncertainties in terms of radiation doses received.[34]

---

31 Daniela L. Stricklin et al., *Proceedings of the Joint Nuclear Weapon Effects Human Response Panel*, DTRA-TR-15-069 (Arlington, VA: Applied Research Associates, May 10, 2016), 21.

32 North Atlantic Treaty Organization (NATO), *AMedP-8(A), Volume I: Medical Planning Guide for the Estimation of NBC Battle Casualties (Nuclear)*, STANAG 2475 (Brussels: NATO, December 2000), 2-1; and Robert A. Zirkle et al., *Verification and Validation of the Representation of Human Response to Insults from Nuclear Detonations in Nuclear, Biological, and Chemical Casualty and Resource Estimation Support Tool (NBC CREST) Version 4.0*, IDA Paper P-4768 (Alexandria, VA: Institute for Defense Analyses, March 2012), 11-12.

33 Messerschmidt, "Results of Animal Experiments," 38.

34 Baum, *The Pathophysiology of Combined Radiation Injuries*, 3.

And, with the possible exception of the Chernobyl accident,[35] it is very rare for these events to include combined injuries involving whole-body radiation effects and thermal burns.[36]

The rise of terrorist bombings with conventional explosives and recent employment of improvised explosive devices in the Middle East and Afghanistan provide a third source for combined injury events with humans. Several casualty databases have been employed to study blast and blast/thermal injuries, including the United Kingdom's Hostile Action Casualty Survey and the UK Joint Theatre Trauma Registry databases, and the Israeli National Trauma Registry.[37] In addition, researchers have looked at injuries resulting from terror incidents such as the 1995 Oklahoma City bombing of the Murrah Federal

---

35 One source claimed that 10 percent of Chernobyl victims suffered from both whole-body radiation effects and thermal burns; see Juliann G. Kiang, Marsha N. Anderson, and Joan T. Smith, "Ghrelin Therapy Mitigates Bone Marrow Injury and Splenocytopenia by Sustaining Circulating G-CSF and KC Increases after Irradiation Combined With Wound," *Cell & Bioscience* 8, no. 27 (2018): 1, https://doi.org/10.1186/ s13578-018-0225-3. Another source wrote that "whole-body irradiation was combined with skin burns caused by thermal effects or beta irradiation in some cases;" see Otfried Messerschmidt, "Combined Effects of Radiation and Trauma," *Advances in Space Research* 9, no. 1 (1989): 197. On the other hand, other sources suggest that most, if not all, burns at Chernobyl were due to exposure to beta radiation rather than thermal; see Andrea DiCarlo et al., "Medical Countermeasures for Radiation Combined Injury: Radiation with Burn, Blast, Trauma, and/or Sepsis: Report of an NIAID Workshop March 26-27, 2007," *Radiation Research* 169 (June, 2008): 713; United Nations Scientific Committee on the Effects of Atomic Radiation, *Sources and Effects of Ionizing Radiation, Volume II, Annex D: Health Effects Due to Radiation from the Chernobyl Accident*, UNSCEAR 2008 (New York City: United Nations, April 2011); and Anzhelika V. Barabanova, "Significance of Beta-Radiation Skin Burns in Chernobyl Patients for the Theory and Practice of Radiopathology," *Vojnosanitetski Pregled* 63, no. 5 (2006): 477-480. Indeed, Barabanova (which was cited by Kiang et al. as the source for their 10 percent figure) makes no mention of thermal burns. Without access to the case files for Chernobyl, it is difficult to ascertain how many, if any, victims suffered from whole-body irradiation and thermal effects alone; victims of whole-body and beta irradiation along with thermal effects would constitute a separate category of combined injury.

36 Messerschmidt, "Combined Effects of Radiation and Trauma," 197.

37 S. G. Mellor and G. J. Cooper, "Analysis of 828 Servicemen Killed or Injured by Explosion in Northern Ireland 1970-84: The Hostile Action Casualty System," *British Journal of Surgery* 76, no. 10 (October 1989): 1006-1010; Ruth McGuire, A. Hepper, and K. Harrison, "From Northern Ireland to Afghanistan: Half a Century of Blast Injuries," *Journal of the Royal Army Medical Corps* 165 (2019): 27-32; J. E. Smith, "The Epidemiology of Blast Lung Injury During Recent Military Conflicts: A Retrospective Database Review of Cases Presenting to Deployed Military Hospitals, 2003-2009," *Philosophical Transactions of the Royal Society B* 366 (2011): 291-294; and Kobi Peleg et al., "Do Burns Increase the Severity of Terror Injuries?" *Journal of Burn Care and Research* 29, no. 6 (November/December 2008): 887-892.

Building,[38] the 2004 Madrid bombings,[39] and the 2005 London bombings.[40] However, there are limitations to using these events.

First of all, it can be difficult to separate trauma related to primary blast effects from other blast effects. Studies of British soldiers injured in terrorist bombings in Northern Ireland found that blast lung injury (the main primary blast injury and the one employed in AMedP-7.5) was frequently found during post mortem examinations, but attributing it as the cause of death was compounded by equally deadly penetrating wounds, head injuries or traumatic amputations. Among survivors, only 1 to 2 percent suffered blast lung injury.[41] A study of British soldiers killed or injured by blast in Iraq and Afghanistan found that only about 6.7 percent (113 out of 1,678) suffered blast lung injury.[42]

Another study, however, suggested that the increased use of body armor might reduce the incidence of combined primary and secondary blast injuries: the body armor would reduce the cases of penetrating injury, but would not protect against the primary blast wave.[43] Furthermore, review of the Madrid bombings suggested that instances of blast lung injury among survivors might increase if the explosion occurred within a confined space due to multiple reflections of the blast wave; anywhere from 63 percent to 94 percent of critically injured survivors from these attacks suffered blast lung injuries.[44]

However, while many terrorist incidents do occur indoors, the victims generally do not wear body armor and the locations typically contain many items (glassware, window glass, furniture, etc.) that can produce secondary blast injuries, making it difficult to find

---

38 Sue Mallonee et al., "Physical Injuries and Fatalities Resulting from the Oklahoma City Bombing," *Journal of the American Medical Association* 276 (August 7, 1996): 382-387.

39 Jose Peral-Gutierrez de Ceballos et al., "11 March 2004: The Terrorist Bomb Explosions in Madrid, Spain – An Analysis of the Logistics, Injuries Sustained and Clinical Management of Casualties Treated at the Closest Hospital," *Critical Care* 9, no. 1 (February 2005): 104-111; and Milagros Marti et al., "Blast Injuries from Madrid Terrorist Bombing Attacks on March 11, 2004," *Emergency Radiology* 13 (2006): 113-122.

40 R. Chukwu-Lobelu et al., "Burn Injuries from the London Suicide Bombings: A New Classification of Blast-Related Thermal Injuries," *Annals of Burns and Fire Disasters* 30, no. 4 (December 2017): 256-260.

41 E. Kirkman, S. Watts, and G. Cooper, "Blast Injury Research Models," *Philosophical Transactions of the Royal Society B* 366 (2011): 145.

42 Smith, "The Epidemiology of Blast Lung Injury During Recent Military Conflicts," 293. During the time of the study, which ran from 2003 to 2009, the cases of blast injury were found to peak in Iraq during 2007 at 7.3 percent and in Afghanistan during 2009 at 11 percent; see Smith, 293.

43 Mellor and Cooper, "Analysis of 828 servicemen killed or injured by explosion in Northern Ireland," 1010.

44 Peral-Gutierrez de Ceballos et al., "11 March 2004," 109, and Marti et al., "Blast Injuries from Madrid Terrorist Bombing Attacks," p. 116.

victims suffering from blast effects due solely to primary blast.[45] Moreover, from a modeling perspective, calculations of peak overpressure resulting from explosions in the open are available and straightforward.[46] However, similar calculations in an enclosed space are more difficult due to the potential for multiple blast wave reflections, generating complex waves and requiring the use of computational fluid dynamic modeling.[47]

A second issue entails the difficulty of finding victims of these events suffering from both primary blast injuries (i.e., blast lung injury) and burn injuries. Primary blast injuries tend to be unique to high-order, or high-energy (HE), explosives, such as TNT, C-4, dynamite and Semtex.[48] These types of explosives, however, usually only lead to superficial flash burns on exposed skin. By contrast, lower-order explosives, such as gunpowder or the explosives typically found in pipe bombs, are not powerful enough to cause primary blast injuries, but they can lead to severe burns by causing fires with high thermal output.[49]

For example, in the survey of British servicemen killed or injured due to explosions in Northern Ireland, the persistent presence of HE explosives can be inferred by the high percentage of blast lung injuries among fatalities.[50] However, out of 828 victims, only 31 sustained burns. Three of these died of other injuries, while the remainder suffered only

---

45 Yancy Y. Phillips III and Donald R. Richmond, "Primary Blast Injury and Basic Research: A Brief History," chap. 6 in *Conventional Warfare: Ballistic, Blast, and Burn Injuries*, ed. Ronald F. Bellamy and Russ Zajtchuk (Washington, D.C.: Department of the Army, Office of the Surgeon General, Center of Excellence in Military Medical Research and Education, Walter Reed Army Medical Center, 1991), 224.

46 See, for example, Philip W. Gibson, *Blast Overpressure and Survivability Calculations for Various Sizes of Explosive Charges*, Technical Report NATICK/TR-95/003 (Natick, MA: Research, Development and Engineering Center, United States Army Natick, November 1994), 4; and James H. Stuhmiller et al., "The Physics and Mechanisms of Primary Blast Injury," chap. 7 in *Conventional Warfare: Ballistic, Blast, and Burn Injuries*, ed. Ronald F. Bellamy and Russ Zajtchuk (Washington, D.C.: Department of the Army, Office of the Surgeon General, Center of Excellence in Military Medical Research and Education, Walter Reed Army Medical Center, 1991), 246.

47 James H. Stuhmiller, "Blast Injury: Translating Research into Operational Medicine," chap. 10 in *Military Quantitative Physiology: Problems and Concepts in Military Operational Medicine*, ed. Karl E. Friedl and William R. Santee (Falls Church, VA: Department of the Army, Office of the Surgeon General, Borden Institute, 2012), 278. While it might be possible to conduct such CFD modeling, it would require the accurate depiction of the interior layout for each historical event—a considerable effort—while the other issues raised here are likely to render this effort moot.

48 Stuhmiller, "Blast Injury," 270; and T. E. Scott, E. Kirkman, M. Haque, I. E. Gibb, P. Mahoney, and J. G. Hardman, "Primary Blast Lung Injury – A Review," *British Journal of Anaesthesia* 118, no. 3 (2017): 312.

49 C. T. Born, "Blast Trauma: The Fourth Weapon of Mass Destruction," *Scandinavian Journal of Surgery* 94 (2005): 280.

50 Mellor and Cooper, "Analysis of 828 Servicemen Killed or Injured by Explosion in Northern Ireland," 1007

superficial burns (for which we would not interested).[51] Thus, data from terrorist incidents might be useful for studying the combined effects of primary blast and burn, but there is likely to be a paucity of appropriate data.

2. Animal Models

Because of the limited amount of reliable human data, researchers in combined injury rely heavily on animal models. But, as discussed below, these types of data also have severe limitations, given the dearth of studies looking at most types of combined injuries and the types of animal models examined. Animal models, in this case, would be used to extrapolate the results of experiments to human dose response. Responses could include different levels of severity in signs and symptoms manifesting in specific physiological systems (e.g., upper gastrointestinal, respiratory) or whole-body effects such as incapacitation or death.

Extrapolating from animal experiments to predicting human responses can be difficult, requiring the use of animal test subjects that perform as similar as possible to humans when exposed to nuclear effects. Non-human primates (NHP) are considered the "gold standard" for studying acute radiation syndrome, though canines and the Gottingen minipig are also considered suitable animal models for certain sub-syndromes of acute radiation sickness.[52]

By contrast, although close to humans with respect to their cutaneous and subcutaneous physiology, NHPs are considered less suitable for cutaneous effects (from both thermal and radioactive burns) due to their fur.[53] When studying thermal injuries, research suggests that pigs are ideal animal models due to their similarities to human hair coat, epidermis, dermis, skin architecture, wound-healing mechanism, and large size allowing for examination of systemic effects.[54]

That said, one workshop report indicated that this model too has limitations: "Pig skin is thicker than human skin, contains different immune-competent mast cells and manifests

---

[51] Mellor and Cooper, "Analysis of 828 Servicemen Killed or Injured by Explosion in Northern Ireland," 1008.

[52] Vijay K. Singh et al., "Animal Models for Acute Radiation Syndrome Drug Discovery," *Expert Opinion on Drug Discovery* 10, no. 5 (2015): 497-517. Canines possess hematopoietic and immune systems similar to humans and they are capable of experiencing vomiting and diarrhea, though their physiology differ from humans; see Singh et al., 507. The pathophysiology of hematopoietic ARS in the minipig is similar to that found in humans and pig skin is considered very similar to humans; see Singh et al., 508.

[53] Jacqueline P. Williams et al., "Animal Models for Medical Countermeasures to Radiation Exposure," Radiation Research 173, no. 4 (2010): 571.

[54] A. Abdullahi, S. Amini-Nik, and M. G. Jeschke, "Animal Models in Burn Research," *Cellular and Molecular Life Sciences* 71 (2014): 3242.

erythema differently than human skin."[55] For primary blast effects, a clear distinction in lethality has been noted between large animals (goats, sheep, dogs) and small animals (rodents and rabbits), the former being much closer to humans in their response.[56] On the other hand, translation effects due to dynamic pressure will be somewhat different in large animal quadrupeds than bipeds (humans), owing to resulting differences in tumbling mechanics.[57]

Mice are the most frequent animal model used for radiological studies and share many traits with humans (including common organs, systems physiology and 95 percent of the human genome), but their use has been largely driven by cost and ease of care concerns.[58] Though murine models are frequently used in burn research, the skin of mice and rats is significantly different from human skin in terms of structure and physiology, leading to different wound-healing mechanisms involving unique enzymes not found in humans, and a lack of scar formation.[59] Perhaps most significant is the difference in wound healing mechanisms between humans, which use re-epithelialization, and rodents, which use contraction, in addition to the time involved in wound healing as a by-product of this difference and epithelial composition.[60]

Moreover, differences in wound healing due to variations in skin anatomy and physiology exist between mice and rats themselves, and even by gender within the

---

55 Daniela Stricklin et al., *Combined Injury Modeling: Radiation and Burn Workshop Report*, DTRA-TR-10-48 (Arlington, VA: Applied Research Associates, Inc., October 2010), 14.

56 Clayton S. White et al., *The Biodynamics of Airblast*, DNA 2738T (Albuquerque, NM: Lovelace Foundation for Medical Education and Research, July 1, 1971), 3-4.

57 Jacqueline Wentz, Daniela Stricklin, and Kyle Millage, *Updates to Blast Injury Criteria Models for Nuclear Casualty Estimation*, DTRA-TR-15-23 (Arlington, VA: Applied Research Associates, Inc., December 2005), 25.

58 For example, 2010 Ledney and Elliott noted limitations with the clinical relevance of the mouse model for assessing wound and burn injuries from radiation and trauma. They selected a mouse model for their study because "they are the least sentient animal relative to other higher order animals and provide adequate numbers for statistical determinations." G. David Ledney and Thomas B. Elliott, "Combined Injury: Factors with Potential Impact Radiation Dose Assessments," *Health Physics* 98, no. 2 (February 2010): 146-150. Also see Singh et al., "Animal Models for Acute Radiation Syndrome Drug Discovery," 507; and Karl T. Butterworth and Jacqueline P. Williams, "Animal Models for Radiotherapy Research: All (Animal) Models Are Wrong But Some Are Useful," *Cancers* 13 (2021): 13.

59 Abdullahi, Amini-Nik, and Jeschke, "Animal Models in Burn Research," 3242-3243.

60 Abdullahi, Amini-Nik, and Jeschke, "Animal Models in Burn Research," 3242-3243; Helena D. Zomer and Andrea G. Trentin, "Skin Wound Healing in Humans and Mice: Challenges in Translational Research," *Journal of Dermatological Science* 90, no. 1 (April 2018): 3-12; Daniel S. Masson-Meyers et al., "Experimental Models and Methods for Cutaneous Wound Healing Assessment," *International Journal of Experimental Pathology* 101, (2020): 21-37, https://doi.org/10.1111/iep.12346; and Diana G. Sami, Hana H. Heiba, and Ahmed Abdellatif, "Wound Healing Models: A Systematic Review of Animal and Non-Animal Models," *Wound Medicine* 24 (2019): 8-17.

species.[61] There are also differences in the cellular and molecular components of human and rodent immune responses involved in tissue repair. For example, certain cytokines involved in re-epithelialization, tissue remodeling, and angiogenesis (IL-8, CXCL-7, CXCL-11, and monocyte chemoattractant) are present in humans but not in mice.[62]

Unfortunately, not only are there uncertainties and limitations with respect to observed correlations between humans and animals, but the correlations generally do not hold when examining combined effects.[63] Adding to these difficulties, the mechanisms underlying these synergies are just beginning to be understood and often vary across animal models.[64] Attempts to integrate across animal models may fail to capture synergies between injury types and system response due to interspecies differences.[65] As one review noted, when studying the combined effect of radiation and thermal exposure:

> Experimental evidence is difficult to acquire because of differences between humans and smaller animals in their reaction to shock. Larger animals such as dogs, sheep, pigs, or monkeys are preferred when extrapolating experimental data to man; but none of these animals respond the same as humans to both nuclear radiation and burns.[66]

Nonetheless, in general, larger mammals are preferable to smaller mammals when it comes to extrapolating to human responses.[67] Despite this, as seen below, most recent research has been conducted using small mammals. Experimental studies evaluating combined effects from radiation and thermal insults rely on murine models and do not provide further understanding of the underlying mechanisms of observed synergies

---

61 Masson-Meyers et al., "Experimental Models and Methods for Cutaneous Wound Healing Assessment," 23.

62 Zomer and Trentin, "Skin Wound Healing in Humans and Mice: Challenges in Translational Research," 7.

63 Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*, 61.

64 Juliann G. Kiang and Ayodele O. Olabisi, "Radiation: A Poly-Traumatic Hit Leading to Multi-Organ Injury," *Cell & Bioscience* 9 (2019): 2, https://doi.org/10.1186/s13578-019-0286-y; and T. C. Pellmar, *Combined Injury: Radiation in Combination with Trauma, Infectious Disease or Chemical Exposures*, RTO-TR-HFM-099 (Bethesda, MD: Armed Forces Radiobiology Research Institute, 2009), 2-3.

65 Differences have been noted within strains of the same species: mice, for example, are known to differ by strain in terms of their sensitivity to radiation; see Singh et al., "Animal Models for Acute Radiation Syndrome Drug Discovery," 502.

66 Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*, 33.

67 Andre Paredes et al., "The New Zealand White Rabbit Animal Model of Acute Radiation Syndrome: Hematopoietic and Coagulation-Based Parameters by Radiation Dose Following Supportive Care," *International Journal of Radiation Biology* 79, no. S1 (2020): S46; Abdullahi, Amini-Nik, and Jeschke, "Animal Models in Burn Research," 3243; and I. G. Bowen et al., ""Biophysical Mechanisms and Scaling Procedures Applicable in Assessing Responses of the Thorax Energized by Air-Blast Overpressures or by Nonpenetrating Missiles," *Annals of the New York Academy of Science*, 152, no. 1 (October 1968): 134-135.

between physiological effects.[68] And, despite the difference in term of blast effects between large and small mammals, the latter are now employed in blast research owing to the lack of large-scale testing facilities; research now takes place using small laboratory shock tubes.[69] Moreover, ethical concerns and adverse publicity have limited recent research to small mammals.[70]

a. Pre-1990 Studies

In 1991, Siegmund Baum of Technico Southwest surveyed the scientific literature on combined effects. He examined 171 studies, mostly with animals as test subjects, from 1933 through to 1990.[71] An earlier joint study by DNA and the U. S. Army Nuclear and Chemical Agency (USANCA) covered much of the same literature, at least through the time of its publication (1979).[72] Each discussed the available animal studies for the various combinations of radiation, blast, and thermal.

Together, the two reviews found eight studies that combined radiation and thermal exposure, with five different animal models employed: one study used swine, one a canine model, one a rat model, one a guinea pig model, and four employed the mouse model.[73] A synergistic effect was seen when both insults were delivered simultaneously, with a third reviewer noting, "An extreme increase in lethality was observed, especially for the larger

---

68 M. Epperly et al., "A Murine Combined Injury Model of Total Body Irradiation and Skin Wound," *International Journal of Radiation Oncology, Biology, Physics* 99, no. 2 (October 1, 2017): E588, DOI: https://doi.org/10.1016/j.ijrobp.2017.06.2015; Stewart R. Carter et al., "Intestinal Barrier Disruption as a Cause of Mortality in Combined Radiation and Burn Injury," *Shock* 40, no. 4 (2013): 281-289; and Daniela Stricklin, Terry Pellmar, and Darren Oldson, *Literature Survey for Combined Injury Modeling*, ARA/HS-TM-11-005, (Arlington, VA: Applied Research Associates, 2015), 13-16.

69 See, for example, Maciej Skotak et al., "Rat Injury Model Under Controlled Field-Relevant Primary Blast Conditions: Acute Response to a Wide Range of Peak Overpressures," *Journal of Neurotrauma*, 30 (July 1, 2013): 1147-1160; Nabil M. Elsayed et al., "Antioxidant Loading Reduces Oxidative Stress Induced by High-Energy Impulse Noise (Blast) Exposure," *Toxicology*, 155 (2000): 91-99; and William Brad Hubbard et al., "Examining Lethality Risk for Rodent Studies of Primary Blast Lung Injury," *Biomedical Sciences Instrumentation*, 50 (2014): 92-99.

70 As far back as 1979, neither the Armed Forces Radiobiology Research Institute (AFRRI) nor Lovelace Clinic were willing to carry out such research; see Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*, 61. Due to their status as a pet, researchers have, in particular, moved away from using dogs as research subjects in Western countries; see Kasandra S. Hunter et al., "Interagency Approaches to Animal Models for Acute Radiation Exposure," *International Journal of Radiation Biology* 97, no. S1 (2021): S3.

71 Baum, *The Pathophysiology of Combined Radiation Injuries.*

72 Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*.

73 Baum, *The Pathophysiology of Combined Radiation Injuries*, 4-16; and Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*, 31-33. Both reviews missed a study from the early 1950s that exposed mice to irradiation and thermal burns; see W. H. Parr et al., *A Study of Combined Thermal Radiation Burn and X-Irradiation Effects on Mice*, Report No. 94 (Fort Knox, KY: Army Medical Research Laboratory, September 4, 1952).

test animals such as dogs and pigs…"[74] Nonetheless, the DNA-USANCA review found it difficult to extrapolate these results to humans because of the differences in their response from human to the combination of radiation and burns. [75]

Baum discussed four studies that looked at radiation combined with primary blast effects: two employing sheep, one swine, and one rats.[76] The DNA-USANCA effort reviewed these four as well plus two sets of studies from the 1950s that employed mice.[77] Baum suggested that the results were inconclusive, though the DNA-USANCA study concluded the following:

> The simultaneous combination of higher levels of direct blast and nuclear radiation resulted in increased mortality (probably synergistically) over a 60-day period. There was no increase in early lethality…The simultaneous combination of a sublethal dose of radiation with blast in the lethal range did not increase the early or delayed mortality above that for blast alone.[78]

Nonetheless, given the limited number of studies and that half of those involved rats or mice, it is difficult to extrapolate these results to humans.

Both reviews found only one study that exposed test animals to both primary blast and thermal insults.[79] The animal model used was the rat, making it very difficult to extrapolate to humans. Similarly, both reviews found only one study that combined all three insults, again using rats as the test subject and making any extrapolation to humans very difficult.[80]

By contrast, reviews found a large number of studies that subjected test animals to some combination of radiation plus skin wounds, soft tissue damage, or bone fractures (i.e., injuries typical of secondary or tertiary blast effects).[81] However, the test animals were predominantly small mammals—rodents and rabbits—with only one study with a large mammal (canine) as a test subject, again making it difficult to extrapolate results to humans.

---

74 Messerschmidt, "Results of Animal Experiments," 39.

75 Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*, 33.

76 Baum, *The Pathophysiology of Combined Radiation Injuries*, 17-19

77 Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*, 33-39.

78 Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*, 39.

79 Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*, 43; and Baum, *The Pathophysiology of Combined Radiation Injuries,* 41

80 Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*, 47; and Baum, *The Pathophysiology of Combined Radiation Injuries,* 44.

81 Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*, 39-43; and Baum, *The Pathophysiology of Combined Radiation Injuries,* 20-40.

For many years, a primary site for U.S. military studies on the effects of blast (from both nuclear and conventional sources) was the blast overpressure research complex at Kirtland Air Force Base, New Mexico. The Lovelace Foundation for Medical Education and Research ran this complex from 1951 to 1984. In addition to running test programs at live nuclear events, Lovelace conducted simulated nuclear blast tests at the complex's test facility. From 1964 to 1971, this work included research on combined injury from exposure to sublethal doses of radiation, blast, and thermal insults using large animal models such as swine and sheep. The Baum and DNA-USANCA reviews discussed much of this work.[82]

From 1984 to 1988, the complex was run by Los Alamos National Laboratory and continued work on blast effects, though did not look further at combined effects. The complex was run by EG&G Mason Research Institute from 1988 to 1997 and, while research on blast effects continued during this timeframe, the focus was on blast effects from conventional weapons. The complex was shuttered in 1998.[83] No comparable facility has been built since to take its place in terms of large-scale animal testing.

b. Post-1990 Classified Studies

The IDA research team conducted a search on SIPRNet for relevant classified documents published over the last 30 years on the subject of combined nuclear effects. Search terms included effects such as combined radiation injury, combined injury, combined nuclear effects, and research organizations such as the Lovelace Foundation and its affiliates, as well as the Armed Forces Radiobiology Research Institute (AFRRI). No such classified documents were identified.

c. Post-1990 Unclassified Studies

A search by the IDA research team (using Google Scholar, PubMed, and other techniques) of the unclassified literature found 129 nuclear combined injury-related studies published since 1990. Of these, 36 were conducted by researchers in the United States, most resulting from an initiative begun by the National Institutes of Health's National Institute of Allergy and Infectious Disease (NIAID) in 2008 to develop animal models and medical countermeasures relevant to radiation combined injury. In fact, though a few were conducted prior to the start of the NIAID-funded effort, all of the U.S. studies identified by

---

[82] Baum, *The Pathophysiology of Combined Radiation Injuries*; and Wolfe et al., *Combined Injury from Nuclear-Weapons Effects*.

[83] A review of activities at Kirtland AFB can be found in Berlinda S. Martinez, *Blast Overpressure Research Program, Kirtland Air Force Base, 1951-1998*, Jaycor Technical Report J2997.74-99-106 (San Diego, CA: JAYCOR, November 1999), 1-13.

the IDA team dealt with combined effects that included radiation (see Table 2). All of these studies used small mammals as their test subjects, with all but one using a murine model.[84]

Only one study examined the combination of radiation and primary blast effects, and that study looked at the effect of primary blast on traumatic brain injury, not on pulmonary injury (the focus of the AMedP methodology).[85] Of the remainder, the studies were split evenly between those that exposed test animals to radiation and thermal effects[86] and those that subjected the animals to radiation and effects leading to injuries consistent with secondary or tertiary blast effects.[87] None of the studies found by the IDA research team

---

[84] The one exception used minipigs as test subjects, see Philippe Foubert et al., "Development of a Combined Radiation and Full Thickness Burn Injury Minipig Model to Study the Effects of Uncultured Adipose-Derived Regenerative Cell Therapy in Wound Healing," *International Journal of Radiation Biology* (2016): 1-11, http://dx.doi.org/10.1080/09553002.2017.1242814.

[85] Antino R. Allen et al., "Effects of Radiation Combined Injury on Hippocampal Function are Modulated in Mice Deficient in Chemokine Receptor 2 (CCR2)," *Radiation Research* 180, no. 1 (2013): 78-88.

[86] G. D. Ledney, T. B. Elliott, and M. M. Moore, "Modulation of Mortality by Tissue Trauma and Sepsis in Mice after Radiation Injury," in *The Biological Basis of Radiation Protection Practice*, eds. K. L. Mossman and W. A. Mills (Baltimore, MD: Williams & Wilkins, 1992), 202-217; R. S. Boudagov, L. P.Oulianova, and A. F. Tsyb, *The Pathogenesis and Therapy of Combined Radiation Injury*, DTRA-TR-06-24 (Alexandria, VA: ITT Industries, Inc, October 2006); Ledney and Elliott, "Combined Injury," 145-152; Edward A. Carter et al., "Combination of Radiation and Burn Injury Alters FDG Uptake in Mice," *Journal of Burn Care and Research* 33, no. 6 (2012): 723-730; April Elizabeth Mendoza et al. "Radiation Combined with Thermal Injury Induces Immature Myeloid Cells," *Shock* 38, no. 5 (November 2012): 532-542; Juliann G. Kiang and G. David Ledney, "Skin Injuries Reduce Survival and Modulate Corticosterone, C-Reactive Protean, Complement Component 3, IgM, and Prostaglandin E_2 after Whole-Body Reactor-Produced Mixed Field (n + γ-Photons) Irradiation," *Oxidative Medicine and Cellular Longevity* (2013): 1-10, http://dx.doi.org/10.1155/2013/821541; G. Tajima et al., "Immune System Phenotyping of Radiation and Radiation Combined Injury in Outbred Mice," *Radiation Research* 179, no. 1 (January 2013): 101-112; Stewart R. Carter et al., "Intestinal Barrier Disruption,"281-289; Jonathan D. Cherry et al., "Thermal Injury Lowers the Threshold for Radiation-Induced Neuroinflammation and Cognitive Dysfunction," *Radiation Research* 180, no. 4 (October 2013): 398-406; Jessica L. Palmer et al., "Combined Radiation and Burn Injury Results in Exaggerated Early Pulmonary Inflammation," *Radiation Research* 180, no. 3 (2013): 276-283; Juliann G. Kiang et al., "Ghrelin Therapy Improves Survival after Whole-Body Ionizing Irradiation or Combined with Burn or Wound: Amelioration of Leukocytopenia, Thrombocytopenia, Splenomegaly, and Bone Marrow Injury," *Oxidative Medicine and Cellular Longevity* (2014): 1-12, http://dx.doi.org/10.1155/2014/215858; Aminul Islam et al., "An Exploration of Molecular Correlates Relevant to Radiation Combined Skin-Burn Trauma," *PLoS One* 10, no. 8 (August 6, 2015): 1-16, http://doi.org/10.1371/journal.pone.0134827; Sachin S. Jadhav et al., "Effect of Combined Radiation Injury on Cell Death and Inflammation in Skin," *Apoptosis* 20 (2015): 892-906; Stewart R. Carter et al., "Neutrophil Accumulation in the Small Intestine Contributes to Local Tissue Destruction Following Combined Radiation and Burn Injury," *Journal of Burn Care and Research* 37, no. 2 (March/April 2016): 97-105; Foubert et al., "Development of a Combined Radiation and Full Thickness Burn Injury Minipig Model," 1-11; Nikolai V. Gorbunov and Juliann G. Kiang, "Ghrelin Therapy Decreases Incidents of Intracranial Hemorrhage in Mice after Whole-Body Ionizing Irradiation Combined with Burn Trauma," *International Journal of Molecular Sciences* 18 (2017): 1-13, http://dx.doi.org/10.3390/ijms18081693.

[87] Ledney, Elliott, and Moore, "Modulation of Mortality by Tissue Trauma and Sepsis," 202-217; Vijaya Vegesna et al., "The Effect of Local and Systemic Irradiation on Impairment of Wound Healing in Mice," *Radiation Research* 135, no. 3 (September 1993): 431-433; Kavin G. Shah et al., "Human

looked at primary blast combined with thermal effects nor with the combination of radiation, blast, and thermal.

Table 2. U.S.-Based Combined Injury Studies Post-1990

	Animal Model			
Insult Combination	**Rats/Mice**	**Dog**	**Minipig**	**Rabbit**
Radiation-Thermal	16	0	1	0
Radiation-Primary Blast	1	0	0	0
Radiation-Secondary/Tertiary Blast	16	0	0	0
Thermal-Primary Blast	0	0	0	0
Radiation-Thermal-Primary Blast	0	0	0	0

Ghrelin Ameliorates Organ Injury and Improves Survival after Radiation Injury Combined with Severe Sepsis," *Molecular Medicine* 15, no. 11/12 (November/December 2009): 407-414; Ledney and Elliott, "Combined Injury," 145-152; Juliann G. Kiang et al., "Wound Trauma Increases Radiation-Induced Mortality by Activation of iNOS Pathway and Elevation of Cytokine Concentrations and Bacterial Infection," *Radiation Research* 173, no. 3 (March 2010): 319-332; Kiang and Ledney, "Skin Injuries Reduce Survival and Modulate Corticosterone," 1-10; Juliann G. Kiang et al., "Ghrelin Therapy Improves Survival," 1-12; Juliann G. Kiang and Risaku Fukumoto, "Ciprofloxacin Increases Survival After Ionizing Irradiation Combined Injury: g-H2AX Formation, Cytokine/Chemokine, and Red Blood Cells," *Health Physics*, 106, no. 6 (June 2014): 720-726; Juliann G. Kiang and Nikolai V. Gorbunov, "Bone Marrow Mesenchymal Stem Cells Increase Survival after Ionizing Irradiation Combined with Wound Trauma: Characterization and Therapy," *Journal of Cell Science and Therapy* 5, no. 6 (2014): 1-21, http://doi.org/10.4172/2157-7013.1000190; Janice A. Zawaski et al., "Radiation Combined Injury Models to Study the Effects of Interventions and Wound Biomechanics," *Radiation Research* 182, no. 6 (December 2014): 640-652; Juliann G. Kiang et al., "Hemorrhage Exacerbates Radiation Effects on Survival, Leukocytopenia, Thrombopenia, Erythropenia, Bone Marrow Cell Depletion and Hematopoiesis, and Inflammation-Associated microRNAs Expression in Kidney," *PLoS One* 10 (September 30, 2015): 1-25, https://doi.org/10.1371/journal.pone.0139271; Joshua M. Swift, Joan T. Smith, and Juliann G. Kiang, "Hemorrhage Trauma Increases Radiation-Induced Trabecular Bone Loss and Marrow Cell Depletion in Mice," *Radiation Research* 183 (2015): 578-583; Joshua M. Swift et al., "Skin Wound Trauma, Following High-Dose Radiation Exposure, Amplifies and Prolongs Skeletal Tissue Loss," *Bone* 81 (2015): 487-494; M. Epperly et al., "A Murine Combined Injury Model of Total Body Irradiation and Skin Wound,"E588; Juliann G. Kiang et al., "Hemorrhage Enhances Cytokine, Complement Component 3, and Caspase-3, and Regulates Micro-RNAs Associated with Intestinal Damage after Whole-Body Gamma-Irradiation in Combined Injury," *PLoS One* 12, no. 9 (September 21, 2017): 1-25, https://doi.org/10.1371/journal.pone.0184393; Juliann G. Kiang et al., "Combined Therapy of Pegylated G-CSF and Alxn4100TPO Improves Survival and Mitigates Acute Radiation Syndrome after Whole-Body Ionizing Irradiation Alone and Followed by Wound Trauma," *Radiation Research* 188 (2017): 476-490; Kiang, Anderson, and Smith, "Ghrelin Therapy Mitigates Bone Marrow Injury,"1-13; Juliann G. Kiang et al., "Ghrelin, a Novel Therapy, Corrects Cytokine and NF-kB-ADT-MAPK Network and Mitigates Intestinal Injury Induced by Combined Radiation and Skin-Wound Trauma," *Cell & Bioscience* 10 (2020): 1-17, https://doi.org/10.1186/s13578-020-00425-z; and Meetha Medhora et al., "Wound Trauma Exacerbates Acute, but not Delayed, Effects of Radiation in Rats: Mitigation by Lisinopril," *International Journal of Molecular Sciences* 21 (2020): 1-14, https://doi.org/10.3390/ijms21113908.

Another 93 studies identified by the IDA team were conducted by organizations outside the United States (see Table 3). The vast majority of these studies (87) were conducted in China by various military-affiliated medical universities. The Chinese studies again predominantly used small mammals, with 80 employing murine models, one a swine model (minipig), and one a rabbit model. Three Chinese studies did use a canine model, the only studies published during this period found to have employed large mammals.[88]

Of the Chinese studies, the majority exposed test animals to a combination of radiation and thermal (61 studies, two of which included a canine model)[89] or radiation and effects leading to injuries consistent with secondary/tertiary blast effects (20 studies).[90] The Chinese were the only researchers found by the IDA team to have studied thermal and primary blast (pulmonary) effects (six studies, with one using a canine model).[91] Of the

---

88 Xin-Ze Ran et al., "Experimental Research on the Management of Combined Radiation-Burn Injury in China," *Radiation Research* 175, no. 3 (March 2011): 382-389; and Quan Hu et al., "Development of an Animal Model for Burn-Blast Combined Injury and Cardiopulmonary System Changes in the Early Shock Stage," *Indian Journal of Surgery* 77, supplement no. 3 (December 2015): S9777-S984.

89 Guoping Ai et al., "Relationship Between Change of Small Intestinal Mucosal Immunity and Enterogenous Infection in Mice with Combined Radiation Burn Injury," *Chinese Journal of Radiological Medicine and Protection* 19, no. 1 (1999): 15-17; Tianmin Cheng et al., "Experimental Studies on the Treatment and Pathological Basis of Combined Radiation and Burn Injury," *Chinese Medical Journal* 115, no. 12 (200): 1763-1766; Xin-Ze Ran et al., "Effects of Serum from Rats with Combined Radiation-Burn Injury on the Growth of Hematopoietic Progenitor Cells," *Journal of Trauma* 62, no. 1 (January 2007): 193-198; Zhongmin Zou et al., "Progress in Research on Radiation Combined Injury in China," *Radiation Research* 169, no. 6 (June 2008): 722-729; and Ran et al., "Experimental Research on the Management of Combined Radiation-Burn Injury in China," 382-389.

90 Q. Gu et al., "Effects of Radiation on Wound Healing," *Journal of Environmental Pathology, Toxicology, and Oncology*, 17, no. 2 (1998): 117-123; Jifu Qu et al., "Reduced Presence of Tissue-Repairing Cells in Wounds Combined with Whole-Body Irradiation Injury Is Associated with Both Suppression of Proliferation and Increased Apoptosis," *Medical Science Monitor* 9, no. 10 (2003): BR370-BR377; Chun-Meng Shi, Ji-Fu Qu, and Tian-Min Cheng, "Effects of the Nerve Growth Factor on the Survival and Wound Healing in Mice with Combined Radiation and Wound Injury," *Journal of Radiation Research* 44 (2003): 223-228; Zou et al., "Progress in Research on Radiation Combined Injury in China," 722-729; Chao Yang et al., "Effects of Adipose-Derived Stem Cells-Hyaluronic Acid Composite on Healing of Wound Combined with Radiation Injury," *Zhongguo Xui Fu Chong Jian Wai Ke Za Zhi* 25, no. 12 (December 2011): 1499-1503, Chinese; and Qiong Ma et al., "Effects of Neuro-Immuno-Modulation on Healing of Wound Combined with Local Radiation Injury in Rats," *Chinese Journal of Traumatology* 20 (2017): 270-274.

91 Y. T. Yan, "Effect of Burn Injury, Blast Injury and Combined Burn-Blast Injury on Immune Reactions of Thymocytes and Splenocytes in Rats," *Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi* 9, no. 4 (July 1993): 280-283, Chinese; H. Zheng, T. Cheng, and Y. Lin, "Ultrastructural Changes in Pulmonary Microvascular Damage in Rats Inflicted with Burn, Blast and Combined Burn-Blast Injury, *Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi* 11, no. 6 (November 1995): 425-429, Chinese; Jia-ke Chai et al., "A Novel Model of Burn-Blast Combined Injury and Its Phasic Changes of Blood Coagulation in Rats," *Shock* 40, no. 4 (2013): 297-302; Jai-ke Chai et al., "Role of Neutrophil Elastase in Lung Injury Induced by Burn-Blast Combined Injury in Rats," *Burn* 39 (2013): 745-753; W. Liu and J. K. Chai, "Influences of Ulinastatin on Acute Lung Injury and Time Phase Changes of Coagulation Parameters in Rats with Burn-Blast Combined Injuries," *Zhonghua Shao Shang Za Zhi* 34, no. 1 (January 2018): 32-

remaining six studies found by the IDA team conducted by organizations outside the United States, four were Russian, in which mice were exposed to radiation and thermal.[92] Finally, there was one study each from Canada[93] and Germany,[94] both of which exposed rats to radiation and effects leading to injuries consistent with secondary/tertiary blast effects. Again, none of the studies conducted outside the United States looked at combined radiation, blast, and thermal.

Table 3. Non-U.S.-Based Combined Injury Studies Post-1990

	Animal Model			
Insult Combination	**Rats/Mice**	**Dog**	**Minipig**	**Rabbit**
Radiation-Thermal	63	2	0	0
Radiation-Primary Blast	0	0	0	0
Radiation-Secondary/Tertiary Blast	20	0	1	1
Thermal-Primary Blast	5	1	0	0
Radiation-Thermal-Primary Blast	0	0	0	0

Although generally consistent with the pre-1990 studies, nearly all of the post-1990 studies identified by the IDA research team collected data on production or loss of certain biomolecules and/or descriptions of detailed physiological processes, as opposed to more macro-level signs/symptoms needed to determine dose-response for humans. However, weight loss, wound healing, and deaths were often recorded depending on the study. Overall, given the nature of the effects examined, the animal models employed, and the data collected, it is very difficult to extrapolate these post-1990s results to dose-responses in humans.

39, Chinese; and for the dog model, see Hu et al., "Development of an Animal Model for Burn-Blast Combined Injury."

92 R. S. Budagov and L. P. Ul'ianova, "Comparative Analysis of Proinflammatory Cytokines in Plasma of Mice Exposed to Radiation or in Combined Radiation Injury," *Radiation Biology, Radioecology* 40, no. 2 (March/April 2000): 188-191, Russian; R. S. Budagov and L. P. Ul'ianova, "Effect of Microbial Derived Agents on the Level of Blood Cytokines, Hematological Status and Survival of Mice Following Combined Radiation Injury," *Radiation Biology, Radioecology* 41, no. 1 (January/February 2001): 38-42, Russian; R. S. Budagov et al., "Increase in the Level of Metallothioneins in Mouse Liver after Administration of Cadmium Chloride Does Not Protect From Combined Radiation-Thermal Injury," *Radiation Biology, Radioecology* 41, no. 6 (November/December 2001): 671-676, Russian; and R. S. Budagov and L. P. Ul'ianova, "Role of Interleukin-6 (IL-6) in the Pathogenesis of Combined Radiation/Thermal Injuries," *Radiation Biology, Radioecology* 44, no. 4 (July/August 2004): 398-402, Russian.

93 Dale Dantzer et al., "Effect of Radiation and Cell Implantation on Wound Healing in a Rat Model," *Journal of Surgical Oncology* 83 (2003): 185-190.

94 Michael Schaffer et al., "Differential Expression of Inflammatory Mediators in Radiation-Impaired Wound Healing," *Journal of Surgical Research* 107 (2002): 93-100.

C. Mechanistic Models/HENRE

A third approach to developing a synergistic combined methodology uses the insights and results of various mechanistic models to look at human response to various combinations of radiation, blast, and thermal. The Health Effects from Nuclear and Radiological Environments (HENRE) tool, developed by Applied Research Associates (ARA) in support of the Defense Threat Reduction Agency (DTRA), is one such model.

1. Mechanistic Model Description

Mechanistic modeling entails the mathematical representation of certain physiological processes and their interactions, usually at the individual organ level. It has long been used in the field of radiobiology and increasingly used in chemical toxicology and burn therapy.[95] Mechanistic models of radiation effects were incorporated into the Radiation-Induced Performance Decrement (RIPD) model,[96] which was the successor to the IDP modeling effort, and are used for radiation and thermal effects (including combined effects) in the HENRE model, described further below.

Some researchers assert that "[m]echanistic modeling will enable more accurate predictions of the outcomes expected in combined injury casualties."[97] However, despite the promise, there are serious limitations with applying existing experimental results from animal models to mechanistic models designed to represent human nuclear combined injury effects.

2. Implications of Animal Model Data for Mechanistic Models

Despite advances in computational biology, mechanistic models are most useful when the underlying mechanisms of the biological processes being simulated are well understood. Developing such models requires robust experimental data derived from animal and/or human studies. When using animal-derived data, mechanistic models may provide hypothesis testing for learning about biological processes, such as inflammatory

---

[95] Stephen J. McMahon and Kevin M. Prise, "Mechanistic Modeling of Radiation Responses," *Cancers* 11 (2019): 1-23, https://doi.org/10.3390/cancers11020205; Y. M. Tan et al., "Challenges Associated with Applying Physiologically Based Pharmacokinetic Modeling for Public Heath Decision-Making," *Toxicological Sciences* 162, no. 2 (April 1, 2018): 341; J. Bert et al., "Fluid Resuscitation Following a Burn Injury: Implications of a Mathematical Model of Microvascular Exchange," *Burn* 23, no. 2 (1997): 93-105; and Weizhong Dai et al., "A Mathematical Model for Skin Burn Injury Induced by Radiation Heating," *International Journal of Heat and Mass Transfer* 51 (2008): 5497-5510.

[96] Terry C. Pellmar and Darren R. Oldson, *Critical Review of Selected Components of RIPD (Radiation-Induced Performance Decrement)*, DTRA-TR-12-047 (Arlington, VA: Applied Research Associates, Inc., December 2012), 2.

[97] Stricklin, Pellmar, and Oldson, *Literature Survey for Combined Injury Modeling*, ARA/HS-TM-11-005 (Arlington, VA: Applied Research Associates, Inc., December 7, 2010), 21.

processes, but require validation against human clinical data to establish clinical relevance.[98]

It has been noted elsewhere that small mammals, such as rodents, can be useful animal models for exploring underlying mechanisms arising from exposure to radiation.[99] However, as noted in the previous section, the physiological differences between rodents and humans—including immunological differences and dissimilarities in wound healing times—make comparable claims for combined effects problematic. There are extensive knowledge gaps concerning the underlying mechanisms of combined effects and limitations with animal studies; consequently, creating a mechanistic model of human effects that appropriately reflects physiological processes of combined nuclear injuries and provides predictive outcomes is highly uncertain at this time.

Future improvements for mechanistic models of combined nuclear effects will require further understanding of physiological mechanisms driving synergistic effects in combined injuries, as well as foundational research on integrating multiple models derived from clinically relevant animal data.

3. HENRE Model

The HENRE tool attempts to predict "medical and performance consequences from radiation and combined injuries."[100] The model is composed of three sets of tools and outcomes, which rely in part on mechanistic models, and includes a version of the RIPD code to estimate performance degradation following radiation exposure.[101]

The model estimates the probability of various outcomes based on exposure to radiation, blast, or thermal alone. HENRE uses a probit methodology to estimate probability of severe injury due to secondary and tertiary blast effects, and probability of death due to tertiary blast effects.[102] The latter blast effect includes probabilities of severe

---

[98] Marcella Torres et al., "Identifying Important Parameters in the Inflammatory Process with a Mathematical Model of Immune Cell Influx and Macrophage Polarization," *PLOS Computational Biology* 15, no. 7 (July 31, 2019): 1-27, https://doi.org/10.1371/journal.pcbi.1007172.

[99] Alison Deckhut Augustine et al., "Animal Models for Radiation Injury, Protection and Therapy," *Radiation Research* 164, no. 1 (July 2005): 107.

[100] Daniela Stricklin et al., *An Overview of the Technical Basis of HENRE 2.0 Models*, DTRA-TR-15-070 (Arlington, VA: Applied Research Associates, Inc., August 2015), 2.

[101] Amy Creel et al., *HENRE 3.0 Technical Reference Manual,* DTRA-TR-20-006, (Arlington, VA: Applied Research Associates, Inc., October 2021), 3-5, CONTROLLED UNCLASSIFIED INFORMATION.

[102] There is also an option for the model to output probability of death due to primary blast effects (peak overpressure) based on a probit model, but the user must supply the necessary overpressure value resulting in median probability of death and the associate probit slope; see Creel et al., *HENRE 3.0 Technical Reference Manual*, 147-151.

injury and lethality for decelerative tumbling in an open field and an urban environment and due to perpendicular impact.

The model also estimates probability of death over various time frames resulting from exposure to radiation (over 2 days and overall) and thermal fluence (over 2 days, 30 days, and 60 days).[103] This portion of the code does not have an option to calculate effects (e.g., death) due to primary blast effects.

In terms of combined effects, the model estimates probability of death for various combinations of radiation, blast, and thermal, and provides output from various mechanistic models for combined radiation and thermal. The model considers the synergistic effects on probability of death only for combined radiation and thermal (over 2 days and 60 days), based in part on a combination of mechanistic and probit models.[104] The probability of lethality for all other combinations of insult—radiation and blast, thermal and blast, radiation and thermal combined plus blast—is based on the largest probability in the combination, and thus does not consider the synergistic effects of blast combined with radiation and/or thermal.[105]

For combined radiation and thermal, the model uses mechanistic models to estimate early changes in plasma volume, perturbations in hematopoietic cell kinetics, and perturbations in small intestine epithelial cell kinetics. These models do attempt to look at synergistic effects from these combined exposures; however, it is difficult to translate the output from these models (e.g., production or loss of biochemicals or disruptions to physiological processes) directly into a set of signs and symptoms over time as needed by the AMedP methodology. The one case in the model where this is done—the RIPD modeling tool for examining the effects of radiation exposure alone—illustrates the difficulties involved.

The model's RIPD methodology converts the output from four mechanistic models into time-dependent signs and symptoms severity levels for the six physiological categories

---

[103] The radiation module outputs a probability of death within 2 days, an overall probability of death and a time to death, all based on different probit models and output from the MarCell mechanistic model (examining bone marrow depletion); see Creel et al., *HENRE 3.0 Technical Reference Manual*, 49-53. The thermal module outputs a probability of death within 2 days, 30 days and 60 days, all based on different probit models; see Creel et al., *HENRE 3.0 Technical Reference Manual*, 137-140.

[104] For combined radiation and thermal exposure, the model uses either a probit model and output from the Coupled Starling mechanistic model (estimates minimal plasma volume) or a regression model, depending on the level of radiation exposure, for 2 days and a regression model for 60 days; see Creel et al., *HENRE 3.0 Technical Reference Manual*, 152-153 and 156. The regression model is based on extrapolation from Alpen and Sheline (1954) study on rats exposed to radiation and thermal; see Daniela Stricklin, *Development of a Logistic Regression Model for Radiation and Burn Combined Injury Mortality*, ARA/HS-TN-13-009-A (Arlington, VA: Applied Research Associates, Inc., September 6, 2013), CONTROLLED UNCLASSIFIED INFORMATION.

[105] Creel et al., *HENRE 3.0 Technical Reference Manual*, 155-157.

of acute radiation syndrome developed under the IDP program. The HENRE code provides equations for converting the mechanistic model outputs into signs/symptoms severity progressions, which are then used to estimate performance degradation over time, just as in the IPD and Combined Injury methodologies. To indicate the effort required, the development of one of these equations—that for converting the output from the mechanistic Neuroactive Agents model (also referred to as the Upper Gastrointestinal (UG) model or the UG distress model) to the sign/symptom severity progression for the UG category—will be examined here. This model was chosen as it is the only HENRE sub-model for which the conversion process is clearly illustrated by the model developers.

That said, while other HENRE sub-models reflected underlying physiological mechanics with greater fidelity, the UG has been described by one set of reviewers as "theoretical" and that its "underlying process had not been linked to any known mechanisms."[106] Nonetheless, the reviewers noted that the model's predictions are consistent with clinical data on human response from accidents and radiation therapy.[107]

The Neuroactive Agents model represents the emetic pathways, examining the disturbances in these pathways initiated by exposure to a mid-line tissue radiation dose rate. The model is essentially a set of three coupled differential equations containing seven different parameters. The model outputs the production and clearing of humoral toxins.[108] The IDP effort developed five severity levels for UG distress in humans, with descriptions of signs and symptoms associated with each (see Table 4). The amount of released neuroactive agent (toxin) present (A) is converted to a severity level (S) through the following transition equation:[109]

$$S = 1 + 4\left(1 - \exp\left(-ln2 * \left(\frac{A}{A_{0.5}}\right)^{\gamma}\right)\right)$$

[106] Pellmar and Oldson, *Critical Review of Selected Components of RIPD*, 16 and 19. This review went on to note that this model "does not attempt to model the many and complex pathways contributing to behavior. The compartments are theoretical and their interrelationships are defined by parameters developed to fit the empirical data;" see Pellmar and Oldson, *Critical Review of Selected Components of RIPD*, 19.

[107] Pellmar and Oldson, *Critical Review of Selected Components of RIPD*, 16 and 19; and George H. Anno, Gene E. McClellan, and Michael A. Dore, *Protracted Radiation-Induced Performance Decrement Volume 1-Model Development*, DNA-TR-95-117-V1 (Santa Monica, CA: Pacific-Sierra Research Corp., May 1996), 3-21. The model was also found to be in reasonable agreement with experiments looking at protracted radiation exposure using ferrets, which are known to have an emetic response very similar to humans; see Pellmar and Oldson, *Critical Review of Selected Components of RIPD*, 19.

[108] Creel et al., *HENRE 3.0 Technical Reference Manual*, 59-60.

[109] Pellmar and Oldson, *Critical Review of Selected Components of RIPD*, 18.

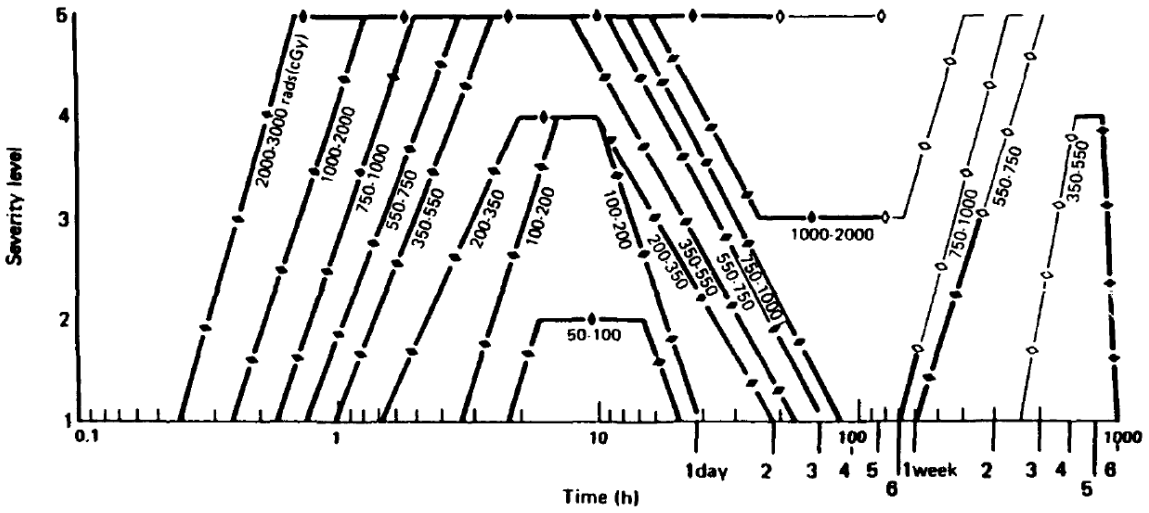
This particular form of the equation was chosen by the RIPD model developers because it displays a threshold behavior, consistent with observed clinical responses, and is designed such that the mid-range toxin value ($A_{0.5}$) corresponds to the mid-range severity level (3).[110]

Table 4. Severity Levels of UG Distress in Humans

Severity Level	Signs and Symptoms
1	No effect
2	Upset stomach; clammy and sweaty; mouth waters and swallows frequently.
3	Nauseated; considerable sweating; swallows frequently to avoid vomiting
4	Vomited once or twice; nauseated and may vomit again
5	Vomited several times including the dry heaves; severely nauseated and will soon vomit again

Note: Derived from George H. Anno et al., *Biological Effects of Protracted Exposure to Ionizing Radiation*, 134.

The original sign/symptom severity progressions derived during the IPD effort were discontinuous and quantized to integer values only, as shown in Figure 6.[111]



Note: Derived from George H. Anno et al., Biological Effects of Protracted Exposure to Ionizing Radiation, 140.

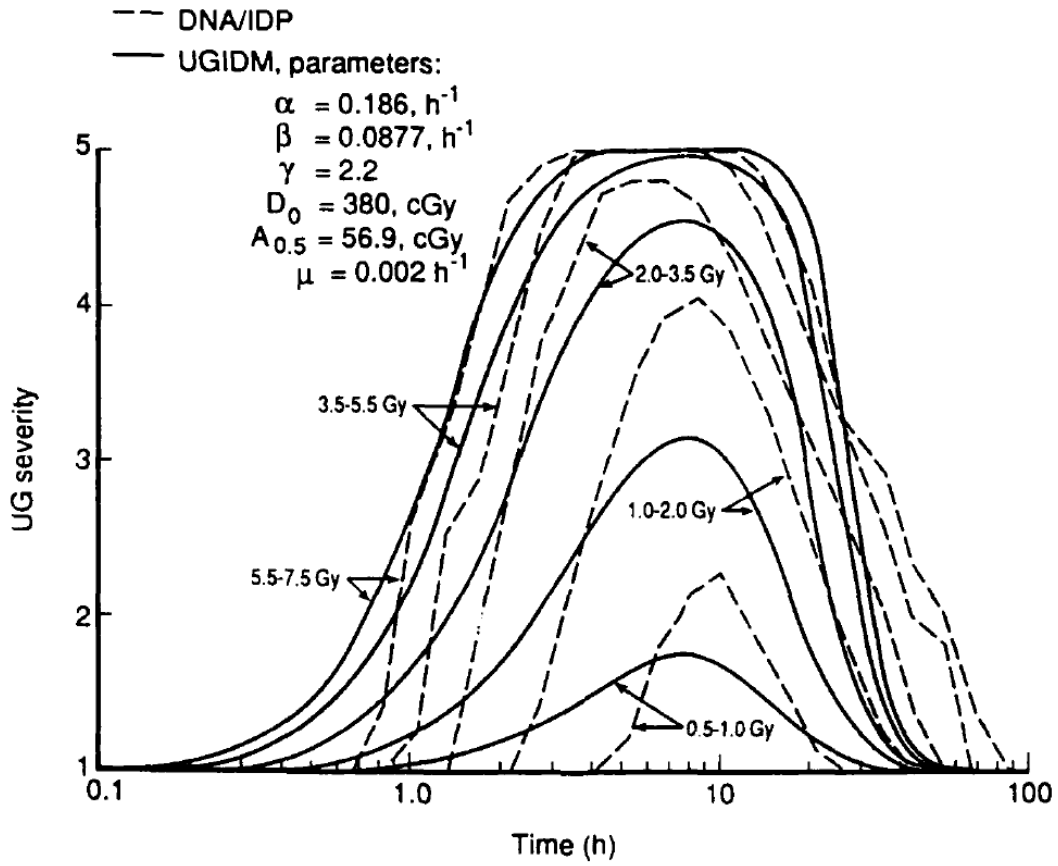
Figure 6. UG Severity Levels for Prompt Radiation Dose Ranges from IDP Program

[110] George H. Anno et al., *Biological Effects of Protracted Exposure to Ionizing Radiation: Review, Analysis, and Model Development*, DNA-TR-90-157 (Santa Monica, CA: Pacific-Sierra Research Corp., November 1991), 138.

[111] The AMedP-7.5 progressions are similarly discontinuous and quantized only to integer values.

To help fit the progressions to the proposed continuous equation, the RIPD model developers "rounded" these graphs and extended the peak of the 2.0-3.5 Gy curve to be between severity levels 4 and 5. The authors provided no discussion of how this rounding was done nor a justification for modifying the 2.0-3.5 Gy curve.[112] The result of these modifications is shown by the dashed lines in Figure 7.

The RIPD model developers then optimized the seven parameters from the Neurotoxin Agent model and the two parameters from the proposed transition equation in order to minimize the root-mean-square difference between the IDP curves and the transition equation.[113] The plots resulting from this optimization are shown by the solid lines in Figure 7.



Source: George H. Anno et al., *Biological Effects of Protracted Exposure to Ionizing Radiation*, 142.

Figure 7. Modified UG Severity Levels for Prompt Radiation Dose Ranges from RIDP Program

---

[112] Anno et al., *Biological Effects of Protracted Exposure to Ionizing Radiation*, 141-142.

[113] Anno et al., *Biological Effects of Protracted Exposure to Ionizing Radiation*, 142-143.

Regardless of how one judges the resulting RIPD methodology, it relies on having the sign/symptom severity progressions developed during the IDP effort. To implement a similar procedure for combined effects would require having the relevant combined sign/symptom progressions. Unfortunately, as mentioned earlier, the signs/symptoms severity progressions for combined efforts, developed during the design of the Combined Injury Methodology, are no longer available. Thus, the output of the mechanistic models in HENRE designed to model response to combined radiation and thermal cannot be converted to signs/symptom severity curves using a similar (though admittedly very laborious and uncertain) approach.

To summarize the problems so far with using HENRE to develop a synergist combined effects approach for the AMedP methodology:

- The only synergistic combined effects modeled in HENRE are radiation and thermal.
- With the exception of some probability of death calculations, these synergist effects are modeled using mechanistic models largely developed with data from experiments using rodents as animal test subjects.
- There are unresolved issues with using murine models to examine combined effects.
- Even if these issues were resolved or ignored, it is very difficult to convert the output from mechanistic models into signs/symptom severity progressions.
- The only approach used so far in the model, that from radiation effects alone in RIPD, requires having signs/symptom progressions for combined effects and such plots are not currently available.

There is a final, largely separate methodology (the Injury Severity methodology) that HENRE employs to generate casualty streams following a nuclear event for use with the Medical Planner's Toolkit (MPTk) and the Joint Medical Planning Tool (JMPT). The HENRE model developers developed a set of injury severity bins for prompt radiation, blast, and thermal, though it is not clear from the documentation reviewed by the IDA team how these bins were generated. The model developers than mapped all of the resulting combinations of radiation, blast, and thermal injury severity bins to existing patient codes, which are maintained and updated by the Naval Health Research Center. However, it is unclear how this representation can be used to develop combined synergistic signs/symptoms progressions in the AMedP methodology.

This page is intentionally blank.

4. Conclusion/Recommendation

In general, the situation regarding data to support modeling combined nuclear effects in the AMedP methodology has changed little since AMedP-8(C). The combined injury profiles developed during the Combined Injury Study remain unavailable and are unlikely to be recoverable in the future. Not enough reliable clinical data exists to develop a synergistic effects representation, though recently developed databases on conventional blast events may provide some insight.

Likewise, animal experiments conducted during the 1950s through the 1980s failed to produce sufficient data to develop a synergistic effects approach. A large number of combined radiation studies have occurred in the last 10 to 15 years, but the vast majority have used small mammals (mostly rodents) as test subjects, making extrapolation of these results to humans problematic. Differences between humans and these small mammals (largely rodents) could be ignored and expected human responses described in terms of these animal models.

However, such an approach is unlikely to be accepted during a subsequent validation process for a number of reasons, including: 1) the underlying mechanisms associated with combined effects are poorly understood, and 2) the available animal models are unreliable human surrogates for combined effects. Moreover, the available mechanistic models of combined injury do not provide output that is readily transferrable to the AMedP methodology (e.g., signs/symptom progressions).

HENRE, which incorporates mechanistic models and examines combined effects, does not look at combined blast effects synergistically and does not provide output for the synergistic effects of radiation plus thermal in a fashion transferable to the AMedP methodology.[114] The one general approach in HENRE that might have been useful in converting mechanistic model outputs to signs/symptom severity levels—illustrated in the conversion (however uncertain) of the radiation mechanistic model outputs from HENRE to signs/symptom severity progressions in the RIPD module—relies on the presence of

[114] Nonetheless, HENRE's approach to tertiary blast effects, particularly lethal effects in the open, should be explored for potential incorporation into the next iteration of AMedP-7.5. These effects do not rely on mechanistic models.

signs/symptoms severity curves that, as mentioned above, are unavailable for combined effects.[115]

That does lead to two possible approaches to developing a synergistic combined injury methodology: recreate the development process employed in the Combined Injury Study or explore the use of lab-on-a-chip technology to generate human-comparable data for the systems of interest. The former effort would entail the following:

- Identify and assemble a group of SMEs well-versed on the effects of radiation and thermal, radiation and primary blast, thermal and primary blast, and radiation, thermal and primary blast.
- Present the SMEs with individual signs/symptoms severity progressions that are used in AMedP-7.5 for each of the three insults and their respective five range bands across each applicable physiological system.
- Either have the SMEs generate new sign/symptom severity curves for all 112 insult combinations (the curves in which only one insult rises above the "no effect" level are already determined) or, to save time, have the SMEs generate new sign/symptom severity curves for the 27 mid-range insult combinations for each applicable physiological system. In the latter case, some means (perhaps another set of rules (algorithms) with accompanying justifications) would need to be developed to extrapolate to the remaining 85 "extreme" insult combinations for each applicable physiological system.

It should be recognized, however, that this would be a very time-consuming and labor-intensive process. Just locating the correct SMEs to invite could prove difficult. Several different meetings with different SMEs would likely be required; for example, SMEs with expertise in radiation and thermal effects are unlikely to be knowledgeable about the radiation and blast effects. Maintaining active participation over what is likely to be a long and pain-staking process could be difficult. All that said, it could be the only reliable means of developing a synergistic combined injury methodology in the short term (i.e., consistent with the timeline for the next iteration of AMedP-7.5).

The latter would entail the following:

---

[115] It should be that, besides validation efforts directed at the UG sub-model, the lower gastrointestinal (LG) or gut injury model, was validated against rodent data that included the onset of diarrhea and fluid loss. A review of the HENRE models found that the LG "model predictions showed good correlation with experimental data;" see Pellmar and Oldson, *Critical Review of Selected Components of RIPD*, 26; and Anno et al., *Biological Effects of Protracted Exposure to Ionizing Radiation*, 178-188. The experimental data were derived from T. Matsuzawa and R. Wilson, "The Intestinal Mucosa of Germfree Mice After Whole-Body X-Irradiation with 3 Kilogoentgents," *Radiation Research* 25 (May 1965): 15-24; and K. L. Jackson and J. P. Geraci, *Physiological Mechanisms of Acute Intestinal Radiation Death*, DNA-TR-86-241 (Washington, D.C.: Defense Nuclear Agency, June 1, 1986).

- Identify a research lab with advanced lab-on-a-chip technology and assemble a team with expertise in nuclear effects to help with experimental design.
- Manufacture a synthetic environment with the multiple organ systems of interest (i.e., cardiovascular, immune, gastrointestinal, respiratory, skin).
- Design an experiment simulating combined nuclear injuries suitable for use on a miniaturized scale.
- Examine synergistic effects over time.
- Translate observations to signs/symptoms progressions consistent with the current AMedP methodology.

As with the potential solution described above, this effort would be a very time-consuming, labor-intensive, and costly process. Moreover, it is uncertain whether this effort would succeed because, to IDA's knowledge, it has not been attempted. Currently, there are few research labs with sufficiently advanced lab-on-a-chip technology that could support a sophisticated study on multi-system synergistic effects from nuclear insults. The IDA team corresponded with one group at the Wake Forest Institute for Regenerative Medicine (WFIRM), recognized as pioneers in regenerative medicine. WFIRM was funded by DTRA to develop a synthetic environment of bio-printed miniaturized human organs to model human response to chemical agents and potential therapies.[116]

In addition, WFIRM has used its body-on-a-chip platform to compare drug response in human tissues and organs to animal tissues and organs, with results reportedly demonstrating the technology's superiority over animal models for clinical research.[117] Based on these and other uses that examine multi-organ human response, one of the lab's principal investigators postulated that it may be plausible to use this platform to study combined injuries from nuclear effects.[118] However, confirming the feasibility of such an effort would require further investigation of the lab and technology's capabilities and additional consideration of experimental design.

Finally, owing to the time and effort involved in the first suggested alternative and the early nature of the research entailed in the second, the methodology could continue to

---

[116] "Military Applications," Wake Forest University School of Medicine Website, accessed September 8, 2022, https://www.school.wakehealth.edu/research/institutes-and-centers/wake-forest-institute-for-regenerative-medicine/research/military-applications. WFIRM is also investigating the effects of chlorine gas on the lungs for the Biomedical Advanced Research and Development Authority (BARDA); "BARDA's Expanding CBRN Medical Countermeasures Portfolio," U.S. Department of Health & Human Services, BARDA Website, accessed September 8, 2022, https://www.medicalcountermeasures.gov/barda/cbrn#portfolio.

[117] Unfortunately, the results of this project are not publicly available at the request of the sponsoring agency, DTRA; email communication with Gary Green, WFIRM, August 30, 2022.

[118] Email communication with Gary Green, WFIRM, August 30, 2022.

use the current approach, one that ignores synergistic effects. Incorporating such effects into the methodology would then await further research in this subject area. Given expected deadlines, this final approach is probably the best one to adopt for the next iteration of AMedP-7.5.

Appendix A. Illustrations

Figures

Tables

This page is intentionally blank.

Appendix B. References

Abdullahi, A., S. Amini-Nik, and M. G. Jeschke. "Animal Models in Burn Research." *Cellular and Molecular Life Sciences* 71 (2014): 3241-3255.

Ai, Guoping, Yongping Su, Xiachong Liu, Donghai Wang, Junping Wang, Tianmin Cheng, and Xinze Ran. "Relationship Between Change of Small Intestinal Mucosal Immunity and Enterogenous Infection in Mice with Combined Radiation Burn Injury." *Chinese Journal of Radiological Medicine and Protection* 19, no. 1 (1999): 15-17.

Allen, Antino R., Kirsten Eilertson, Sourabh Sharma, Danielle Schneider, Jennifer Baure, Barrett Allen, Susanna Rosi, et al. "Effects of Radiation Combined Injury on Hippocampal Function are Modulated in Mice Deficient in Chemokine Receptor 2 (CCR2)." *Radiation Research* 180, no. 1 (2013): 78-88.

Alpen, Edward L., and Glenn E. Sheline. "The Combined Effects of Thermal Burns and Whole Body X Irradiation on Survival Time and Mortality." *Annals of Surgery* 140, no. 1 (July 1954): 113-118.

Anno, George H., Gene E. McClellan, and Michael A. Dore. *Protracted Radiation-Induced Performance Decrement Volume 1-Model Development*. DNA-TR-95-117-V1. Santa Monica, CA: Pacific-Sierra Research Corp., May 1996.

Anno, George H., Gene E. McClellan, Michael A. Dore, and Siegmund J. Baum. *Biological Effects of Protracted Exposure to Ionizing Radiation: Review, Analysis, and Model Development*. DNA-TR-90-157. Santa Monica, CA: Pacific-Sierra Research Corp., November 1991.

Anno, G. H., D. B. Wilson, and S. J. Baum. *Severity Levels and Symptom Complexes for Acute Radiation Sickness: Description and Quantification*. DNA-TR-86-94. Los Angeles, CA: Pacific-Sierra Research Corporation, November 30, 1985.

Anno, G. H., D.B. Wilson, and M.A. Dore. *Acute Radiation Effects on Individual Crewmember Performance*. DNA-TR-85-52. Los Angeles, CA: Pacific-Sierra Research Corporation, August 31, 1984.

Augustine, Alison Deckhut, Timothy Gondre-Lewis, William McBride, Lara Miller, Terry C. Pellmar, and Sara Rockwell. "Animal Models for Radiation Injury, Protection and Therapy." *Radiation Research* 164, no. 1 (July 2005): 100-109.

Barabanova, Anzhelika V. "Significance of Beta-Radiation Skin Burns in Chernobyl Patients for the Theory and Practice of Radiopathology." *Vojnosanitetski Pregled* 63, no. 5 (2006): 477-480.

Baxter, Hamilton, John A. Drummond, L. G. Stephens-Nesham, and Robert G. Randall. "Reduction of Mortality in Swine from Combined Total Body Radiation and Thermal Burns by Streptomycin." *Annals of Surgery* 137, no. 4 (April 1953): 450-455.

Baum, Siegmund J. *The Pathophysiology of Combined Radiation Injuries: A Review and Analysis of the Literature on Non-Human Research*. DNA-TR-90-211. Los Alamos, NM: Technico Southwest, Inc., July 1991.

Baum, Siegmund J., George H. Anno, Robert W. Young, and H. Rodney Withers. *Symptomatology of Acute Radiation Effects in Humans After Exposure to Doses of 75 to 4500 Rads (cGy) Free-in-Air*. DNA-TR-85-50. Los Angeles, CA: Pacific-Sierra Research Corporation, August 31, 1984.

Born, C. T., "Blast Trauma: The Fourth Weapon of Mass Destruction." *Scandinavian Journal of Surgery* 94 (2005): 280.

Boudagov, R. S., L. P.Oulianova, and A. F. Tsyb. *The Pathogenesis and Therapy of Combined Radiation Injury*. DTRA-TR-06-24. Alexandria, VA: ITT Industries, Inc., October 2006.

Bowen, I. G., E. R. Fletcher, D. R. Richmond, F. G. Hirsch and C. S. White. "Biophysical Mechanisms and Scaling Procedures Applicable in Assessing Responses of the Thorax Energized by Air-Blast Overpressures or by Nonpenetrating Missiles." *Annals of the New York Academy of Science*, 152, no. 1 (October 1968): 122-146.

Brooks, James W., Everett Idris Evans, William T. Ham and J. Douglas Reid. "The Influence of External Body Radiation on Mortality from Thermal Burns." *Annals of Surgery* 136, no. 3 (September 1952): 533-544.

Budagov, R. S., and L. P. Ul'ianova. "Comparative Analysis of Proinflammatory Cytokines in Plasma of Mice Exposed to Radiation or in Combined Radiation Injury," *Radiation Biology, Radioecology* 40, no. 2 (March/April 2000): 188-191. Russian.

Budagov, R. S., and L. P. Ul'ianova. "Effect of Microbial Derived Agents on the Level of Blood Cytokines, Hematological Status and Survival of Mice Following Combined Radiation Injury." *Radiation Biology, Radioecology* 41, no. 1 (January/February 2001): 38-42. Russian.

Budagov, R. S., and L. P. Ul'ianova. "Role of Interleukin-6 (IL-6) in the Pathogenesis of Combined Radiation/Thermal Injuries." *Radiation Biology, Radioecology* 44, no. 4 (July/August 2004): 398-402. Russian.

Budagov, R. S., L. P. Ul'ianova, O. A. Smoryzanova, and G. M. Rott. "Increase in the Level of Metallothioneins in Mouse Liver after Administration of Cadmium Chloride Does Not Protect From Combined Radiation-Thermal Injury." *Radiation Biology, Radioecology* 41, no. 6 (November/December 2001): 671-676. Russian.

Butterworth, Karl T., and Jacqueline P. Williams. "Animal Models for Radiotherapy Research: All (Animal) Models Are Wrong But Some Are Useful." *Cancers* 13 (2021): 13.

Carter, Edward A., David Winter, Crystal Tolman, Kasie Paul, Victoria Hamrahi, Ronald Tompkins, and Alan J. Fischman. "Combination of Radiation and Burn Injury Alters FDG Uptake in Mice." *Journal of Burn Care and Research* 33, no. 6 (2012): 723-730.

Carter, Stewart R., Michael M. Chen, Jessica L. Palmer, Lu Wang, Luis Ramirez, Timothy P. Plackett, Richard L. Gamelli, et al. "Neutrophil Accumulation in the Small Intestine Contributes to Local Tissue Destruction Following Combined Radiation and Burn Injury." *Journal of Burn Care and Research* 37, no. 2 (March/April 2016): 97-105.

Carter, Stewart R., Anita Zahs, Jessica L. Palmer, Lu Wang, Luis Ramirez, Richard L. Gamelli, and Elizabeth J. Kovacs. "Intestinal Barrier Disruption as a Cause of Mortality in Combined Radiation and Burn Injury." *Shock* 40, no. 4 (2013): 281-289.

Chai, Jai-ke, Jian-hua Cai, Hu-ping Deng, Xiao-fang Zou, Wei Liu, Qing-gang Hu, Chuan-an Shen, et al. "Role of Neutrophil Elastase in Lung Injury Induced by Burn-Blast Combined Injury in Rats." *Burn* 39 (2013): 745-753.

Chai, Jia-ke, Wei Liu, Hu-ping Deng, Kian-hua Cai, Qing-gang Hu, Xiao-fang Zou, Chuan-an-Shen, et al. "A Novel Model of Burn-Blast Combined Injury and Its Phasic Changes of Blood Coagulation in Rats." *Shock* 40, no. 4 (2013): 297-302.

Cheng, Tianmin, Zongrong Chen, Yongtan Yan, Xinze Ran, Yongping Su, and Guoping Ai. "Experimental Studies on the Treatment and Pathological Basis of Combined Radiation and Burn Injury." *Chinese Medical Journal* 115, no. 12 (200): 1763-1766.

Cherniavskiy, Igor, and Volodymyr Vinnikov. "Prognostic Assessment of the Zone of Occurrence of Radiation Combined Injuries within a Nuclear Blast Area." *International Journal of Radiation Biology* 98, no. 5 (2022): 878-889. https://doi.org/10.1080/09553002.2021.1998707.

Cherry, Jonathan D., Jacqueline P. Williams, M. Kerry O'Banion, and John A. Olschowka. "Thermal Injury Lowers the Threshold for Radiation-Induced Neuroinflammation and Cognitive Dysfunction." *Radiation Research* 180, no. 4 (October 2013): 398-406.

Chukwu-Lobelu, R., A. Appukuttan, D. S. Edwards, and H. D. L. Patel. "Burn Injuries from the London Suicide Bombings: A New Classification of Blast-Related Thermal Injuries." *Annals of Burns and Fire Disasters* 30, no. 4 (December 2017): 256-260.

Conklin, James J., Richard I. Walker, and Dennis L. Kelleher. "Evaluation and Treatment of Nuclear Casualties: Part III – Management of Combined Injuries." *Medical Bulletin of the US Army, Europe* 40, no. 12 (December 1983): 17-22.

Creel, Amy, Tyler Dant, Rachel Jennings, Darren Oldson, Aaron Parks, and Kiran Sewsankar. *HENRE 3.0 Technical Reference Manual.* DTRA-TR-20-006. Arlington, VA: Applied Research Associates, Inc., October 2021. CONTROLLED UNCLASSIFIED INFORMATION.

Curling, Carl A., Julia K. Burr, Lusine Danakian, Deena S. Disraelly, Lucas A. LaViolet, Terri J. Walsh, and Robert A. Zirkle. *Technical Reference Manual: NATO Planning Guide for the Estimation of Chemical, Biological, Radiological, and Nuclear (CBRN) Casualties, Allied Medical Publication-8(C).* IDA Document D-4082. Alexandria, VA: Institute for Defense Analyses, August 2010.

Dantzer, Dale, Peter Ferguson, Richard P. Hill, Armand Keating, Rita A. Kandel, Jay S. Wunder, Brian O'Sullivan, et al. "Effect of Radiation and Cell Implantation on Wound Healing in a Rat Model." *Journal of Surgical Oncology* 83 (2003): 185-190.

DiCarlo, Andrea L., Richard J. Hatchett, Joseph M. Kaminski, G. David Ledney, Terry C. Pellmar, Paul Okunieff, and Narayani Ramakrishnan. "Medical Countermeasures for Radiation Combined Injury: Radiation with Burn, Blast, Trauma, and/or Sepsis: Report of an NIAID Workshop March 26-27, 2007." *Radiation Research* 169 (June, 2008): 712-721.

DiCarlo, Andrea L., Narayani Ramakrishnan, and Richard J. Hatchett. "Radiation Combined Injury: Overview of NIAID Research." *Health Physics* 98, no. 6 (June 2010): 863-867.

Elsayed, Nabil M., Karyn L. Armstrong, Myron T. William, and Mary F. Cooper. "Antioxidant Loading Reduces Oxidative Stress Induced by High-Energy Impulse Noise (Blast) Exposure." *Toxicology*, 155 (2000): 91-99.

Epperly, M., A. Bellare, J. S. Greenberger, R. Fisher, P. Wipf, and G. Julie. "A Murine Combined Injury Model of Total Body Irradiation and Skin Wound." *International Journal of Radiation Oncology, Biology, Physics* 99, no. 2 supplement (October 1, 2017): E588.

Foubert, Philippe, Melanie Doyle-Eisele, Andreina Gonzalez, Felipe Berard, Waylon Weber, Dina Zafra, Zeni Alfonso, et al. "Development of a Combined Radiation and Full Thickness Burn Injury Minipig Model to Study the Effects of Uncultured Adipose-Derived Regenerative Cell Therapy in Wound Healing." *International Journal of Radiation Biology* (2016): 1-11. http://dx.doi.org/10.1080/09553002.2017.1242814.

Gibson, Philip W. *Blast Overpressure and Survivability Calculations for Various Sizes of Explosive Charges*. Technical Report NATICK/TR-95/003. Natick, MA: Research, Development and Engineering Center, United States Army Natick, November 1994.

Goans, Ronald E. *Medical Management of Radiological Casualties*. 4th ed. Bethesda, MD: Armed Forces Radiobiology Research Institute, July 2013.

Gorbunov, Nikolai V., and Juliann G. Kiang. "Ghrelin Therapy Decreases Incidents of Intracranial Hemorrhage in Mice after Whole-Body Ionizing Irradiation Combined with Burn Trauma." *International Journal of Molecular Sciences* 18 (2017): 1-13. http://dx.doi.org/10.3390/ijms18081693.

Gu, Q., D. Wang, C. Cui, Y. Gao, G. Xia, and X. Cui. "Effects of Radiation on Wound Healing." *Journal of Environmental Pathology, Toxicology, and Oncology* 17, no. 2 (1998): 117-123.

Hu, Quan, Jiake Chai, Sen Hu, Jun Fan, Hong-wei Wang, Li Ma, Hong-jie Duan, et al. "Development of an Animal Model for Burn-Blast Combined Injury and Cardiopulmonary System Changes in the Early Shock Stage." *Indian Journal of Surgery* 77, supplement no. 3 (December 2015): S9777-S984.

Hubbard, William Brad, Christina Hall, Venkata Siva Sai Sujith Sajja, Erin Lavik, and Pamela VandeVord. "Examining Lethality Risk for Rodent Studies of Primary Blast Lung Injury." *Biomedical Sciences Instrumentation* 50 (2014): 92-99.

Hunter, Kasandra S., Lisa S. Carnell, Andrea L. DiCarlo, Corey M. Hoffman, Shannon G. Loelius, and Mary Homer. "Interagency Approaches to Animal Models for Acute Radiation Exposure." *International Journal of Radiation Biology* 97, no. S1 (2021): S2-S5.

Islam, Aminul, Svetlana Ghimbovschi, Min Zhai, and Joshua M. Swift. "An Exploration of Molecular Correlates Relevant to Radiation Combined Skin-Burn Trauma." *PLoS One* 10, no. 8 (August 6, 2015): 1-16. http://doi.org/10.1371/journal.pone.0134827.

Jackson K. L. and J. P. Geraci. *Physiological Mechanisms of Acute Intestinal Radiation Death*. DNA-TR-86-241. Washington, DC: Defense Nuclear Agency, June 1, 1986.

Jadhav, Sachin S., Christopher J. Meeks, Nicholas M. Mordwinkin, Theresa B. Espinoza, Stan G. Louie, Gere S. diZerega, and Kathleen E. Rodgers. "Effect of Combined Radiation Injury on Cell Death and Inflammation in Skin." *Apoptosis* 20 (2015): 892-906.

Kiang, Juliann G., Marsha N. Anderson, and Joan T. Smith. "Ghrelin Therapy Mitigates Bone Marrow Injury and Splenocytopenia by Sustaining Circulating G-CSF and KC Increases after Irradiation Combined with Wound." *Cell & Bioscience* 8, no. 27 (2018): 1-13. https://doi.org/10.1186/ s13578-018-0225-3.

Kiang, Juliann G., and Risaku Fukumoto. "Ciprofloxacin Increases Survival After Ionizing Irradiation Combined Injury: γ-H2AX Formation, Cytokine/Chemokine, and Red Blood Cells." *Health Physics*, 106, no. 6 (June 2014): 720-726.

Kiang, Juliann G., and Nikolai V. Gorbunov. "Bone Marrow Mesenchymal Stem Cells Increase Survival after Ionizing Irradiation Combined with Wound Trauma: Characterization and Therapy." *Journal of Cell Science and Therapy* 5, no. 6 (2014): 1-21. http://doi.org/10.4172/2157-7013.1000190.

Kiang, Juliann G., Wan Jiao, Lynnette H. Cary, Steven R. Mog, Thomas B. Elliott, Terry C. Pellmar, and G. David Ledney. "Wound Trauma Increases Radiation-Induced Mortality by Activation of iNOS Pathway and Elevation of Cytokine Concentrations and Bacterial Infection." *Radiation Research* 173, no. 3 (March 2010): 319-332.

Kiang, Juliann G., and G. David Ledney. "Skin Injuries Reduce Survival and Modulate Corticosterone, C-Reactive Protean, Complement Component 3, IgM, and Prostaglandin E_2 after Whole-Body Reactor-Produced Mixed Field (n + γ-Photons) Irradiation." *Oxidative Medicine and Cellular Longevity* (2013): 1-10. http://dx.doi.org/10.1155/2013/821541.

Kiang, Juliann G., and Ayodele O. Olabisi. “Radiation: A Poly-Traumatic Hit Leading to Multi-Organ Injury.” *Cell & Bioscience* 9 (2019): 1-15. https://doi.org/10.1186/s13578-019-0286-y.

Kiang, Juliann G., Joan T. Smith, Marsha N. Anderson, Thomas B. Elliott, Paridhi Gupta, Nagaraja Balakathiresan, Radha K. Maheshwari, et al. “Hemorrhage Enhances Cytokine, Complement Component 3, and Caspase-3, and Regulates Micro-RNAs Associated with Intestinal Damage after Whole-Body Gamma-Irradiation in Combined Injury.” *PLoS One* 12, no. 9 (September 21, 2017): 1-25. https://doi.org/10.1371/journal.pone.0184393.

Kiang, Juliann G., Joan T. Smith, Marsha N. Anderson, Joshua M. Swift, Christine L. Christensen, Paridhi Gupta, Nagaraja Balakathiresan, et al. “Hemorrhage Exacerbates Radiation Effects on Survival, Leukocytopenia, Thrombopenia, Erythropenia, Bone Marrow Cell Depletion and Hematopoiesis, and Inflammation-Associated microRNAs Expression in Kidney.” *PLoS One* 10 (September 30, 2015): 1-25. https://doi.org/10.1371/journal.pone.0139271.

Kiang, Juliann G., Joan T. Smith, Georgette Cannon, Marsha A. Anderson, Connie Ho, Min Zhai, Wanchang Cui, et al. “Ghrelin, a Novel Therapy, Corrects Cytokine and NF-kB-ADT-MAPK Network and Mitigates Intestinal Injury Induced by Combined Radiation and Skin-Wound Trauma.” *Cell & Bioscience* 10 (2020): 1-17. https://doi.org/10.1186/s13578-020-00425-z.

Kiang, Juliann G., Min Zhai, David L. Bolduc, Joan T. Smith, Marsha N. Anderson, Connie Ho, Bin Lin, et al. “Combined Therapy of Pegylated G-CSF and Alxn4100TPO Improves Survival and Mitigates Acute Radiation Syndrome after Whole-Body Ionizing Irradiation Alone and Followed by Wound Trauma.” *Radiation Research* 188 (2017): 476-490.

Kiang, Juliann G., Min Zhai, Pei-Jyun Liao, Thomas B. Elliott, and Nikolai V. Gorbunov. “Ghrelin Therapy Improves Survival after Whole-Body Ionizing Irradiation or Combined with Burn or Wound: Amelioration of Leukocytopenia, Thrombocytopenia, Splenomegaly, and Bone Marrow Injury.” *Oxidative Medicine and Cellular Longevity* (2014): 1-12. http://dx.doi.org/10.1155/2014/215858.

Kirkman, E., S. Watts, and G. Cooper. “Blast Injury Research Models.” *Philosophical Transactions of the Royal Society B* 366 (2011): 144-159.

Ledney, G., D., T. B. Elliott, and M. M. Moore. “Modulation of Mortality by Tissue Trauma and Sepsis in Mice after Radiation Injury.” In *The Biological Basis of Radiation Protection Practice*, edited by K. L. Mossman and W. A. Mills, 202-217. Baltimore, MD: Williams & Wilkins, 1992.

Levin, Sheldon G. *The Effect of Combined Injuries from a Nuclear Detonation on Soldier Performance*. DNA-TR-92-134. Espanola, NM: Technico Southwest, Inc., June 1993.

Levin, Sheldon G., and James W. Fulton. *Consolidated Human Response Nuclear Effects Model (CHRNEM)*. DNA-TR-93-45. Espanola, NM: Technico Southwest, Inc., September 1993.

Liu, W., and J. K. Chai. “Influences of Ulinastatin on Acute Lung Injury and Time Phase Changes of Coagulation Parameters in Rats with Burn-Blast Combined Injuries.” *Zhonghua Shao Shang Za Zhi* 34, no. 1 (January 2018): 32-39. Chinese.

Ma, Qiong, Jin-Iing Cai, Xiu-Jie Pan, Li Du, Xiao-Yun Yang, Yong-Xue Liu, Qing-Lin Zhang, et al. “Effects of Neuro-Immuno-Modulation on Healing of Wound Combined with Local Radiation Injury in Rats.” *Chinese Journal of Traumatology* 20 (2017): 270-274.

Mallonee, Sue, S. Shariat, G. Stennies, R. Waxweiler, D. Hogan, and F. Jordan. “Physical Injuries and Fatalities Resulting from the Oklahoma City Bombing.” *Journal of the American Medical Association* 276 (August 7, 1996): 382-387.

Marti, Milagros, Manuel Parron, Franziska Baudraxler, Aranzazu Royo, Nieves Gomez Leon, and Rodolfo Alvarez-Sala. “Blast Injuries from Madrid Terrorist Bombing Attacks on March 11, 2004.” *Emergency Radiology* 13 (2006): 113-122.

Martinez, Berlinda S. *Blast Overpressure Research Program, Kirtland Air Force Base, 1951-1998*. Jaycor Technical Report J2997.74-99-106. San Diego, CA: JAYCOR, November 1999.

Masson-Meyers, Daniel S., Thiago A. M. Andrade, Guilherme F. Caetano, Francielle R. Guimaraes, Marcel N. Leite, and Saulo N. Leite. “Experimental Models and Methods for Cutaneous Wound Healing Assessment.” *International Journal of Experimental Pathology* 101, (2020): 21-37. https://dio.org/10.1111/iep.12346.

Matsuzawa, T. and R. Wilson. “The Intestinal Mucosa of Germfree Mice After Whole-Body X-Irradiation with 3 Kilogoentgents.” *Radiation Research* 25 (May 1965): 15-24.

McGuire, Ruth, A. Hepper, and K. Harrison. “From Northern Ireland to Afghanistan: Half a Century of Blast Injuries.” *Journal of the Royal Army Medical Corps* 165 (2019): 27-32.

Medhora, Meetha, Tracy Gasperetti, Ashley Schamerhorn, Feng Gao, Jayashree Narayanan, Zelmira Lazarova, Elizabeth R. Jacobs, et al. “Wound Trauma Exacerbates Acute, but not Delayed, Effects of Radiation in Rats: Mitigation by Lisinopril,” *International Journal of Molecular Sciences* 21 (2020): 1-14. https://doi.org/10.3390/ijms21113908.

Mellor, S. G., and G. J. Cooper. “Analysis of 828 Servicemen Killed or Injured by Explosion in Northern Ireland 1970-84: The Hostile Action Casualty System.” *British Journal of Surgery* 76, no. 10 (October 1989): 1006-1010.

Mendoza, April Elizabeth, Crystal Judith Neely, Anthony G. Charles, Laurel Briane Kartchner, Willie June Brickey, Amal Lina Khoury, Gregory D. Sempowski, et al. “Radiation Combined with Thermal Injury Induces Immature Myeloid Cells.” *Shock* 38, no. 5 (November 2012): 532-542.

Messerschmidt, Otfried. “Combined Effects of Radiation and Trauma.” *Advances in Space Research* 9, no. 1 (1989): 197-201.

Messerschmidt, Otfried. “Results of Animal Experiments as a Basis for Recommendations on Therapy of Combined Injuries (Radiation Injury Plus Wounds.” In *Pathophysiology of Combined Injury and Trauma*, edited by Richard I. Walker, Dale F. Gruber, Thomas J. MacVittie, and James J. Conklin, 36-50. Bethesda, MD: Armed Forces Radiobiology Research Institute, 1983.

Messerschmidt, O., R. Hennebert, E. Metzger, P. Schick, H. Sedlmeier, K. R. Trott, and F. Verspohl. *Investigations Concerning the Pathogenesis and Therapy of Combined Injuries.* Munich: Federal Republic of Germany Ministry of Defense, 1974.

Millage, Kyle, Gene McClellan, Erica Findley, and Karen Cheng. *Overview of the Implementation of NucModel*. Arlington, VA: Applied Research Associates, November 20, 2007.

North Atlantic Treaty Organization (NATO). *AMedP-8(A), Volume I: Medical Planning Guide for the Estimation of NBC Battle Casualties (Nuclear)*. STANAG 2475. Brussels: NATO, December 2000.

Oxford, Sean M., Lucas A. LaViolet, Kristen A. Bishop, Julia K. Burr, Carl A. Curling, Lusine Danakian, Deena S. Disraelly et al. *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5) NATO Planning Guide for the Estimation of CBRN Casualties*. IDA Document D-8122. Alexandria, VA: Institute for Defense Analyses, October 2016.

Palmer, Jessica L., Cory R. Deburghgraeve, Melanie D. Bird, Martin Hauer-Jensen, Michael M. Chen, Sherri Yong, and Elizabeth J. Kovacs. “Combined Radiation and Burn Injury Results in Exaggerated Early Pulmonary Inflammation,” *Radiation Research* 180, no. 3 (2013): 276-283.

Paredes, Andre, Matthew Lindeblad, Rachana Patil, Matthew D. Neal, Yuanfan Hong, Brett Smith, Joy P. Nanda, et al. “The New Zealand White Rabbit Animal Model of Acute Radiation Syndrome: Hematopoietic and Coagulation-Based Parameters by Radiation Dose Following Supportive Care.” *International Journal of Radiation Biology* 79, no. S1 (2020): S45-S62.

Parr, W. H., V. M. Daggs, T. A. O’Neill, and S. G. Bush. *A Study of Combined Thermal Radiation Burn and X-Irradiation Effects on Mice*. Report No. 94. Fort Knox, KY: Army Medical Research Laboratory, September 4, 1952.

Peleg, Kobi, Alon Liran, Ariel Tessone, Adi Givon, Arie Orenstein, and Josef Haik. “Do Burns Increase the Severity of Terror Injuries?” *Journal of Burn Care and Research* 29, no. 6 (November/December 2008): 887-892.

Pellmar, T. C. *Combined Injury: Radiation in Combination with Trauma, Infectious Disease or Chemical Exposures*. RTO-TR-HFM-099. Bethesda, MD: Armed Forces Radiobiology Research Institute, 2009.

Pellmar, Terry C., and Darren R. Oldson. *Critical Review of Selected Components of RIPD (Radiation-Induced Performance Decrement)*. DTRA-TR-12-047. Arlington, VA: Applied Research Associates, Inc., December 2012.

Peral-Gutierrez de Ceballos, Jose, Fernando Turegano-Fuentes, Dolores Perez-Diaz, Mercedes Sanz-Sachez, Carmen Martin-Llorente, and Jose E. Guerrero-Sanz. “11

March 2004: The Terrorist Bomb Explosions in Madrid, Spain – An Analysis of the Logistics, Injuries Sustained and Clinical Management of Casualties Treated at the Closest Hospital." *Critical Care* 9, no. 1 (February 2005): 104-111.

Phillips, Yancy Y., III, and Donald R. Richmond. "Primary Blast Injury and Basic Research: A Brief History." Chap. 6 in *Conventional Warfare: Ballistic, Blast, and Burn Injuries*, edited by Ronald F. Bellamy and Russ Zajtchuk. Washington, D.C.: Department of the Army, Office of the Surgeon General, Center of Excellence in Military Medical Research and Education, Walter Reed Army Medical Center, 1991.

Qu, Jifu, Tianmin Cheng, Chunmeng Shi, Yuan Lin, Guohe Yan, and Xinze Ran. "Reduced Presence of Tissue-Repairing Cells in Wounds Combined with Whole-Body Irradiation Injury Is Associated with Both Suppression of Proliferation and Increased Apoptosis." *Medical Science Monitor* 9, no. 10 (2003): BR370-BR377.

Ran, Xin-Ze, Chun-Meng Shi, Huai-En Zheng, Yong-Ping Su, and Tian-Min Cheng. "Experimental Research on the Management of Combined Radiation-Burn Injury in China.." *Radiation Research* 175, no. 3 (March 2011): 382-389.

Ran, Xin-Ze, Yong-Ping Su, Zhao-Wen Zong, Chao-Hua Guo, Huai-En Zheng, Xiao-Hong Chen, Guo-Ping Ai, et al. "Effects of Serum from Rats with Combined Radiation-Burn Injury on the Growth of Hematopoietic Progenitor Cells" *Journal of Trauma* 62, no. 1 (January 2007): 193-198.

Sami, Diana G., Hana H. Heiba, and Ahmed Abdellatif. "Wound Healing Models: A Systematic Review of Animal and Non-Animal Models." *Wound Medicine* 24 (2019): 8-17.

Schaffer, Michael, Wiebke Weimer, Susanne Wider, Christina Stulten, Martina Bongartz, Wilfried Budach, and Horst-Dieter Becker. "Differential Expression of Inflammatory Mediators in Radiation-Impaired Wound Healing." *Journal of Surgical Research* 107 (2002): 93-100.

Scott, T. E., E. Kirkman, M. Haque, I. E. Gibb, P. Mahoney, and J. G. Hardman. "Primary Blast Lung Injury – A Review," *British Journal of Anaesthesia* 118, no. 3 (2017): 311-316.

Shah, Kavin G., Rongqian Wu, Asha Jacob, Steven A. Blau, Youxin Ji, Weifeng Dong, Corrado P. Marini, et al. "Human Ghrelin Ameliorates Organ Injury and Improves Survival after Radiation Injury Combined with Severe Sepsis" *Molecular Medicine* 15, no. 11/12 (November/December 2009): 407-414.

Shi, Chun-Meng, Ji-Fu Qu, and Tian-Min Cheng. "Effects of the Nerve Growth Factor on the Survival and Wound Healing in Mice with Combined Radiation and Wound Injury." *Journal of Radiation Research* 44 (2003): 223-228.

Singh, Vijay K., Victoria L. Newman, Allison N. Berg, and Thomas J. MacVittie. "Animal Models for Acute Radiation Syndrome Drug Discovery." *Expert Opinion on Drug Discovery* 10, no. 5 (2015): 497-517.

Skotak, Maciej, Fang Wang, Aaron Alia, Aaron Holmberg, Seth Harris, Robert C. Switzer, and Namas Chandra. "Rat Injury Model Under Controlled Field-Relevant

Primary Blast Conditions: Acute Response to a Wide Range of Peak Overpressures." *Journal of Neurotrauma*, 30 (July 1, 2013): 1147-1160.

Smith, J. E. "The Epidemiology of Blast Lung Injury During Recent Military Conflicts: A Retrospective Database Review of Cases Presenting to Deployed Military Hospitals, 2003-2009." *Philosophical Transactions of the Royal Society B* 366 (2011): 291-294.

Stricklin, Daniela. *Development of a Logistic Regression Model for Radiation and Burn Combined Injury Mortality*. ARA/HS-TN-13-009-A. Arlington, VA: Applied Research Associates, Inc., September 6, 2013. CONTROLLED UNCLASSIFIED INFORMATION.

Stricklin, Daniela L., Gene E. McClellan, Valerie S. Asadian, and Paul K. Blake. *Proceedings of the Joint Nuclear Weapon Effects Human Response Panel*. DTRA-TR-15-069. Arlington, VA: Applied Research Associates, May 10, 2016.

Stricklin, Daniela, Darren Oldson, Jacqueline Wentz, Brian Sanchez, Kyle Millage, and Gene McClella. *An Overview of the Technical Basis of HENRE 2.0 Models*. DTRA-TR-15-070. Arlington, VA: Applied Research Associates, Inc., August 2015.

Stricklin, Daniela, Terry Pellmar, Darren Oldson, and Kyle Millage. *Combined Injury Modeling: Radiation and Burn Workshop Report*. DTRA-TR-10-48. Arlington, VA: Applied Research Associates, Inc., October 2010.

Stuhmiller, James H. "Blast Injury: Translating Research into Operational Medicine." Chap. 10 in *Military Quantitative Physiology: Problems and Concepts in Military Operational Medicine*, edited by Karl E. Friedl and William R. Santee. Falls Church, VA: Department of the Army, Office of the Surgeon General, Borden Institute, 2012.

Stuhmiller, James H., Yancy U. Phillips III, and Donald R. Richmond. "The Physics and Mechanisms of Primary Blast Injury." Chap. 7 in *Conventional Warfare: Ballistic, Blast, and Burn Injuries*, edited by Ronald F. Bellamy and Russ Zajtchuk. Washington, D.C.: Department of the Army, Office of the Surgeon General, Center of Excellence in Military Medical Research and Education, Walter Reed Army Medical Center, 1991.

Swift, Joshua M., Joan T. Smith, and Juliann G. Kiang. "Hemorrhage Trauma Increases Radiation-Induced Trabecular Bone Loss and Marrow Cell Depletion in Mice." *Radiation Research* 183 (2015): 578-583.

Swift, Joshua M., Sibyl N. Swift, Joan T. Smith, Juliann G. Kiang, and Matthew R. Allen. "Skin Wound Trauma, Following High-Dose Radiation Exposure, Amplifies and Prolongs Skeletal Tissue Loss." *Bone* 81 (2015): 487-494.

Tajima, G., A. J. Delisle, K. Hoang, F. M. O'Leary, K. Ikeda, M. Hanschen, V. M. Stoecklein, et al. "Immune System Phenotyping of Radiation and Radiation Combined Injury in Outbred Mice." *Radiation Research* 179, no. 1 (January 2013): 101-112.

Torres, Marcella, Jing Wang, Paul J. Yannie, Shobha Ghosh, Rebecca A. Segal, and Angela M. Reynolds. "Identifying Important Parameters in the Inflammatory

Process with a Mathematical Model of Immune Cell Influx and Macrophage Polarization." *PLOS Computational Biology* 15, no. 7 (July 31, 2019): 1-27. https://doi.org/10.1371/journal.pcbi.1007172.

United Nations Scientific Committee on the Effects of Atomic Radiation. *Sources and Effects of Ionizing Radiation, Volume II, Annex D: Health Effects Due to Radiation from the Chernobyl Accident*. UNSCEAR 2008. New York City: United Nations, April 2011.

U.S. Department of Health & Human Services, Biomedical Advanced Research and Development Authority Website. "BARDA's Expanding CBRN Medical Countermeasures Portfolio." Accessed September 8, 2022. https://www.medicalcountermeasures.gov/barda/cbrn#portfolio.

Vegesna, Vijaya, H. Rodney Withers, F. Eugene Holly, and William H. McBride. "The Effect of Local and Systemic Irradiation on Impairment of Wound Healing in Mice." *Radiation Research* 135, no. 3 (September 1993): 431-433.

Wake Forest University School of Medicine Website. "Military Applications." Accessed September 8, 2022. https://www.school.wakehealth.edu/research/institutes-and-centers/wake-forest-institute-for-regenerative-medicine/research/military-applications.

Wentz, Jacqueline, Daniela Stricklin, and Kyle Millage. *Updates to Blast Injury Criteria Models for Nuclear Casualty Estimation*. DTRA-TR-15-23. Arlington, VA: Applied Research Associates, Inc., December 2005.

White, Clayton S., Robert K. Jones, Edward G. Damon, E. Royce Fletcher, and Donald R. Richmond. *The Biodynamics of Airblast*. DNA 2738T. Albuquerque, NM: Lovelace Foundation for Medical Education and Research, July 1, 1971.

Williams, Jacqueline P., Stephen L. Brown, George E. Georges, Martin Hauer-Jensen, Richard P. Hill, Amy K. Huser, David G. Kirsch, et al. "Animal Models for Medical Countermeasures to Radiation Exposure." *Radiation Research* 173, no. 4 (2010): 557-578.

Wolfe, Donis R., Hal F. Stolz, Wayne D. Willis, and Donald R. Richmond. *Combined Injury from Nuclear-Weapons Effects*. Joint DNA-USANCA Study. Washington DC: Defense Nuclear Agency, 1979.

Yan, Y. T. Yan. "Effect of Burn Injury, Blast Injury and Combined Burn-Blast Injury on Immune Reactions of Thymocytes and Splenocytes in Rats." *Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi* 9, no. 4 (July 1993): 280-283. Chinese.

Yang, Chao, Xin Xing, Dayuan Xu, Jianguo Xu, and Junhui Li. "Effects of Adipose-Derived Stem Cells-Hyaluronic Acid Composite on Healing of Wound Combined with Radiation Injury." *Zhongguo Xui Fu Chong Jian Wai Ke Za Zhi* 25, no. 12 (December 2011): 1499-1503. Chinese.

Zawaski, Janice A., Charles R. Yates, Duane D. Miller, Caterina C. Kaffes, Omaima M. Sabek, Solmaz F. Afshar, Daniel A. Young, et al. "Radiation Combined Injury Models to Study the Effects of Interventions and Wound Biomechanics." *Radiation Research* 182, no. 6 (December 2014): 640-652.

Zheng, H., T. Cheng, and Y. Lin. “Ultrastructural Changes in Pulmonary Microvascular Damage in Rats Inflicted with Burn, Blast and Combined Burn-Blast Injury.” *Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi* 11, no. 6 (November 1995): 425-429. Chinese.

Zirkle, Robert A., Deena S. Disraelly, Mary Catherine Flythe, Jessica L. Knight, Timothy Ni, and Terri J. Walsh. *Verification and Validation of the Representation of Human Response to Insults from Nuclear Detonations in Nuclear, Biological, and Chemical Casualty and Resource Estimation Support Tool (NBC CREST) Version 4.0*. IDA Paper P-4768. Alexandria, VA: Institute for Defense Analyses, March 2012.

Zomer, Helena D., and Andrea G. Trentin. “Skin Wound Healing in Humans and Mice: Challenges in Translational Research.” *Journal of Dermatological Science* 90, no. 1 (April 2018): 3-12.

Zou, Zhongmin, Huiqin Sun, Yongping Su, Tianmin Cheng, and Chengji Luo. “Progress in Research on Radiation Combined Injury in China.” *Radiation Research* 169, no. 6 (June 2008): 722-729.

Appendix C. Abbreviations & Acronyms

AFRRI	Armed Forces Radiobiology Research Institute
AMedP	Allied Medical Publication
ARA	Applied Research Associates
cal/cm^2	calories per centimeter squared
CBRN	Chemical, Biological, Radiation, and Nuclear
cGy	centigray
CHRNEM	Consolidated Human Response Nuclear Effects Model
DNA	Defense Nuclear Agency
DTRA	Defense Threat Reduction Agency
Gy	Gray
HE	High Explosive
HENRE	Health Effects from Nuclear and Radiological Environments
IDA	Institute for Defense Analyses
IDP	Intermediate Dose Program
JMPT	Joint Medical Planning Tool
kPa	kilopascals
kt	kiloton
MPTk	Medical Planner's Toolkit
NATO	North Atlantic Treaty Organization
NBC CREST	Nuclear Biological Chemical Casualty and Resource Estimation Support Tool
NHP	Non-Human Primate
NIAID	National Institute of Allergy and Infectious Disease
%BSA	Percent Body Surface Area
psi	pounds per square inch
RIPD	Radiation-Induced Performance Decrement
SME	Subject Matter Expert
UG	Upper Gastrointestinal
USANCA	U.S. Army Nuclear and Chemical Agency

This page is intentionally blank.

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188

1. REPORT DATE (DD-MM-YY)	2. REPORT TYPE	3. DATES COVERED (From – To)
xx-10-2022	Final	

4. TITLE AND SUBTITLE	5a. CONTRACT NO.
Combined Nuclear Effects Feasibility Study	HQ0034-14-D-0001
	5b. GRANT NO.
	5c. PROGRAM ELEMENT NO(S).

6. AUTHOR(S)	5d. PROJECT NO.
Robert A. Zirkle Janet C. Marroquin Pineda	5e. TASK NO. FN-6-4947
	5f. WORK UNIT NO.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NO.
Institute for Defense Analyses 730 E.Glebe Rd Alexandria, VA 22305	IDA Paper P-33233 Log: H 22-000377

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR'S / MONITOR'S ACRONYM(S)
Office of The Surgeon General DHHQ 7700 Arlington Blvd. Falls Church, VA 22042-5143	OTSG
	11. SPONSOR'S / MONITOR'S REPORT NO(S).

12. DISTRIBUTION / AVAILABILITY STATEMENT

Distribution Statement A. Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This Institute for Defense Analyses (IDA) paper examines the feasibility of incorporating synergistic combined nuclear effects into the next iteration of Allied Medical Publication-7.5 (AMedP-7.5). After describing the current—non-synergistic—approach taken to combine effects in the AMedP nuclear methodology, IDA researchers describe three broad alternatives for developing a synergistic methodology: output and/or products from the 1990s Combined Methodology Study, applying data from human clinical or animal experimental studies, and employing output and/or products from various mechanistic models (in particular, the HENRE model developed by Applied Research Associates). IDA researchers determined that none of these approaches could be used to develop a synergistic methodology at this time. That said, the development approach employed in the Combined Methodology Study—developing the required sign/symptom progressions through meetings with subject matter experts—might be used to develop a new set of combined progression curves that incorporate synergistic effects. Such an approach, however, would be difficult to conduct and would likely be very time-consuming. Otherwise, the best approach for now would be to continue using the non-synergistic methodology currently employed in the AMedP methodology.

15. SUBJECT TERMS

AMedP-7.5, combined nuclear effects, casualty estimation, Combined Methodology, mechanistic models, HENRE

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NO. OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			LTC Mark T. Williams
U	U	U	U	68	19b. TELEPHONE NUMBER (Include Area Code) 703-681-8188

This page is intentionally blank.