Congressional Testimony

Subcommittee on Investigations and Oversight

Committee of Science and Technology

United States House of Representatives

Congressional Hearing: "Caught by Surprise: Causes and Consequences of the Helium-3 Supply Crisis"

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Statement of

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Chairman Miller, Ranking Member Broun, Members of the Subcommittee, I'm honored to be asked to testify today. My name is Dr. Jason Woods; I am an Assistant Professor of Radiology, Physics, and Molecular Biophysics and Assistant Dean of Arts & Sciences at Washington University and an the Program Director for the Hyperpolarized Media Study group of the International Society for Magnetic Resonance in Medicine. I have been involved with medical imaging—specifically hyperpolarized ^{3}He MRI—since 1997. My education and background are in nuclear-spin physics, ^{3}He MRI, and the use of MR imaging for pulmonary physiology and pathophysiology. My research has focused on the use of ^{3}He as a diagnostic imaging tool to understand regional lung ventilation, to precisely quantify lung microstructure and acinar connectivity, and to use imaging to guide new minimally-invasive interventions. In my testimony I attempt to represent the field of ^{3}He MRI and the impact of the shortage on this field. I focus on the revolutionary way that ^{3}He MRI has illuminated pulmonary ventilation and microstructure, how its physical properties make it unique and irreplaceable in many instances, its potential for guiding interventions and drug development, and how a developing recycling technology can allow significant, sustained research into the future with approximately 2000 liters per year. In so doing I specifically address the questions outlined in your letter to me dated April 9, 2010.

SUMMARY

If we ask seasoned pulmonologists today how much the practice of pulmonary medicine has changed in the last 25 years, responses will largely be that very little has changed—a few new drugs are available, but there is largely the same technology for measuring lung function and for treatment. ^{3}He MRI, however, is beginning to emerge as a new "gold standard" and revolutionary biomarker for measuring pulmonary function and structure. Its high signal creates detailed images of lung ventilation and dynamics, and its physical properties allow precise measurement of alveolar size, microstructure, and regional lung function. This makes ^{3}He MRI particularly sensitive to changes in both global and regional lung function and structure. We are at the cusp of leading pulmonary medicine to a renaissance of new drug development and image-guidance of surgical interventions for various lung diseases, such as asthma, fibrosis, and COPD, which currently affect 11% of the US population. This imaging technology, as I speak, is currently serving as a catalyst for pulmonology to see significant advances in the next 10 years. A lack of supply of ^{3}He gas will stifle these advances.

This ^{3}He shortage affects *my* research acutely; it affects my employees and collaborators, and the research and livelihood of MRI groups in at least 11 US universities and at least that many universities abroad. For me personally, a lack of gas will likely mean that my research is shut down, and I would join the ranks of the unemployed. To be clear, however, I think the larger impact of this technology is not on my research group but in drug development, in much easier determination of the effectiveness of new pharmacologic agents, and in guiding new minimally-invasive interventions (my most recent work). The lack of big leaps forward in drugs to treat lung diseases—asthma, COPD, pulmonary fibrosis—has largely been due to the combination of the exceptional cost to bring drugs to market and the lack of a precise biomarker to determine changes in the lung. Pulmonary function tests, the decades-old standard in pulmonary medicine, have notoriously high measurement errors. Obstructive lung diseases (asthma and COPD), taken together, afflict approximately 35 million Americans; COPD alone is the 4th leading cause of death and is the only major cause of death that is steadily increasing [1, 2]. The financial and human impacts of the shortage are significant.

One recent example of drug efficacy testing illustrates the lack of a precise biomarker and its impact: in 2007 GlaxoSmithKline released results of an Advair study, entitled "Toward a revolution in COPD health (TORCH)." The total cost was estimated at $500 million dollars for this study in over 6,000 moderate and severe COPD patients. The study endpoint was death from all causes, which ranged from a high of 16% to a low of 12.6% for those on Advair. The key question was "Does Advair reduce mortality by as much as 20%?" Unfortunately for GSK, the question remained unanswered, because the statistical p-value of the difference was 0.052. This means the difference in mortality had a 5.2% chance of occurring randomly, whereas the generally accepted limit is 5%. This $500M thus was largely wasted; the company couldn't answer the question about benefit, and patients and society received no benefit or increased understanding from the study. If the ^{3}He diffusion MRI techniques that our group has developed, for example, were used as a biomarker and endpoint (not possible when the study began), 6,000 patients could have turned into fewer than 500 patients, saving around 90% of the cost of the study, or $450M. And the question about efficacy would likely have been answered. This is only one example of the type of significant impact that I think ^{3}He MRI is going to have on pulmonary medicine.

There has been some discussion in the scientific literature about using hyperpolarized ^{129}Xe instead of ^{3}He gas for specific future studies, and for some studies this *may* be a viable alternative within the next 5-10 years

[3], though the intrinsic physical properties of ^{129}Xe reduce the signal by a factor or 3-5 compared to ^{3}He. Some damage to the field could be tempered by outside assistance in developing this infrastructure and technology. However, many studies, like my NIH-funded research, rely upon ^{3}He's large diffusion coefficient for large-distance measurements, and for this xenon will *not* be an alternative [4]. On the bright side, the ^{3}He that we use is nearly 100% recyclable, but we do not yet have the recycling technology in place to begin to do this. I believe firmly that the development of efficient and commercially viable recycling schemes will allow this important work to continue, with a total allotment of around 2,000 Liters STP per year.

Lastly, I note that in 2009 an allocation of ^{3}He was made specifically for the NIH-funded medical imaging community. This was offered through Spectra Gases (now Linde Gas) at $600/L STP – an approximately 500% increase over previous years. Because the price of ^{3}He increased so quickly and by so much, research groups (who have strict budgets from federal or private grants) were not able to plan for the cost increase and are now scrambling for supplementary funding sources. This is the reason why all of the ^{3}He recently set aside for various medical imaging groups has not been instantly purchased.

BACKGROUND

Conventional MRI relies upon a large magnetic field to generate a net alignment of nuclear spins (generally within the hydrogen atoms of water molecules), which can be manipulated to create images with high contrast. The technology allows images to answer specific questions about structure and function of the brain, joints, or other parts of the body [5, 6]. MRI of gas is not generally used, since the density of a gas is about 1000 times less than tissues, and there is not enough signal to generate an image. The unique properties of the ^{3}He atom allow us to align a large fraction of its nuclear spins via a laser polarization technique with a magnetic field; this is often called "hyperpolarization" [7, 8]. Hyperpolarized ^{3}He gas has signals enhanced by a factor of 100,000 or more—allowing detailed images of the gas itself to be generated in an MRI scanner. Since helium gas (either ^{4}He or ^{3}He) has a solubility of essentially zero and is arguably the most inert substance in the universe, inhaled hyperpolarized ^{3}He allows the generation of exceptional quality, gas-MR images of ventilated lung airspaces with no ionizing radiation or radioactivity [9]. Further, traditional technologies for measuring pulmonary function (*e.g.*, pulmonary function tests or nuclear ventilation scans) have either high errors on reproducibility or low content of regional information. While x-ray CT has some potential for quantifying lung

structure (not function), its large amount of ionizing radiation raises cancer risks and prevents it from being used in longitudinal studies for drug development or in vulnerable populations, such as children [10, 11]. ^{3}He is inert and has proven to be very safe in studies to date (helium-oxygen mixtures[12] are used routinely in pulmonary and critical care); it is, however, currently regulated as an investigational drug by the US FDA.

THE REVOLUTION OF ^{3}HE MRI ON PULMONARY IMAGING

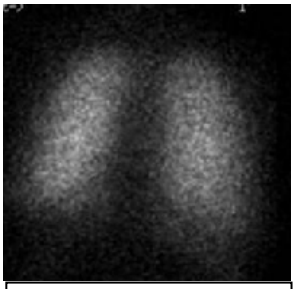


Figure 1: Nuclear ventilation scan

Ventilation

Previous technologies for imaging pulmonary ventilation generally involved the inhalation of radioactive gas over a period of one to several minutes, and then detecting what parts of the chest emitted the most radioactivity over several minutes. This technology (nuclear ventilation scans) had low spatial and temporal resolution (Figure 1). ^{3}He ventilation MRI represented a clear step forward in depicting not only precise, 3-D regional ventilation, but also in beginning to understand the regional dynamics of human ventilation in health and disease.

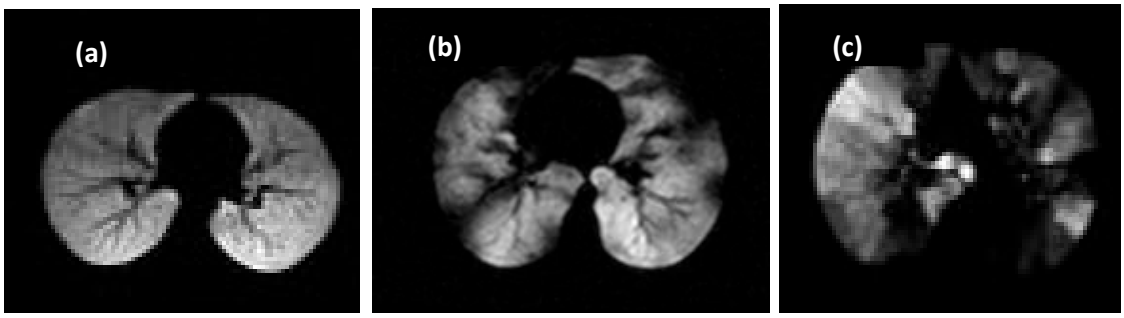


Figure 2: High-resolution transverse ventilation images of (a) a healthy volunteer and patients with (b) asthma and (c) COPD. This type of ventilation imaging represented a huge leap forward in our ability to visualize and quantify regional ventilation distribution and dynamics.

At present, ^{3}He ventilation imaging is being used in a wide variety of studies and holds high promise in increasing our understanding of the regional effects of asthma and its treatment [13-16], in addition to COPD, and various types of lung fibrosis [17, 18]. For example, it was recently found (Figure 2) that many ventilation defects persisted over time, opening the door to new regional treatments for asthma—an idea not previously

pursued [19]. Because asthma is the most prevalent pulmonary disease in the US, improved medical and interventional therapies, facilitated by ^{3}He MRI, can significantly improve care and lower health care costs.

Diffusion and In-vivo Morphometry

Three unique physical properties of ^{3}He make it particularly well suited for measuring lung airspace size, geometry, and connectivity, by quantifying its restriction to thermal diffusion in the lung. These properties are 1) its small size (and thus large thermal diffusion coefficient), 2) its lack of solubility in tissue, and 3) its long relaxation time, T_1. Since ^{3}He is insoluble and has a large diffusion coefficient, collisions with airway and alveolar walls restrict the movement of the gas. This restriction can be measured and quantified using diffusion MRI. In fact, our group in particular has had a focus on ^{3}He diffusion MRI; we have shown that the technique is extraordinarily sensitive to airspace enlargement and has better discrimination than quantitative histology—the gold standard for airspace quantification in lung parenchyma (Figure 3). We have recently shown that the technique can be used to measure the size and geometry of alveolar ducts—allowing regional morphometry of the human lung, in vivo (Figure 4). These types of measurements are not available by any other noninvasive technique and represent a leap forward in our understanding of lung microstructure and our ability to quantify early disease.

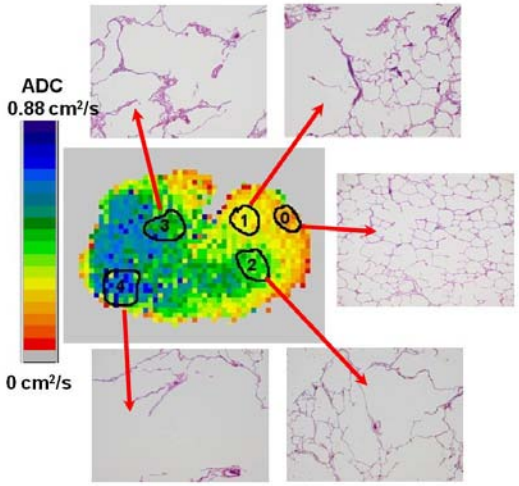


Figure 3: ^{3}He diffusion image (color) of a human lung with heterogeneous COPD, demonstrating the ability of the ^{3}He ADC to predict morphometry.

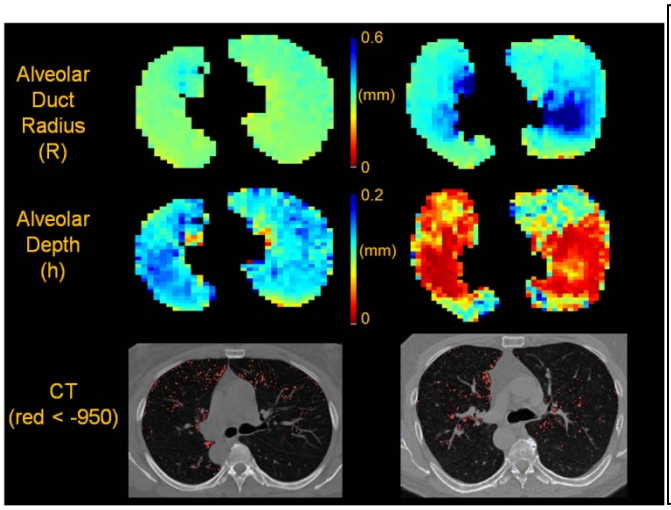
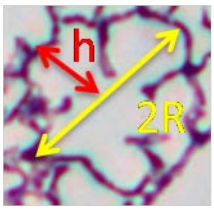


Figure 4: Maps of lung microstructure (color) obtained from gas diffusion imaging, in two volunteers with normal lung function and normal CT, yet the patient on the right is a current smoker and has a greatly reduced alveolar depth. *R* and *h* are depicted below within an individual alveolar duct (perpendicular to the page).



Airspace enlargement (emphysema) is a significant component of chronic obstructive pulmonary disease (COPD)—the only leading cause of mortality with dramatic *increases* in the US and the world [2]. Quantifying this airspace enlargement in a reliable and precise way, as ^{3}He MRI easily can, has enormous potential therapeutic benefit for patients with COPD. No other measurement modality has such potential to detect early disease, disease progression, or to quantify microstructural parameters in the ^{3}He MRI can. Figure 4 demonstrates this in two volunteers with normal lung function by pulmonary function test and with normal CT scans; ^{3}He MRI, however, can distinguish early lung disease in the smoker at right. This extraordinary sensitivity to early disease makes it a prime biomarker for use in drug development and efficacy testing.

One particularly unique quality of ^{3}He comes from the combination of its large gas diffusion coefficient and insolubility in tissue. This allows us to the diffusion of the gas over very long distances (2-5 cm) and has been called “long-range diffusion”. Because these distances are larger than any acinar dimension, the technique is sensitive to the extent of “collateral” or short-circuits pathways other than the airway tree in the lung. These collateral pathways are essential to quantify for two minimally-invasive interventions that are being developed for end-stage COPD: transbronchial stents (Broncus Technologies, Inc.; Mountain View, CA) and one-way exit valves in segmental bronchi (Spiration, Inc.; Redmond, WA). My most recent NIH-funded research involves the use of long-range ^{3}He diffusion to guide and predict the efficacy of these minimally-invasive interventions under development. Early results are quite promising, and demonstrate that the imaging will do quite well at guiding the therapy, but the shortage of ^{3}He has had a negative impact on the study.

Regional Pulmonary Oxygen Monitoring

The long relaxation time T_1 of ^{3}He and its sensitive dependence on oxygen concentration allow us to measure the regional partial pressure of oxygen in the lung. Maps of this partial pressure (pAO_2) in the lung can be used to understand regional pulmonary blood flow and diffusion of oxygen into capillaries--the essential purpose of the organ. Not only can pAO_2 be used to measure deficiencies in the partial pressure of oxygen, but it can be employed to understand the regional relationship between structure and function in the lung, at its most fundamental level (oxygen and CO_2 transfer). Again, this is a technique only possible via ^{3}He MRI.

Partial List of Currently Funded ^{3}He Imaging Projects in North America

The following list of current ^{3}He MRI research projects is far from complete but represents the broad range of lung diseases studied and research funded by both the NIH and by US-based private industry:

Assessing drugs for treatment of cystic fibrosis*:* University of Massachusetts (Dr. Albert*, et al.)*

Detecting early and preclinical COPD*:* Washington University (Dr. Yablonskiy, *et al*.)

Detection of pulmonary metastases with ^{3}He*:* Duke University (Dr. Driehuys, *et al*.)

Detecting and treating pulmonary embolism: University of Massachusetts (Dr. Albert, *et al*.)

Diffusion kurtosis imaging in asthma, COPD and in the lungs of 9/11 NYC firefighters*:* New York University (Dr. Johnson, *et al.)*

Drug Efficacy in preclinical models of asthma and COPD*:* Duke University (Dr Driehuys, *et al*.)

Early detection of bronchiolitis obliterans syndrome in lung transplant recipients*:* Washington University (Dr. Woods, *et al*.)

Evaluation of endobronchial interventions for COPD*:* Washington University (Dr. Woods, *et al*.), Robarts Imaging Institute (Dr. Parraga, *et al.,* University of Virginia (Dr. Altes*, et al.)*

Evaluation of a novel treatment for asthma: University of Virginia (Dr. Altes, *et al.)*

Evaluation of a novel treatment for cystic fibrosis: University of Virginia (Dr. Mugler, *et al.)*

Imaging of small-animal models of diseases*:* Duke University (Dr. Johnson *et al.),* Washington University (Dr. Woods, *et al.)*

In-vivo morphometry with ^{3}He diffusion MRI*:* Washington University (Dr. Yablonskiy, *et al*.)

Measuring regional pulmonary oxygen pressure by ^{3}He MRI: University of Pennsylvania (Dr. Rizi, *et al*)

Monitoring Progression of COPD*:* Duke University (Dr Driehuys, et al.), Robarts Imaging Institute (Dr. Parraga, *et al*.), University of Virginia (Dr. Mugler, *et al*.), Washington University (Dr. Yablonskiy, *et al.)*

Neonatal ventilation and dynamics under mechanical ventilation*:* Harvard University (Dr. Patz *et al*.), University of Virginia (Dr. Miller, *et al.)*

Noninvasive methods for measuring alveolar surface area*:* Harvard University (Dr. Patz, *et al*.), Washington University (Dr. Yablonskiy, *et al.*)

Persistence of Ventilation Defects in patients with asthma: University of Virginia (Dr. Altes, *et al*.), University of Massachusetts (Dr. Albert, *et al*.)

Predicting ventilation changes caused by radiation therapy: Robarts Imaging Institute (Dr. Parraga, *et al*.), University of Virginia (Dr. Mugler*, et al.)*

Probing the fundamental limits of MRI resolution by diffusion*:* Duke University (Dr. Johnson*, et al*.)

Pulmonary Gas flow Measurements and Dynamic ^{3}He MRI of the Lungs*:* New York University (Dr. Johnson*, et al.)*

A Specialized Clinically Oriented Center of Research for COPD: (Dr. Holtzman and Dr. Woods, *et al.)*

THE ^{3}HE SHORTAGE AND ITS EFFECTS

Timeline

Late in 2008 our research group and others became aware that there was a supply issue with ^{3}He gas, through conversations with Spectra Gases, Inc. We immediately purchased some gas to continue imaging

studies in COPD patients. In March, 2009, we were told there was no gas available for medical applications and that the price of non-medical ^{3}He had risen to near $400/L STP. Conversations with colleagues at the University of Virginia, Harvard University, and the University of Pennsylvania confirmed that others were also unable to purchase ^{3}He gas. In April - June of 2009, we worked with Spectra Gases and other universities to state our ^{3}He requirements to continue NIH- and NSF-funded research in 2009; Spectra Gases then met with the Department of Energy (DOE) in July and August to make clear that US Government-funded research was being affected. In August 2009, Spectra approached me and the other officers of the Hyperpolarized Media Study Group of the International Society for Magnetic Resonance in Medicine (the primary professional organization for ^{3}He MRI researchers) to write a letter to the Isotope Work Group of the DOE, stating how ^{3}He is unique in medical imaging and that a significant amount of NIH-funded research would be effectively shut down without access to the small amount of gas that our community uses (2000 L STP / year, approximately). Dr. William Hersman and I drafted this letter, dated September 4, 2009; it is attached to the end of this written testimony. In October 2009 we were notified by Spectra Gases that an algorithm for obtaining a small amount of ^{3}He gas for NIH-funded studies had been achieved. In order to obtain any gas, we were to list each federally-funded grant's title and number, and for each a requested amount of gas for the subsequent 6 months of usage. ^{3}He was offered to our group for $600/ L STP, an approximately 500% increase from previous years. I also drafted a letter in support of Spectra's modification of their permit for ^{3}H (tritium) limits with ^{3}He, in addition to letters of support for allocation of ^{3}He to two non-US researchers who do important work; these are also attached to this testimony. At a recent AAAS meeting (April, 2010), it was made clear that the White House Office of Science and Technology Policy (OSTP) had been diligently and actively pursuing a solution to this shortage by facilitating discussions between DOE and DHS. My understanding is that OSTP was helpful in (perhaps in large part responsible for) the 2009 and 2010 allocation of ^{3}He gas to NIH-funded projects.

Impact of the Shortage upon Medical Imaging Research

While I have stated that I think the biggest impact of ^{3}He MRI *technology* is in drug development, efficacy monitoring, and in guiding new minimally-invasive interventions, the impact of the shortage was most keenly felt by those of us in the middle of performing NIH- and industry-funded research studies. Some of us (like our group at Washington University) were able to continue to perform studies at a lower rate and were able to purchase gas at $600/L STP, once it became available. Other groups, such as the Robarts Imaging Institute,

have not been able to continue ^{3}He studies, even if these studies were funded by US companies. Even for US, NIH-funded researchers, however, the price of ^{3}He increased so quickly and by so much that research groups were not able to plan for the cost increase and are now scrambling for supplementary funding sources. This is the reason why all of the ^{3}He recently set aside for various medical imaging groups has not been instantly purchased. The shortage has had a significant negative impact on the continued productivity of our research community and on the probability of future research. Importantly, if sufficient ^{3}He is not allocated to medical imaging at reasonable cost, this will likely curtail the revolution in pulmonary medicine currently in progress.

Financial and Scientific Impact

It is difficult to gauge the precise financial impact of the ^{3}He shortage on the field of hyperpolarized-gas MRI. It is clear that fewer studies are being conducted and planned as a result of this shortage. It is probably safe to say that all studies mentioned previously have been scaled back by a factor of 2 or more. By my count, the National Institutes of Health are currently supporting at least 25 active projects requiring ^{3}He, with over $4M allocated for FY2010. If we assume similar funding for the past 8 years, with less funding before that, this represents an investment of over $32M via NIH funding alone. When added to the significant (but more difficult to quantify) investment from the NSF, private and public universities, and private industry, the total investment in ^{3}He MRI is likely between $60M and $100M over the past 10 years.

While the above numbers represent an enormous investment in ^{3}He polarization and MRI infrastructure, it is my opinion that the biggest financial impact of the shortage is on future drug development, efficacy monitoring, and in guiding new surgical and minimally-invasive interventions. Through the use of more precise biomarkers, such as we have developed via ^{3}He MRI, the number of patients required to determine the true efficacy of a drug or device can be reduced by large fractions (up to 90% by a recent calculation from our techniques), which would translate directly into proportionate cost savings. The GSK example of the TORCH study mentioned in the Summary is illustrative. The key question was “Does Advair reduce mortality by as much as 20%?” Unfortunately for GSK, the question remained unanswered after studying 6000 patients and expending $500M, because the statistical significance was not high enough to determine an answer to the vital question. If the ^{3}He diffusion MRI techniques that have been discussed here were used as a biomarker and endpoint (not possible when the study began), 6,000 patients could have turned into fewer than 500 patients, saving around 90% of the cost of the study, or $450M. The question about efficacy would likely have been

answered, and the company could have devoted its efforts to the marketplace, if successful, or to newer and more innovative solutions, if unsuccessful.

The scientific impact of the shortage is serious. Scientific studies and investigations into lung physiology and pathophysiology and new treatments are being scaled back; without a clear solution in place, the revolution in pulmonary medicine will be at least partially curtailed. In one case that I'm very familiar with, research has ceased entirely because of a lack of ^{3}He gas. The Robarts Research Institute in London, Canada was established in part with capital funding provided by and research partnerships with Merck Research Laboratories (Imaging, Westpoint PA USA) and General Electric Health Care (GEHC, Milwaukee WI). They have been performing ^{3}He MRI studies in animal models of respiratory disease, in healthy volunteers, and patients with lung disease (COPD, asthma, cystic fibrosis, radiation-induced lung injury). Their human studies are funded by Merck, GEHC, the Canadian Lung Association and Canadian Institutes of Health Research. Without a small allocation of ^{3}He to this institution, their entire pulmonary MRI operation will be shut down, and further investment by US companies will be lost.

POTENTIAL ALTERNATIVES TO ^{3}HE

Two noble gas isotopes (^{3}He and ^{129}Xe) were originally identified as having potential for use in pulmonary MRI, since they could be hyperpolarized to 10% or more with sufficient laser power (originally very expensive and technically complex). Other gases (e.g. ^{83}Kr, ^{21}Ne) have potential for low levels of hyperpolarization, but their nuclear and physical properties will prevent high polarizations in bulk gas or their widespread use in human MRI. When high-power, low-cost diode laser technology became available in the 1990s, these lasers were used to produce macroscopic quantities of ^{3}He at high polarization (~50-60%), and ^{129}Xe at much lower polarization (≤ 10%). The comparative physical properties of the gases and early hyperpolarization technology led to near-universal adoption of ^{3}He as the gas of necessity for pulmonary gas MRI. These properties are outlined below.

1. The magnetic moment of ^{129}Xe is only about ⅓ that of ^{3}He; this is directly related to the signal strength in MRI. Further, the natural abundance of ^{129}Xe is only 26%; both of these reduce the available signal in the hyperpolarized gas intrinsically by a factor of 6. Enrichment of the isotope (at significant cost, since ^{129}Xe is close in weight to the abundant isotopes of Xe) can reduce this intrinsic signal reduction to a factor of 3 below ^{3}He. The achievable polarization with xenon has also been historically lower than with ^{3}He, and the delivered

dose of xenon gas is limited by its anesthetic activity. In short, hyperpolarized xenon does not yield the high signal-to-noise that ^{3}He does, which means that xenon delivers poorer quality images and less physiological information. The sum of the effects of lower magnetic moment (gyromagnetic ratio), lower abundance, lower polarization, and lower dose add up to an approximate reduction in signal by a factor of 50. The efforts of Dr. William Hersman (XeMed, LLC) have helped to increase ^{129}Xe polarizations, but this new technology requires new, significant capital investment by each hyperpolarized group wishing to switch to ^{129}Xe. Even with "perfect" new technology which achieves comparable polarization and with isotopically enriched gas, the signal reduction is still intrinsically limited by the magnetic moment and limited dose—a factor of 3-5—and many experiments and clinical trials are not possible with ^{129}Xe. This is particularly true for measurements of lung morphometry and connectivity.

2. The free diffusivity of ^{3}He is extremely large, because of its low mass and small collisional cross-section. This property is crucial to measurements of long-range diffusivity in lungs, which have been shown to be more sensitive to emphysema than short-range diffusivity. By comparison, the much lower free diffusivity of xenon greatly reduces the distances that can be explored with the long-range technique. To our knowledge, no one has even reported long-range diffusion measurements in lungs with hyperpolarized xenon for this reason. Several of our NIH-funded projects rely upon a measurement of long-range ^{3}He diffusion and would not be completed without the ^{3}He isotope. Further, larger field gradients are required even for short-range diffusion experiments; this may require further capital costs.

3. The long T_1 of ^{3}He allows it to be shipped by air freight. This has been demonstrated in Europe and the Mayo Clinic (in addition to a current proposal by Dr. Hoffman's group at the University of Iowa) as a feasible business-model for polarized gas use in hospitals, removing the necessity of each hospital having its own dedicated polarizer (a requirement that has so far limited the clinical utilization of polarized gas). By comparison, the T_1 of xenon is shorter (of order 2 hours), making air shipment virtually impossible to orchestrate.

^{3}He will remain a necessity for MRI researchers because of the physical properties mentioned above (specifically its high diffusion coefficient). The intrinsic properties of ^{129}Xe will necessarily limit the images to have a factor of 3 reduction in signal compared to ^{3}He images. The polarization of ^{129}Xe has seen significant improvement in the past 3-4 years, however, and some recent images of ventilation have had acceptable contrast, even though the signals were not as high as for ^{3}He. And while the relatively large solubility in tissue

has an anesthetic effect on animals and humans, this property can be capitalized upon in an attempt to quantify diffusion across gas-tissue barriers. There is thus a potential role for ^{129}Xe in perhaps half of the future hyperpolarized-gas MRI studies.

RECYCLING ^{3}HE

Since helium is not soluble in the tissues of the body, it can be very highly recoverable, yet most research groups do not have systems currently in place to recapture and compress exhaled gas. The hyperpolarized helium research community has demonstrated in the past that inexpensive technologies can be assembled for easily solvable problems within the field, and the technology for recycling of ^{3}He is straightforward. (For example, since ^{3}He is a liquid at 4 K [4 degrees above absolute zero], all other gases, particulate and biological matter can be frozen out by passing through a liquid ^{4}He bath at 4 K.) Both Washington University (Dr. Woods, et al.) and the University of Virginia (Dr. Miller, et al.) are currently collaborating with Walter Whitlock, of Conservation Design Services, Inc., in North Carolina, to develop commercially-viable recycling for wide use in the ^{3}He MRI community. This recycling collaboration is not yet funded but is currently underway. I believe that the important and significant scientific research outlined in this testimony can be sustained and performed with around 2,000 total STP liters of ^{3}He per year, after development of good recovery/recycling systems for ^{3}He.

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Cc: Spectra Gases, Inc. (Jack Faught, Keith Darabos)
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September 4, 2009

RE: ^{3}He is unique and irreplaceable - Letter to the Isotope Work Group of the US Government in relation to release of ^{3}He for medical imaging.

Dear Keith,

Our understanding is that the US government's "isotope work group" may benefit from some additional information and a statement from the hyperpolarized-gas community concerning the necessity of ^{3}He as the hyperpolarized isotope of choice for our pulmonary imaging studies and clinical trials. ^{3}He has emerged as a new and unique standard for pulmonary imaging, both for its high signal, physical properties (specifically, a high diffusion coefficient, allowing morphometric measurements of alveolar spaces), developed infrastructure, and mature polarization technology. There has been some discussion in the literature about using hyperpolarized xenon instead of ^{3}He gas for specific future studies, but it is clear to us that hyperpolarized xenon is simply not suitable to replace ^{3}He at this point, both for scientific and practical reasons. We outline these reasons below. In the long run, we believe that significant scientific research can be performed with around 1000-2000 STP liters of ^{3}He after development of good recovery/recycling systems for ^{3}He.

1. The magnetic moment of ^{129}Xe (the spin ½ stable isotope) is only about 1/3 that of ^{3}He, and the natural abundance of ^{129}Xe is only 26%; both of these reduce the available signal in the hyperpolarized gas. The achievable polarization with xenon has also been historically lower than with ^{3}He, and the delivered dose of xenon gas is limited by its anesthetic activity. In short, hyperpolarized xenon does not yield the high signal-to-noise that ^{3}He does at this point in time, which means that xenon delivers poorer quality images and less physiological information. The sum of the effects of lower gyromagnetic ratio, lower abundance, lower polarization, and lower dose add up to an approximate reduction in signal by a factor of 50. In the future, the achievable

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polarizations of xenon are expected to improve, though we do not view this as a viable replacement for ^{3}He for the reasons stated herein. The efforts of Dr. Bill Hersman (XeMed, LLC) have helped to increase ^{129}Xe polarizations, but this new technology requires new, significant capital investment by each hyperpolarized group wishing to switch to ^{129}Xe. Even with "perfect" new technology which achieves comparable polarization and with isotopically enriched gas, the signal reduction is still limited by the gyromagnetic ratio and limited dose—a factor of 3-5—and many experiments and clinical trials are not possible with ^{129}Xe.

2. Different physical properties of Xe and He lead to differences in the investigations that can be performed with the two gases. One big difference is the self diffusion coefficient; the free diffusivity of ^{3}He is extremely large, because of its low mass and small collisional cross-section. This property is crucial to measurements of long-range diffusivity in lungs, which have been shown to be more sensitive to emphysema than short-range diffusivity. By comparison, the much lower free diffusivity of xenon (neat, or mixed with air or nitrogen) greatly reduces the distances that can be explored with the long-range technique. To our knowledge, no one has even reported long-range diffusion measurements in lungs with hyperpolarized xenon for this reason. Several of our NIH-funded projects rely upon a measurement of long-range ^{3}He diffusion and would not be completed without the ^{3}He isotope.

3. The long T_1 of ^{3}He allows it to be shipped by air freight. This has been demonstrated in Europe and the Mayo Clinic (in addition to a current proposal by the Iowa group) as a feasible business-model for polarized gas use in hospitals, removing the necessity of each hospital having its own dedicated polarizer (a requirement that has so far limited the clinical utilization of polarized gas). By comparison, the T_1 of xenon is shorter (of order 2 hours), making air shipment virtually impossible to orchestrate. Further, the hyperpolarized helium research community has demonstrated that inexpensive technologies can be assembled for recapturing and recycling of the ^{3}He gas used for medical imaging. Since helium is not soluble in the tissues of the body, it can be very highly recoverable.

4. Many groups in the field using hyperpolarized ^{3}He have existing, funded grants, most of which are from the National Institutes of Health, representing a $100 million investment over the past decade in infrastructure and expertise. A substantial decrease in availability or increase in price of ^{3}He would be an insurmountable burden on these groups and their research efforts. In this regard, we ask that you note that switching from ^{3}He to xenon (assuming xenon is suitable for the proposed measurements; see above) would entail large equipment expenses, which current funding would not cover. A conversion of existing polarizers on loan from General Electric (or built in-house by scientists) would require major, expensive changes; imaging would have to occur with new rf coils (now often complex multi-receiver "phased arrays"), pulse and sequence development, and an established multi-year safety record. Even with such a large capital and time investment for xenon substitution, resultant images with ^{129}Xe would be inferior to what our current ^{3}He studies require.

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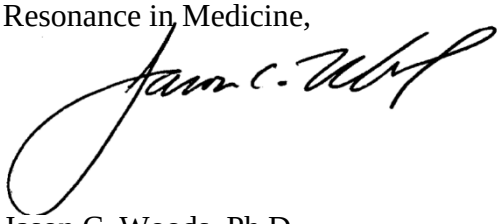
In summary, we see a huge loss of scientific productivity, a wasting of a large investment in medical research infrastructure, a forestalling of medical advances for the US patient population, and irreparable damage to careers of scientists and students without an immediate release of ^{3}He for use by the medical research community. While hyperpolarized xenon may, in the long term, meet some of the medical needs presently served by ^{3}He, we do not see this making an impact without a large investment in time (several years) and research dollars (>$10M), the funds for which do not exist. Even if that investment were made, clinical trials currently underway would have to be restarted. If, on the other hand, a programmatic release of ^{3}He over the next several years were allowed, important research with the existing infrastructure could continue. Market forces or quantity restrictions will rapidly result in technological and methodological ways of maximizing the progress using as little ^{3}He gas as possible.

On behalf of the Hyperpolarized Media Study Group of the International Society of Magnetic Resonance in Medicine,



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September 30, 2009

RE: modification of Spectra Gases' permit (license # 29-30779-01) for tritium contained within helium gas.

To whom it may concern:

We understand that the US Nuclear Regulatory Commission may benefit from some additional information and a statement from the hyperpolarized-gas community regarding the modification of Spectra Gases' license for tritium limits within the stable isotope ^{3}He, which our community uses routinely for pulmonary medical imaging via MRI. Our position is that the levels of allowed tritium within inhaled ^{3}He gas (5×10^{-6} μCi/cc) is many orders of magnitude below any level potentially harmful to humans. This position is based upon our own calculations and those provided by the Department of Energy, within the Handbook, *Tritium Handling and Safe Storage* (DOE-HDBK-1129-99). We urge that the requested modification to the license, which will allow more ^{3}He to be used for NIH-sponsored and other research projects within our scientific community, be granted expeditiously.

We offer a calculation below to illustrate the safety of the allowed level of tritium within ^{3}He gas. Since each research group uses a slightly different amount of ^{3}He per experiment (which range from 300 mL to 1000 mL) we assume the maximum of 1000 mL ^{3}He per experiment and 3000 mL ^{3}He per imaging session in the calculations.

The DOE Handbook *Tritium Handling and Safe Storage* correctly notes that tritium is not readily absorbed from inhaled gases or through the skin. (This is due to its very low solubility in tissue and blood—near the low value of ^{3}He gas itself.) They state on p. 5 that, "A very small fraction of the inhaled hydrogen isotopes, in gaseous form, is not exhaled, but is dissolved in the blood stream and then exhaled after a few minutes." This handbook concludes that a 0.5 μCi/cc concentration of tritium gas inhaled occupationally for 1 year would be the equivalent of a 5 rem dose. Therefore, the allowed level of tritium in ^{3}He (via Spectra Gases' license—5×10^{-6} μCi/cc)

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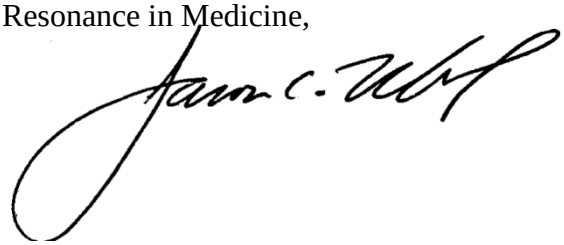
would be equivalent to 5×10^{-5} rem if exposed occupationally to this concentration over an entire year (assumes 2400 m^3 of gas at that concentration was inhaled--much more than ever feasibly inhaled for medical imaging). A typical value of a very large dose of ^{3}He (30 L, or 3 L per session for 10 sessions) would result in a dose of 6.3×10^{-10} rem.

The average American is subjected to multiple sources of radiation exposure, many of them from natural sources. By far the largest natural source of radiation exposure to humans is from radon (200 mrem/yr). However, even the chemical makeup of the human body includes carbon-14 and potassium-40 (40 mrem/yr). Cosmic rays deliver a continuous natural source of ionizing radiation (27 mrem/yr). Because the dose calculated above for tritium in ^{3}He is a roughly billion times smaller than the one year burden from these natural exposures, we argue that its contribution constitutes an insignificant risk.

On behalf of the Hyperpolarized Media Study Group of the International Society of Magnetic Resonance in Medicine,



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November 18, 2009

RE: release of ^{3}He gas

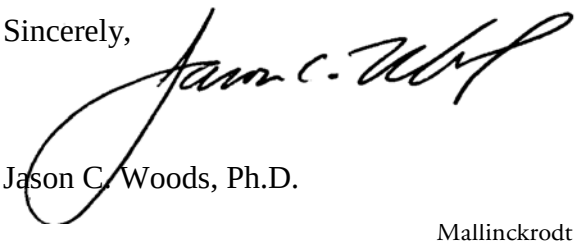
To whom it may concern:

I write in support of the release of ^{3}He gas for medical imaging to Dr. Giles Santyr and Dr. Grace Parraga, of the Robarts Research Institute in London, Ontario. Both Dr. Santyr and Dr. Parraga are pillars of the hyperpolarized gas community. They have active collaborations within the United States, are both at the cutting edge of medical-imaging research; their requests for gas release should be granted.

The pulmonary-imaging group at Robarts has broken new ground in the quantification of ventilation defects and their relationship to disease severity and progression in both asthma and COPD. Researchers and clinicians in the United States have directly benefited from their work and will continue to do so if this request is granted. Their research is mainly funded by the Canadian Institutes of Health (similar to our National Institutes of Health), and they have advisers and collaborations with researchers in the United States. I personally have visited their facility in the past 6 months, in part to discuss a collaboration with our group at Washington University and in part in an advisory role, as I serve on an external board of advisors to one of their CIHR grants.

In addition to being active contributors to the US and international community of medical imaging, they have developed good educational-industrial partnerships with US companies such as General Electric. Their past work with US companies has resulted in significant improvements of ultrasound, CT, and MRI technology, which benefits the US companies, US researchers, and US citizens at large. A failure to release ^{3}He gas to this research team would significantly impede progress in the field and would have a detrimental impact on collaborations with US researchers and corporations.

Sincerely,



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November 19, 2009

RE: release of ^{3}He gas

To whom it may concern:

I write in support of the release of ^{3}He gas for medical imaging to Dr. Frank Thien, of Monash University & Box Hill Hospital in Melbourne, Australia. Dr. Thien has recently been successful in performing ^{3}He MRI with gas transported via an intercontinental commercial airline. Their work supports the success of a model of central production and distribution, even to a destination halfway around the earth from the production facility.

Dr. Thien is funded by the National Health and Medical Research Council, which is the Australian equivalent of our National Institutes of Health. He has active collaborations in Europe and in the United States with Dr. Kim Prisk at the University of California San Diego. Their collective work together is very scientifically productive and important to the field of hyperpolarized-gas imaging. Researchers and clinicians in the United States have directly benefited from their work and will continue to do so if this request is granted.

In addition, the amount requested (30 STP liters) is rather modest and will represent only a very small fraction of the total medical-gas utilization of ^{3}He.

Sincerely,

Jason C. Woods, Ph.D.
Program Director, ISMRM Hyperpolarized Media Study Group

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