REPORT DOCUMENTATION PAGE

AFRL-SR-AR-TR-04-

0502

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPOI
	29 SEP 04	FINAL REPORT 1 JAN 01 TO 31 MAR 04

4. TITLE AND SUBTITLE
IMMUNOTOXICOLOGY OF JP-8 JET FUEL

5. FUNDING NUMBERS
F49620-01-1-0149

6. AUTHOR(S)
PROF. DAVID T. HARRIS

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
UNIVERSITY OF ARIZONA
DEPT. OF MICROBIOLOGY & IMMUNOLOGY
1501 CAMPBELL AVE
LIFE SCIENCES NORTH, 6TH FLOOR
TUCSON, AZ 85724

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
AFOSR/NL
4015 WILSON BLVD., STE 713
ARLINGTON, VA 22203-1954

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT
APPROVE FOR PUBLIC RELEASE; DISTRIBUTION UNLIMITED

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

We have examined the immunotoxicological effects of JP-8 jet fuel exposure. Inbred C57BL6 mice were exposed to varying concentration (100-250 mg/m3) of aerosolized JP-8 jet fuel varying periods of time, using a variety of experimental models. Animal exposure was performed via nose-only presentation while the animals were held in individual subject loading tubes. The tubes were nose cone fitted to receiving adapters that originated from a common anodized aluminum exposure chamber. Nose only exposure was utilized to minimize ingestion of jet fule during self-grooming, and to simulate human occupational exposures. Animals were rotated on a daily basis through the 12 adapter positions on the exposure chamber. This rotation was done to minimize proximity to the ject fuel source as a variable in exposure concentration or composition. Exposure concentration was determined by a seven-stage cascade impactor, and was measured after each exposure (1,2). At various times after the jet fuel exposures the animals were sacrificed and examined for changes in immune system composition and function. The major immune system organ systems (i.e., spleen, thymus, lymph nodes, blood and bone marrow) were recovered and examined for changes in organ weight, total cell numbers, immune cell components (by differential histochemical staining), and lymphocyte subpopulations by flow cytometric analyses. Assays were also performed to assess any changes in immune function in these organs. In some experiments the animals were administered an aerosolized concentration of the neuropeptide substance P (SP) in an effort to protect from or reverse the effects of JP-8 exposure.

14. SUBJECT TERMS			15. NUMBER OF PAGES
			16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

FINAL TECHNICAL REPORT

"IMMUNOTOXICOLOGY OF JP-8 JET FUEL"

#F49620-01-1-0149 (UA # 325040)

September 2004

David T. Harris, Ph.D.
Dept. of Microbiology & Immunology
1501 Campbell Ave.
Life Sciences North, 6th Floor
University of Arizona
Tucson, AZ 85724
Tel:(520)626-5127
FAX:(520)626-2100
Email:davidh@U.Arizona.EDU

ABSTRACT

Chronic jet fuel exposure could be detrimental to Air Force personnel, by not only adversely affecting their work performance but also by predisposing these individuals to increased incidences of infectious disease, cancer and autoimmune disease. Chronic exposure to jet fuel has been shown to cause human liver dysfunction, emotional dysfunction, abnormal electroencephalograms, shortened attention spans, and decreased sensorimotor speed. Recently, several cancer clusters have been identified in proximity to military bases that use jet fuel, and have led to speculation that human exposures to jet fuel may directly participate in the development of malignancy. Currently, there are no standards for personnel exposure to jet fuels of any kind, let alone JP-8 jet fuel (although the National Academy of Sciences is in progress to publish recommended exposure levels until more is known about jet fuel exposures). Kerosene based petroleum distillates have been associated with hepatic, renal, neurological and pulmonary toxicity in animals models and human occupational exposures. The U.S. Department of Labor, Bureau of Labor Statistics estimates that over 1.3 million workers were exposed to jet fuels in 1992. Thus, jet fuel exposure may not only have serious consequences for USAF personnel, but also may have potential harmful effects for a significant number of civilian workers. Short-term (7 day) JP-8 jet fuel exposure has been shown to cause lung injury as evidenced by increased pulmonary resistance, a decrease in bronchoalveolar lavage concentrations of substance P, increased lung/body wet weight ratios, and increased alveolar permeability. Long-term exposures, although demonstrating evidence of lung recovery, result in injury to secondary organs such as liver, kidneys and spleen.

We have observed that short-term (7 days) exposure of C57BL6 mice to low concentrations (100-1000 mg/m^3) of JP-8 jet fuel results in profound and significant alterations in the immune system. Organ weights (spleen and thymus) and total cell numbers recovered from each of the major immune system organs (spleen, thymus, lymph nodes, bone marrow and peripheral blood) were significantly reduced. Flow cytometric analyses revealed that T cell populations were lost with significant increases in inflammatory and B cell populations in these organs. JP-8 exposure resulted in a

significant depression of immune function (as measured by proliferative assays) of the residual cells which could not be overcome by the addition of exogenous immune response modifiers, and which may be indicative of a generalized inflammatory response. Further, JP-8 exposure resulted in a loss of natural killer (NK) cell function, lymphokine activated killer (LAK) cell activity, and cytotoxic T lymphocyte (CTL) capacity. Additional analyses demonstrated that precursor cells for both cytotoxic and helper T cells were affected by the exposures. Further, the detrimental effects of JP-8 exposure on the immune system were evidenced after only a single day of (1 hour/day) exposure. That is, it did not require 7 days of exposure to observe significant changes in the immune system. These experiments revealed that the effects on the immune system could be observed with as little as 1 hour of JP-8 exposure. The damage to the immune system occurred rapidly and was cumulative in nature. JP-8 exposure rapidly induced high levels of IL-10 and PGE2 in the serum of exposed mice. These immunosuppressive cytokines may be a possible contributory mechanism for the observed loss of immune function, but cannot entirely explain such findings as prevention of PGE2 increases (with COX-2 inhibitors) did not prevent immune dysfunction. Finally, the observed immunotoxicity was not limited to JP-8 jet fuel as similar effects were induced by exposure to JP-8+100 and Jet A1 jet fuel sources.

Mice exposed to 7 days of JP-8 jet fuel exhibited the ability to recover from the observed immune alterations. Although immune organ weights recovered to normal levels within a week of cessation of jet fuel exposure, up to one month was required to return immune organ cell numbers to baseline levels in the spleen and thymus. Cell numbers in the bone marrow, lymph nodes and peripheral blood recovered more quickly. Significantly, recovery of immune function was more profoundly affected, taking more than one month to recover to normal levels. Thus, short-term, low concentration exposures to JP-8 jet fuel resulted in long lasting immune alterations. Similar results have been reported after dermal jet fuel exposures. Military and civilian personnel who work with jet fuel daily however, will not be able to abstain from exposures for such long periods of time as appears to be required for recovery.

Furthermore, it has now been shown that dermal exposures to JP-8 jet fuel are also equally immunotoxic (in terms of immune function) as aerosol exposures, with similar long-lasting effects. Whether or not the mechanisms of action on the immune system are identical is as yet unknown. However, these observations provide additional impetus for studies on the effects of jet fuel exposure on the immune system, as this additional route of exposure significantly increases the numbers of exposed individuals.

Interestingly, treatment of mice with the neuropeptide substance P immediately after JP-8 exposure (1 uM, 15 minutes) was able to reverse/prevent many of the observed effects. That is, substance P administration was able to protect/reverse the effects of JP-8 jet fuel exposure on immune organ weights, immune organ numbers, and immune function. The role of substance P in this process was confirmed by the finding that administration of substance P inhibitors made the effects of JP-8 exposure worse. Additional substance P experimentation revealed that it was possible to wait for 1 or 6 hours post-JP-8 exposure to administer substance P and reverse the effects seen in the immune system. Furthermore, administration of substance P 15 minutes prior to JP-8 exposure could prevent the JP-8-induced immunotoxicity. Administration of substance P either 1 or 6 hours prior to JP-8 exposure was not effective. These results seem to indicate that it may be possible to administer substance P (somewhat) prophylactically. Similar protective effects have been reported in the pulmonary system.

During the past year we have found and confirmed that JP8 exposure potentiated the growth and metastatic spread of intravenously injected B16 tumors in an animal model. Mice exposed to JP-8 prior to tumor induction had an 8.63-fold increase in tumors, while those animals exposed to JP-8 at the time of tumor induction had a 5.48-fold increase in tumor numbers. We have confirmed these findings and have now extended the observations to an experimental subcutaneous tumor model. JP-8 exposure at the time of tumor induction in this model did not affect the growth of the tumor. However, JP-8 exposed, tumor-bearing animals died at an accelerated rate as compared to air-exposed, tumor-bearing mice.

Additionally, we discovered that in utero JP-8 exposure had significant immunotoxicological effects in an animal model. It was observed that fewer pups were born to JP-8-exposed mothers as compared to sham (air)-exposed mice. In particular, significantly fewer male offspring were born. It was observed that pups born to JP-8-exposed mothers had decreased immune organ weights, decreased immune organ cell numbers, and suppressed immune function (even 8 weeks post-birth and post-in utero exposure). Immune dysfunction has now been analyzed by sex and by mother's immune status after JP-8 exposure. It was found that male offspring were more adversely affected than female offspring. Further, pups born to mothers that were most affected by JP-8 exposure demonstrated the greatest deleterious effects after birth.

In an infectious disease model, preliminary analyses of mice exposed to JP-8 and infected with influenza virus have been performed. Mice exposed to JP-8 for 7 days, subsequently infected with a sub-lethal dose of virus, and then analyzed 1 week later demonstrated increased morbidity, suppressed cellular immune responses to infection, decreased numbers of T cells after infection, and decreased immune cell viability after infection. Organ weights were not affected.

Finally, the effects of occupational JP-8 exposure on military personnel have been investigated. Peripheral blood was obtained in a blinded study (performed in collaboration with Dr. T. Risby, Johns Hopkins University) from exposed individuals, immune cells were isolated, and immune analyses performed. Extremely low level JP-8 exposure (less than 50 mg/m^3) resulted in decreased total leukocyte numbers, increased neutrophils immediately after exposure, increased eosinophil numbers immediately after exposure, and increased plasma PGE2 levels. Preliminary analyses indicated that there might be more susceptible subpopulations within the human population as a whole.

Thus, due to the observed immune effects, exposure of individuals to JP-8 (as well as other) jet fuel may result in increased risk of infectious disease and cancer. However, it may be possible to reverse or prevent many of these effects through the administration of substance P. It is absolutely critical to ascertain and understand the potential

consequences of immune function alterations as it pertains to the short-term and long-term health and well being of exposed personnel, as well as their treatment before and after exposure. This information can only be obtained through elucidation of the mechanisms of action of both jet fuel exposure and the immunomodulator, substance P.

In the current proposal we will perform studies to elucidate the potential mechanisms of JP-8 exposure on the immune system, as well as the mechanisms by which substance P treatment protects the immune system. Experiments will be performed to determine if jet fuel exposure mediates its effects directly or indirectly on the immune system. Further, experiments will be performed to ascertain if substance P (SP) mediates its protective effects locally in the lung, or peripherally after JP8 exposure.

It is absolutely critical to ascertain and understand the mechanisms of immune function alterations caused by jet fuel exposure as it pertains to the short-term and long-term health and well being of exposed personnel. Knowing the mechanisms of action of both JP-8 and substance P it may be possible to prevent or at least ameliorate the detrimental effects of such exposures on the immune system. The results obtained in these studies should have significant implications for the health, well being and medical treatment of JP-8 exposed individuals.

OBJECTIVES/STATEMENT OF WORK:

STATUS OF EFFORT:

Our investigation of the immunotoxicological effects of exposure to JP-8 jet fuel will focus on the mechanisms of JP-8's actions as well as the mechanisms of substance P's protective effects, making use of our previously characterized murine animal models. Short-term, low-concentration JP-8 exposures resulted in profound and significant alterations in numerous immune parameters (immune organ weights, immune cell numbers, mitogenic responses, CTL, NK and LAK effector cell mechanisms and helper and cytotoxic T cell precursors), as well as several "real-world" model systems (including infectious disease [i.e., influenza], tumor development and metastasis, and in utero exposures). The proposed work will investigate the mechanisms responsible for the effects of jet fuel exposure in these systems. Further, we will conduct studies to ascertain the mechanisms behind the protective effects of substance P therapy. The results from the proposed experiments should allow us to understand the mechanism(s) of the immunotoxicological effects of exposure to JP-8 jet fuel, to estimate with a high degree of probability the potential harmful consequences of JP-8 exposure to USAF personnel, and to devise easily amenable therapies to counteract those effects. We firmly believe that in order to accomplish the stated goals and specific aims that a period of 3 years of investigation will be required.

During the past three years of experimentation we have been able to define the sensitive and reliable immune assays for measuring JP-8 exposure, and to determine the assays that correlate best with toxicological changes seen in the pulmonary and nervous systems. These assays have refined our approach to begin to ascertain the mechanisms of JP-8's actions.

RESULTS

We have examined the immunotoxicological effects of JP-8 jet fuel exposure. Inbred C57BL6 mice were exposed to varying concentrations (100-2500 mg/m^3) of aerosolized JP-8 jet fuel for varying periods of time, using a variety of experimental models. Animal exposure was performed via nose-only presentation while the animals were held in individual subject loading tubes. The tubes were nose cone fitted to receiving adapters that originated from a common anodized aluminum exposure chamber. Nose only exposure was utilized to minimize ingestion of jet fuel during self-grooming, and to simulate human occupational exposures. Animals were rotated on a daily basis through the 12 adapter positions on the exposure chamber. This rotation was done to minimize proximity to the jet fuel source as a variable in exposure concentration or composition. Exposure concentration was determined by a seven-stage cascade impactor, and was measured after each exposure (1,2). At various times after the jet fuel exposures the animals were sacrificed and examined for changes in immune system composition and function. The major immune system organ systems (i.e., spleen, thymus, lymph nodes, blood and bone marrow) were recovered and examined for changes in organ weight, total cell numbers, immune cell components (by differential histochemical staining), and lymphocyte subpopulations by flow cytometric analyses. Assays were also performed to assess any changes in immune function in these organs. In some experiments the animals were administered an aerosolized concentration of the neuropeptide substance P (SP) in an effort to protect from or reverse the effects of JP-8 exposure. These studies have resulted in 8 published manuscripts, 5 other manuscripts submitted for publication or in preparation, and 9 abstracts.

ACCOMPLISHMENTS/NEW FINDINGS:

The following significant observations were obtained during work on these grant projects and are summarized as follows.

Manuscript #1 (Harris et al, Immunotoxicological Effects of JP-8 Jet Fuel Exposure, Toxicology & Industrial Health 13(1):43, 1997).

1. JP-8 exposure results in significant depression in immune organ wet weights (spleen and thymus).

2. JP-8 exposure results in significant losses of immune organ cell numbers (spleen, thymus, lymph nodes, peripheral blood and bone marrow).

3. JP-8 exposure causes a significant loss of immune function, as assessed by mitogenic responses, which cannot be overcome by exogenous growth factors.

4. JP-8 exposure has significant effects on the immune system at concentration exposures as low as 100 mg/m^3 (thymus only).

5. The effects of JP-8 on the immune system are concentration-dependent. The majority of the effects of JP-8 exposure on the immune system are observed to begin at concentration exposures between 250-500 mg/m^3. Concentration exposures of 2500 mg/m^3 are generally thought to be directly toxic to the immune system.

6. No significant differences were observed in immune system effects based on gender of the exposed mice (i.e., male and female animals demonstrated comparable effects).

7. No significant differences were observed in immune system effects using either normal C57Bl/6 mice or enzyme-deficient congenic mice (deficient in two enzymes thought to be involved in hydrocarbon metabolism), indicating that the effects on the immune system were so severe that loss of these putatively important protective enzyme pathways was not relevant.

Manuscript #2 (Harris et al, Short-Term Exposure to JP-8 Jet Fuel Results in Longterm Immunotoxicity, Toxicology & Industrial Health 13(5), 559-570, 1997).

8. Short-term exposures to JP-8 jet fuel results in depressions in wet weights of spleen and thymus, which recover within 1 week, although some overcompensation occurs in the thymus.

9. Short-term exposure to JP-8 jet fuel results in significant losses of immune cells from the spleen, which takes up to 1 month to recover to normal. Cell losses from the thymus however, recover more quickly.

10. Short-term exposure to JP-8 jet fuel does not appear to have any significant long-term effects on immune cell numbers isolated from lymph nodes, peripheral blood or bone marrow.

11. Short-term exposure to JP-8 jet fuel has significant and long-lasting effects on immune function. The higher the exposure concentration, the longer it takes for the immune system to recover (4 weeks or longer).

12. Immune system effects due to short-term (7 day) exposures are reversible (although not completely) after 3-4 weeks, indicating that even short-term, low concentration exposures have long-lasting effects on the immune system.

Manuscript #3 (Harris et al, Protection from JP-8 Jet Fuel Induced Immunotoxicity by Administration of Aerosolized Substance P, Toxicology & Industrial Health 13(5), 571-588, 1997).

13. The effects of JP-8 exposure on the immune system can be reversed/prevented by administration of substance P (1 uM, 15 minutes) immediately after the jet fuel exposure.

14. Concentrations of substance P as low as 1 nM have significant protective effects against JP-8 induced immune system effects.

15. The effects of JP-8 exposure on the immune system are made worse by administration of substance P inhibitors.

Manuscript #4 (Harris et al, Effects of Short-Term JP-8 Jet Fuel Exposure on Cell-Mediated Immunity, Toxicology & Industrial Health 16:78-84, 2000)

16. JP-8 exposure results in the complete loss of natural killer (NK) cell function, which is long-lasting and results in the inability to give rise to lymphokine-activated killer (LAK) cell activity.

17. JP-8 exposure results in the complete loss of cytotoxic T lymphocyte (CTL) function.

18. JP-8 exposure results in the significant suppression of the ability of precursor T cells to give rise to lymphokine producing T cells (i.e., helper T cells).

19. JP-8 exposure results in the significant suppression of the ability of precursor T cells to give rise to cytotoxic T cells (i.e., CTL).

Manuscript #5 (Harris et al, Jet Fuel-Induced Immunotoxicity; Toxicology & Industrial Health 16:261-265, 2000)

20. Exposure of mice to JP-8+100 jet fuel is just as detrimental as exposure to standard JP-8 jet fuel in terms of its effects on the immune system.

21. Exposure of mice to Jet A-1 jet fuel is just as detrimental as exposure to standard JP-8 jet fuel in terms of its effects on the immune system.

Manuscript #6 (Harris et al, Substance P as Prophylaxis for JP-8 Jet Fuel-Induced Immunotoxicity; Toxicology & Industrial Health 16:253-259, 2000)

22. Exposure of mice to aerosolized substance P 15 minutes prior to JP-8 jet fuel exposure protects the immune system from the detrimental effects of JP-8 jet fuel exposure, as does administration 15 minutes post-exposure. However, a 1 or 6 hour pre-exposure treatment is not effective.

23. Exposure of mice to aerosolized substance P 1 or 6 hours post-exposure to JP-8 is almost as effective as exposure to substance P 15 minutes post-JP-8 exposure.

Manuscript #7, (Harris et al, JP-8 Jet Fuel Results in Immediate Immunotoxicity, Which is Cumulative Over Time; Toxicology & Industrial Health 18:77-83, 2002)

24. Exposure of mice to JP-8 for 1 hour/day initiates a cascade of cumulative effects on the immune system, with toxicological results evident as soon as 1 hour post-exposure.

25. There is a cumulative loss of spleen (maximal by day 5) and thymus (maximal by day 4) organ weights due to JP-8 exposure.

26. There is a cumulative loss of immune function due to JP-8 exposure, which is maximal by day 4 of exposure.

Manuscript #8, submitted for publication (Harris et al, JP-8 Exposure Rapidly Induces High Levels of IL-10 Secretion and Is Correlated With Loss of Immune Function; Toxicology & Industrial Health)

27. JP-8 exposure rapidly induces a persistently high level of serum IL-10 and PGE2 at exposure concentrations from 500-2500 mg/m^3.

28. IL 10 levels peak at 2h post-JP-8 exposure and then stabilize at significantly elevated serum levels, while PGE2 levels peak after 2-3 days of exposure and then stabilize.

29. Elevated IL 10 and PGE2 levels may at least partially explain the effects of JP-8 exposure on immune function.

30. Elevated IL 10 and PGE2 levels however, cannot explain all of the effects due to JP-8 exposure (e.g., decreased organ weights and decreased viable immune cells).

31. The elevation in serum PGE2 levels induced by JP-8 exposure can be prevented by treatment of mice with a Cox 2 enzyme inhibitor (e.g., Celebrex), but it does not prevent the jet fuel-induced immunotoxicity.

Manuscript #9, submitted for publication (Harris et al, JP-8 Jet Fuel Exposure Potentiates Tumor Development in an Experimental Murine Lung Metastases Model, Science)

32. JP-8 exposure at the time of tumor induction increases lung tumor foci an average of 548%.

33. JP-8 exposure prior to tumor induction increases lung tumor foci an average of 863%.

34. JP-8 exposure does not seem to affect tumor growth/size in a subcutaneous tumor model. JP-8 exposure however, does seem to decrease animal survival and/or increase tumor metastases in such a model.

Manuscript #10, submitted for publication (Harris et al, Biological and Immunological Effects of In Utero Exposure to JP-8 Jet Fuel, Science)

35. In utero JP-8 exposure affects the number and sex of live offspring born to exposed mothers.

36. The magnitude of the immunotoxicological effects seen in the offspring was correlated to the levels of the immunotoxicological effects observed in the JP-8 exposed mothers.

37. In utero JP-8 exposure affects the immune systems of male offspring more than female offspring.

Manuscript #11, submitted for publication (Harris et al, JP-8 Exposure Suppresses the Immune Response to Viral Infections, Toxicology and Industrial Health)

38. JP-8 exposure worsened influenza infections in mice as evidenced by:
    A. Increased morbidity
    B. Suppressed immune (cellular) responses to infection
    C. Decreased numbers of T cells after infection
    D. Decreased immune cell viability after infection

Manuscript #12, in preparation (Harris et al, Effects of JP-8 Exposure on Immune Parameter of Human Subjects)

39. Preliminary analyses of human occupational exposures to (short-term, low-dose) JP-8 seems to result in:

    A. decreased total leukocyte numbers

    B. increased neutrophils immediately after high exposures

    C. increased eosinophils immediately after high exposures

    D. increased plasma PGE2 levels

40. There is an indication that there may be more susceptible subpopulations within the group as a whole.

Manuscript #13, (Harris, DT and ML Witten. Aerosolized Substance P Protects Against Cigarette Smoke-Induced Lung Damage and Tumor Development, Cell and Molecular Biology 49 (2): 151-157, 2003).

41. Aerosolized substance P protects the lung not only from jet fuel-induced damage but has additional beneficial effects against cigarette smoke and tumor development.

42. Aerosolized substance P protects the lung from both physiological (i.e., damage to epithelial basement membranes) and genotoxic (i.e., induction of micronuclei) damage due to cigarette smoke.

43. Substance P (whether administered in aerosol form or genetically engineered to be secreted by tumor cells) is effective in reducing tumor development and lung metastasis in an experimental murine tumor model, via activation of innate immune mechanisms.

OVERALL CONCLUSIONS

From the experiments that have been performed to date it appears that the immune system is a sensitive indicator of toxicological damage incurred by the individual due to JP-8 jet fuel exposure, as well as exposure to other sources of jet fuel. The results summarized above have indicated that exposure to JP-8 (and other sources of) jet fuel, even at low concentrations and even for short periods of time, has significant and profound effects on the immune system. JP-8 should be considered a significant immunotoxicant. It would be expected that such immune system changes in immunocompetence that have been observed after JP-8 exposure would have significant effects on the exposed individual's health and may adversely affect his/her susceptibility to infectious disease, as well as possibly the development and/or progression of cancer.

PERSONNEL SUPPORTED:

David T. Harris, Ph.D.	Principle Investigator
Thomas Tsang, Ph.D.	Senior Research Scientist
Humphrey He, Ph.D.	Post-Doctoral Fellow
Debbie Sakiestewa, BS	Senior Research Technician

PUBLICATIONS:

The following additional publications either have been published or have been submitted for publication. Abstracts from scientific conferences that have been published are also available upon request.

Harris, DT, D Sakiestewa and ML Witten. JP-8 jet fuel exposure results in immediate immunotoxicity, which is cumulative over time. Toxicology & Industrial Health 18:77-83, 2003.

Harris, DT and ML Witten. Aerosolized substance P protects against cigarette-induced lung damage and tumor development. Cellular and Molecular Biology 49 (2): 151-7, 2003

Harris et al, JP-8 Exposure Rapidly Induces High Levels of IL-10 and PGE2 Secretion and Is Correlated With Loss of Immune Function; Toxicology & Industrial Health, Submitted for Publication

Harris et al, JP-8 Jet Fuel Exposure Potentiates Tumor Development in an Experimental Murine Lung Metastases Model, Science, submitted for publication.

Harris et al, Biological and Immunological Effects of In Utero Exposure to JP-8 Jet Fuel, Science, Submitted for Publication.

Harris et al, Effects of JP-8 Exposure on Immune Parameter of Human Subjects, manuscript in preparation.

Harris et al, JP-8 Exposure Suppresses the Immune Response to Viral Infections, manuscript in preparation.

INTERACTIONS/TRANSITIONS:

1. Meetings, Conferences, Seminars

Invited Speaker, AFOSR JP-8 Jet Fuel Toxicology Workshop, Tucson, AZ, 11-12 January 2000
Invited Speaker, JP8 Jet Fuel Conference, Tucson, AZ, 15-17 May 2002
Invited Speaker, 2nd International Jet Fuel Conference, San Antonio, TX, 7-10 August 2001
Invited Speaker, AFOSR JP8 Conference, Tucson, AZ 14-16 May 2003

2. Consultants

QuReGen (founder and CEO)
Cord Blood Registry, Inc.
NanoTek, Inc.
Medical Advisory Board, Canadian J. Clin. Med-Medical Scope Monthly
Chief Immunologist and Director, Odyssey Corporation (now ImmuneRegen BioSciences, Inc)
Teltech, Inc.
Ageria Corporation

3. Transitions

Please also see Dr. Witten's report for details of the transition of our SP work to the ImmuneRegen BioSciences, Inc. biotechnology company. We are currently in pre-IND talks with the FDA to test SP for the treatment of acute respiratory distress syndrome (ARDS) and as a counter-measure to low level radiation poisoning (i.e., bioterrorism).

PATENTS/INVENTIONS:

The following patents originated from work performed on our Air Force Office of Scientific Research sponsored grant entitled, "Immunotoxicology of Exposure to JP-8 Jet Fuel". The patents, as well as our grant work, have been performed in conjunction with Dr. Mark Witten (Dept. of Pediatrics, University of Arizona). Because of the laws involving public disclosure during the patent process, we have been slightly delayed in some of our publications related to substance P. However, as we are now in discussions with several pharmaceutical companies regarding this discovery, this issue should be shortly resolved. This discovery may have significant clinical benefits in terms of boosting the immune systems of individuals that are immunocompromised (e.g., AIDS patients, cancer patients, aged individuals, etc.), as well as been of benefit to those exposed to environmental toxicants (e.g., hydrocarbons, cigarette smoke, etc.). Further, we are now in discussions with another pharmaceutical company with regard to licensing for effects on cognitive functions.

Substance P Treatment for Immunostimulation-Cancer Therapy, 1999, #5,945,508
Substance P Treatment for Immunostimulation-Immunomodulation, 1999, #5,998,376

Please also see Dr. Witten's report for details of the transition of our SP work to the ImmuneRegen BioSciences, Inc. biotechnology company. We are currently in pre-IND talks with the FDA to test SP for the treatment of acute respiratory distress syndrome (ARDS) and as a counter-measure to low level radiation poisoning (i.e., bioterrorism).

HONORS/AWARDS:

2002	Elected to "Who's Who in America"
2002-2003	Elected to "Who's Who in Science and Engineering"
2002	Elected to "Who's Who in the West"
2002	Elected to "Who's Who in the World
2003	Elected to "Who's Who in the World
2002-2003	Elected to "Who's Who in Medicine and Healthcare

2003	Elected to "Who's Who in America"
2003	Elected to "Who's Who in the West
2004	Elected to "Who's Who in the West

BIOGRAPHY : DAVID T. HARRIS, PH.D.

Dr. Harris is a graduate of Wake Forest University in Winston-Salem, North Carolina where he obtained Bachelor of Science degrees (cum laude) in Biology, Mathematics and Psychology in 1978. He earned a Masters of Medical Sciences (summa cum laude) from Bowman Gray Medical School in 1980 and his Doctorate in Microbiology and Immunology (magna cum laude) from Bowman Gray Medical School in 1982. From 1982-1985 Dr. Harris was a Postdoctorate Fellow at the Ludwig Institute for Cancer Research in Lausanne, Switzerland. In 1985 he joined the faculty at the University of North Carolina-Chapel Hill as a Research Assistant Professor in the Department of Medicine. In 1989 Dr. Harris joined the faculty at the University of Arizona in Tucson as an Associate Professor in the Department of Microbiology & Immunology. In 1996 Dr. Harris was promoted to Professor of Immunology. He currently serves as Director of the Cord Blood Stem Cell Bank, is a member of the Arizona Cancer Center, a member of the Children's Research Center, a member of the Arizona Arthritis Center, and Head of the Gene Therapy Group. Dr. Harris's research interests include immunotoxicology, cancer research, transplantation and gene therapy. He has published more than 200 articles and has served as a consultant to the governments of China, Hong Kong, Singapore and South Korea.