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NATIONAL INSTITUTE FOR
OCCUPATIONAL SAFETY AND HEALTH

ADVISORY BOARD ON RADIATION AND WORKER HEALTH

A REVIEW OF NIOSH'S PROGRAM EVALUATION REPORT
OCAS-PER-008, *MODIFICATION OF NIOSH-IREP CANCER RISK MODEL: EFFECT*
OF "COMBINED" LUNG MODEL ON NON-COMPENSABLE LUNG CANCER CLAIMS

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A Review of NIOSH's Program Evaluation Report OCAS-PER-008, *Modification of NIOSH-IREP Cancer Risk Model: Effect of "Combined" Lung Model on Non-Compensable Lung Cancer Claims*	Page 2 of 26
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Project Manager: _____ Date: _____ John Mauro, PhD, CHP	Reviewer: John Mauro

Record of Revisions

Revision Number	Effective Date	Description of Revision
0 (Draft)	12/15/2010	Initial issue – Cleared for potential Privacy Act-protected information on 01/11/2011

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LIST OF EXHIBITS

ABBREVIATIONS AND ACRONYMS

Advisory Board
or ABRWH   Advisory Board on Radiation and Worker Health

CDC   Centers for Disease Control and Prevention

CFR   *Code of Federal Regulations*

cSv   centi-Sievert

DDREF   Dose and Dose-Rate Effectiveness Factor

DR   Dose Reconstruction

EAR   excess absolute risk

EEOICPA   Energy Employees Occupational Illness Compensation Program Act of 2000

ERR   excess relative risk

GSD   geometric standard deviation

Gy   gray

HHS   Health and Human Services (U.S. Department of)

IREP   Interactive RadioEpidemiologic Program

keV   kilo electron volt

NAS   National Academy of Sciences

NCI   National Cancer Institute

NIH   National Institutes of Health

NIOSH   National Institute for Occupational Safety and Health

OCAS   Office of Compensation Analysis and Support [now known as the Division of Compensation and Analysis Support (DCAS)]

ORAUT   Oak Ridge Associated Universities Team

PEP   Program Evaluation Plan

PER   Program Evaluation Report

PC   Probability of Causation

rad   Radiation Absorbed Dose

RERF   Radiation Effects Research Foundation

rem   Roentgen equivalent man

SEER   Surveillance, Epidemiology, and End Results

Sv   sievert

1.0   STATEMENT OF PURPOSE

To support dose reconstruction (DR), the National Institute for Occupational Safety and Health (NIOSH) and the Oak Ridge Associated Universities Team (ORAUT) assembled a large body of guidance documents, workbooks, computer codes, and tools. In recognition of the fact that all of these supporting elements in DR may be subject to revisions, provisions exist for evaluating the effect of such programmatic revisions on the outcome of previously completed DRs. Such revisions may be prompted by document revisions due to new information, misinterpretation of guidance, changes in policy, and/or programmatic improvements.

The process for evaluating potential impacts of programmatic changes on previously completed DRs has been proceduralized in OCAS-PR-008, *Preparation of Program Evaluation Reports and Program Evaluation Plans* (OCAS 2006a), Revision 2, dated December 6, 2006. This procedure describes the format and methodology to be employed in preparing a Program Evaluation Report (PER) and a Program Evaluation Plan (PEP).

A PER provides a critical evaluation of the effect(s) that a given issue/programmatic change may have on previously completed DRs. This includes a qualitative and quantitative assessment of potential impacts. Most important in this assessment is the potential impact on the Probability of Causation (PC) of previously completed DRs with PCs of <50%.

As needed, a PEP may be issued that serves as a formal notification of an impending PER. The PEP provides a preliminary description of the issue(s) that will be addressed in the PER, and summarizes the likely scope of the effort required to complete the PER.

During an Advisory Board meeting on May 20, 2010, SC&A was tasked by the Advisory Board to conduct a review of OCAS-PER-008, *Modification of NIOSH-IREP Cancer Risk Model: Effect of "Combined" Lung Model on Non-Compensable Lung Cancer Claims* (OCAS 2007). In conducting a PER review, SC&A is committed to perform the following five subtasks, each of which is discussed in this report:

Subtask 1: Assess NIOSH's evaluation/characterization of the "issue" and its potential impacts on DR. Our assessment intends to ensure that the "issue" was fully understood and characterized in the PER.

Subtask 2: Assess NIOSH's specific methods for corrective action. In instances where the PER involves a technical issue that is supported by document(s) (e.g., white papers, technical information bulletins, procedures) that have not yet been subjected to a formal SC&A review, Subtask 2 will include a review of the scientific basis and/or sources of information to ensure the credibility of the corrective action and its consistency with current/consensus science. Conversely, if such technical documentation has been formalized and previously subjected to a review by SC&A, Subtask 2 will simply provide a brief summary/conclusion of this review process.

Subtask 3: Evaluate the PER's stated **approach** for identifying the universe of potentially affected DRs, and assess the **criteria** by which a subset of potentially affected DRs was selected for re-evaluation. The second step may have important implications in instances where the universe of DRs is too large and, for reasons of practicality, NIOSH's re-evaluation is confined to a subset of DRs. In behalf of Subtask 3, SC&A will also evaluate the timeliness for the completion of the PER.

Subtask 4: Conduct audits of DRs affected by the PER under review. Based on information contained in Table 1 (and discussed in Section 3.1 below), the number of DRs selected for audit for a given PER will vary. (It is assumed that the selection of the DRs and the total number of DR audits per PER will be made by the Advisory Board.)

Subtask 5: Prepare a comprehensive written report that contains the results of the above-stated subtasks, along with our review conclusions.

2.0 SUBTASK 1: IDENTIFY THE CIRCUMSTANCES THAT NECESSITATED OCAS-PER-008

Under federal regulations defined in 42 CFR Part 81 published in May 2002, risk models used by NIOSH to adjudicate cancer claims filed by civilian nuclear weapons workers were based on a computational software package referred to as NIOSH-IREP (Interactive RadioEpidemiologic Program). NIOSH-IREP employs the National Cancer Institute's (NCI's) approach to adjust risk estimates that are based on direct evidence from Atomic bomb (A-bomb) survivors who were exposed as **adults**. While the NIOSH-IREP models do incorporate a trend of decreasing risk with increasing age for some cancers, these models do **not** incorporate any age-at-exposure effects for other cancers that include lung cancer (resulting from non-radon exposures).

At the time of the rulemaking, it was acknowledged that, in addition to the A-bomb study cohort, a substantial body of scientific data existed that suggested a variable effect for the age at exposure. While some studies showed no effect, others suggested an increased risk with age at exposure. At the time of the rulemaking, these data were regarded as insufficient to support the selection of age-specific adjustment factors for the determination of risk.

As indicated in the rule, HHS is committed to re-evaluate this issue in response to future advances in scientific information that may affect NIOSH-IREP models.

2.1 NIH-IREP

A concurrent, but separate, computer model referred to as NIH-IREP was developed primarily for the purpose of adjudicating cancer claims filed by veterans exposed to radiation during military service. Initially, NIOSH-IREP and NIH-IREP were essentially identical. However, in May 2003, the NCI substantially updated its NIH-IREP lung model (that includes cancer of the trachea and bronchus) for exposure to radiation other than radon. This revision was based on more recent analysis of lung cancer incidence among A-bomb survivors (Pierce et al. 2003).

In the revised NIH-IREP lung model, the excess relative risk (ERR) is adjusted for age at exposure and age at diagnosis. Currently, the NIOSH-IREP lung model does not adjust for these age-dependent factors. Additionally, the NIH-IREP lung model is less heavily weighted toward the **multiplicative** causal interactions of cigarette smoking and radiation on lung cancer than the NIOSH-IREP lung model.

Due to the fact that the NIH-IREP lung model incorporates more recent data regarding the risk of radiation-induced lung cancer, and in compliance with the regulatory mandate to re-evaluate NIOSH-IREP upon advances in scientific information, NIOSH issued OCAS-PEP-008, *Modification of NIOSH-IREP Lung Cancer Risk Model: Impact of "Combined" Lung Model on Non-compensable Lung Cancer Claims,* on December 7, 2006 (OCAS 2006b), and OCAS-PER-008 on April 12, 2007 (OCAS 2007).

3.0 SUBTASK 2: ASSESS NIOSH'S SPECIFIC METHODS FOR CORRECTIVE ACTION

NIOSH concluded that the same inputs when entered into NIOSH-IREP and NIH-IREP produce PC values that differ significantly and, therefore, posed a potential dilemma to the DR of workers covered under the Energy Employees Occupational Illness Compensation Program Act of 2000 (EEOICPA). To resolve this issue, NIOSH requested SENES Oak Ridge, Inc., to provide an assessment of the differences between the two IREP models. In a report issued in September 2004 (Apostoaei and Trabakla 2004), SENES provided a detailed comparison of the two models. Key differences included the following:

- The NIH-IREP risk model is based on lung cancer incidence and smoking history of A-bomb survivors for the follow-up period of 1950 to 1994, as compared to the NIOSH-IREP lung model that is based on the reduced follow-up period of 1950 to 1990.

- Considered the most significant difference is the dependency on **age at exposure** and attained age at time of cancer diagnosis on the ERR of lung cancer per unit dose (ERR/Sv). **No age dependency** is included in the NIOSH-IREP lung model.

- For a "never smoker," NIH-IREP specifies ERR/Sv for age at exposure of 30 years and attained age of 50 years. (As noted above, in NIOSH-IREP, the ERR/Sv represents any age at exposure or attained age).

- While both lung models account for the interaction of smoking and radiation exposure, their contribution to total risk is modeled differently. In brief, the NIH-IREP lung model relies less on the multiplicative interaction than does the NIOSH-IREP model. Thus, the NIH model generally produces a higher PC value for smokers for some exposure profiles, and the NIOSH model generally yields higher PC values for non-smokers.

To illustrate these differences, SENES derived PC values by means of the NIH-IREP and NIOSH-IREP lung models for a common lung dose of 50 cSv (or 50 rem) delivered acutely or chronically to non-smokers and smokers and for three discrete ages at exposure/attained age profiles. As a convenience to the reader, Tables 2, 3, and 4 of Apostoaei and Trabalka (2004) are enclosed herein as Exhibit 1.

Exhibit 1: Tables 2, 3, and 4 from Apostoaei and Trabalka (2004)

Table 2. Comparison of 99th percentiles of assigned shares (probability of causation) for lung cancer calculated by the NIH and NIOSH versions of IREP for single doses of 50 cSv to a male age 20 at exposure and age 40 at diagnosis

	Acute exposure		Chronic exposure					
	Photons >250 keV		Photons >250 keV		Alpha		Electrons <15 keV	
Smoking status	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH
Never smoker	52.94	53.75	53.66	50.97	74.99	70.73	78.22	76.81
Current smoker								
< 10 cigs/day	48.31	29.53	45.81	29.98	71.85	52.69	71.62	55.83
10-19 cigs/day	47.91	25.62	44.78	25.35	70.76	47.34	70.88	50.85
20–39 cigs/day	47.78	25.00	44.45	24.57	70.58	45.61	70.74	49.96
40+ cigs/day	47.72	24.92	44.32	24.15	70.50	45.54	70.70	49.77

Table 3. Comparison of 99th percentiles of assigned shares (probability of causation) for lung cancer calculated by the NIH and NIOSH versions of IREP for single doses of 50 cSv to a male age 40 at exposure and age 60 at diagnosis

	Acute exposure		Chronic exposure					
	Photons >250 keV		Photons >250 keV		Alpha		Electrons <15 keV	
Smoking status	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH
Never smoker	28.79	53.75	30.94	50.97	54.03	70.73	57.95	76.81
Current smoker								
< 10 cigs/day	26.51	29.53	24.56	29.98	49.63	52.69	49.02	55.83
10-19 cigs/day	25.94	25.62	23.57	25.35	48.97	47.34	48.85	50.85
20–39 cigs/day	25.88	25.00	23.47	24.57	48.86	45.61	48.35	49.96
40+ cigs/day	25.85	24.92	23.35	24.15	48.82	45.54	47.78	49.77

Table 4. Comparison of 99th percentiles of assigned shares (probability of causation) for lung cancer calculated by the NIH and NIOSH versions of IREP for single doses of 50 cSv to a male age 20 at exposure and age 60 at diagnosis

	Acute exposure		Chronic exposure					
	Photons >250 keV		Photons >250 keV		Alpha		Electrons <15 keV	
Smoking Status	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH
Never smoker	44.34	53.75	44.60	50.97	67.76	70.73	71.31	76.81
Current smoker								
< 10 cigs/day	39.66	29.53	37.21	29.98	64.21	52.69	64.07	55.83
10-19 cigs/day	39.22	25.62	35.96	25.35	63.08	47.34	63.35	50.85
20–39 cigs/day	39.17	25.00	35.80	24.57	62.87	45.61	63.12	49.96
40+ cigs/day	39.13	24.92	35.78	24.15	62.79	45.54	63.02	49.77

Inspection of Exhibit 1 demonstrates the following:

- For exposure at age 20 and diagnosis at age 40 (i.e., Table 2 of Exhibit 1), NIH-IREP is more favorable for all profiles other than the acutely exposed non-smoker.

- Table 3 of Exhibit 1, however, shows that for exposure at age 40 and diagnosis at age 60, NIOSH-IREP is more claimant favorable for the non-smoker and select profiles of light smokers.

- Table 4 of Exhibit 1 shows higher PC values for the NIH-IREP lung model for all profiles other than those involving the "never smoker."

- Noteworthy are the **identical PC values** generated by the NIOSH-IREP lung model among the three tables for a given profile that are **independent** of **age at exposure** and at **age of diagnosis**. For example, a single acute lung exposure of 50 rem to a never smoker yields the identical value of 53.75% for a male (1) exposed at age 20 and diagnosed at age 40, (2) exposed at age 40 and diagnosed at age 60, and (3) exposed at age 20 and diagnosed at age 60.

Recommendations Made by SENES

In their report (Apostosei and Trabalka 2004), the authors suggested the following two potential options to NIOSH for resolving differences between the two lung models:

> *. . . update the lung model in NIOSH-IREP because the new lung model represents the most advanced state of knowledge about radiation-induced lung cancer. . . . the newer NIH lung model includes more follow-up years of the Japanese cohort (1950–1994; Pierce et al., 2003). Also, in perhaps more than half of the possible exposure situations the NIH lung model is **more claimant-friendly**.*

> [But] *Since there are categories of people for whom the NIH-IREP lung model is **less friendly**, NIOSH could consider programming NIOSH-IREP to choose between the new NIH-IREP lung model and the current NIOSH-IREP lung model, and report whatever PC is larger for a given exposure situation . . .* [Emphasis added.]

A third suggestion offered by the authors of the SENES report was for NIOSH to seek the opinion of outside experts regarding the use of the two IREP lung models.

Recommendations by Outside Experts

In response to SENES' third suggestion, NIOSH sought the advice of the following four internationally recognized experts:

- David Brenner, PhD, Professor of Radiation Oncology and Public Health, Columbia University of Epidemiology, Columbia University School of Public Health

- David B. Richardson, PhD, Assistant Professor of Epidemiology, University of North Carolina School of Public Health

- Faith G. Davis, PhD., Professor of Epidemiology and Biostatistics, University of Illinois at Chicago, School of Public Health

- Jonathan M. Samet, MD, MS, Professor and Chairman, Department of Epidemiology, John Hopkins University School of Public Health

Responses by these experts prompted a wide array of comments in the form of questions, concerns, and recommendations regarding the selection of either lung model. However, an opinion shared by three of the four experts was that the current state of scientific knowledge and residual uncertainties regarding the available study data do not support the exclusive use of either of the two lung cancer models. For example, in his conclusions, Dr. Jonathan Samet stated (Samet 2005):

> . . . *In this setting of model uncertainty and the impossibility of selecting one model as "correct," maintaining the two models seems warranted. . . . I would not weigh the finding of the new analysis by Pierce et al. so heavily as to use only the NIH model. . . . For these reasons, I favor the retention of both models, with decision-making based on the higher probability of causation.*

Similarly, Dr. David Richardson stated the following in his conclusion (Richardson 2005):

> *The current epidemiological literature provides an inadequate basis for determining whether the current NIOSH-IREP or NIH-IREP model provides a more appropriate characterization of the joint effects of smoking and radiation dose on lung cancer risk. One alternative suggested by NIOSH is to run both models and use the result that provides the higher probability of causation. . . .*

NIOSH agreed with the experts' opinion that the most reasonable option within the context of compensation and claimant favorability was to reprogram NIOSH-IREP to run both models separately and then select the model with the higher PC value for determining the compensability of a claim.

NIOSH-IREP was reprogrammed and, as of February 28, 2006, automatically runs both risk models and reports results associated with the higher PC value at the 99th percentile. Important to note is that the modified "lung (IDC-9 code 162)" risk model (versions 5.5 and 5.5.1) can result in no lower PC value for the same set of claim inputs than had been calculated previously under the old versions (i.e., versions 5.4 and earlier) of NIOSH-IREP.

In addition, the modified NIOSH-IREP versions 5.5 and 5.5.1 incorporate a bias correction factor for random errors in dosimetry for "never smokers" who were also exposed to radon. Due to a programming oversight, this correction had **not** been incorporated in previous versions (version 5.4 and earlier) for "never smokers," but had only been applied to smokers. NIOSH-IREP v.5.5 corrected the error.

4.0   SUBTASK 3: EVALUATE THE PER's STATED APPROACH FOR IDENTIFYING THE POTENTIALLY AFFECTED DRs

On April 12, 2007, NIOSH issued OCAS-PER-008, *Modification of NIOSH-IREP Lung Cancer Risk Model: Effect of "Combined" Lung Model on Non-compensable Lung Cancer Claims.* Due to the fact that for select claimants' exposure profiles, (1) the inclusion of the NIH-IREP model had been shown to both increase as well as decrease PC values relative to those generated by the NIOSH-IREP model (see Exhibit 1 above), and (2) potential differences on PC values for individuals' lung cancer claims were not readily predictable, NIOSH elected to re-evaluate **all non-compensated** (<50% PC) lung cancer claims.

In total, NIOSH identified a total of 920 claims that met this criterion. Of the 920 claims that were re-evaluated, 729 were "single cancer" claims, with the balance of 191 claims representing two or more cancers of which lung (ICD-9 code 162) was at least one of the cancers. The re-evaluation showed that, of the 920 claims, a total of 95 claims now yielded higher PC values due to the inclusion of the alternative NIH lung cancer risk model, with four claims benefiting from the inclusion of the bias correction factor for random errors in dosimetry for never smokers exposed to radon. A summary of these results was cited in Table 1 of OCAS-PER-008, which is reproduced herein in Exhibit 2.

Of the 99 claims with higher PC values, the revised PC for 88 claims, nevertheless, remained below the threshold value of 45% and precluded further evaluation. The remaining 11 claims with **preliminary** PC values of >45% but <50%, were subject to the more rigorous evaluation involving 30 IREP runs with 10,000 iterations each for an average PC value. Lastly, all but 1 of the 11 claims represented a DR that had previously been based on a protocol of "maximizing" or "overestimating" the lung dose and, therefore, intentionally overestimated the original PC. For compensability, these 10 claims, therefore, also required a rework of the organ dose that complied with the "best-estimate" approach. Changes in PC values during these sequential steps and the final outcome for each of the 11 claims are summarized in Table 2 of OCAS-PER-008 and enclosed herein in Exhibit 2. As shown in the last column, only two (i.e., claims #3 and #9) of the original 920 claims that represented the universe of claims potentially impacted by OCAS-PER-008 for compensability did, in fact, transition from being non-compensable to compensable.

Exhibit 2:   Table 1 and Table 2 from OCAS-PER-008

Table 1: Preliminary evaluation of non-compensable lung cancer claims processed before 2/28/06: initial effect of NIOSH-IREP "combined" lung cancer risk model on probability of causation (PC) based on single IREP run at 2000 iterations

Type of Claim	Number of Claims	No PC Increase	PC Increase	Increase Due to NIH Model	Increase Due to Bias Correction Factor	New PC < 45%	New PC = 45 – 49.99%	New PC ≥ 50%
1 cancer	729	652	77	74	3	70	3	4
>1 cancer	191	169	22	21	1	18	4	0
Totals	**920**	**821**	**99**	**95**	**4**	**88**	**7**	**4**

Table 2: Final evaluation of 11 claims in which the PC value had increased to ≥45% after single IREP run at 2000 iterations using NIOSH-IREP v5.5.1 "combined" lung model

Claim No.	Original DR	Original Claim PC (1 IREP Run)	Interim Claim PC (1 IREP Run)	Interim Claim PC (30 IREP Runs)	Final Claim Outcome
1	Overestimate	45.91%	46.05%	45.26%	PC remains below 50%
2	Overestimate	45.50%	45.79%	44.94%	PC remains below 50%
3	Best Estimate	46.14%	50.94%	50.05%	**PC exceeded 50%**
4	Overestimate	38.28%	48.08%	43.33%	PC remains below 50%
5	Overestimate	46.56%	53.03%	49.15%	PC fell below 50% after rework
6	Overestimate	43.81%	49.04%	48.93%	PC remains below 50%
7	Overestimate	44.38%	56.15%	N/A	Reworked for reasons unrelated to lung model; PC decreased to 23.29%
8	Overestimate	34.35%	46.93%	47.44%	PC remains below 50%
9	Overestimate	44.60%	47.56%	52.17%	**After 'best estimate" rework, PC=52.08% (single IREP run)**
10	Overestimate	41.16%	45.08%	45.87%	PC remains below 50%
11	Overestimate	42.72%	53.22%	N/A	PC decreased to 42.82% after rework

4.1   SC&A - GENERAL COMMENTS

Central to the need for the issuance of OCAS-PER-008 was the re-analysis of lung cancer incidence in A-bomb survivors as provided in the 2003 study by Pierce et al. and the adoption of these data for estimating the risk of lung cancer, as defined in the NIH-IREP model. The major change introduced into the NIH-IREP lung model is that the excess relative risk per dose (i.e., ERR/Sv) is affected by the individual's **age at exposure** and **attained age** at time of cancer diagnosis. In the NIH-IREP model for a **given attained age**, the ERR/Sv decreases exponentially between **ages at exposure** of 15 and 30, but is constant above this age interval. Similarly, for a **given age at exposure**, the ERR/Sv decreases linearly with **attained age**, but

only up to the attained age of 50, after which it remains constant. No age-dependency is included in NIOSH-IREP lung model, which was principally based on data contained in the 1985 *Report of the NIH Ad Hoc Working Group to Develop Radioepidemiological Tables* (NIH 1985).

With regard to the interaction of smoking and radiation on the induction of lung cancer, both the NIH and NIOSH versions of IREP have adopted the same smoking-related adjustment factors provided by the Centers for Disease Control and Prevention (CDC) (CDC 1995). However, a difference between the two models is the way in which these factors are applied. In brief, for NIOSH-IREP, smoking adjustment factors are applied to the parameter α (i.e., ERR/Sv), which represents an average for all smoking categories; in contrast, smoking adjustment factors in NIH-IREP are applied to the parameter α that is defined by the ERR/Sv representing the "never smoker."

A brief summary as well as a numerical comparison of parameter values employed in the NIH-IREP and NIOSH-IREP risk models are provided in Appendix A and Appendix B, respectively, of Apostoaei and Trabalka (2004). SC&A verified the accuracy of these summary model data by comparing them against those originally reported by Land et al. 2003 and Land et al. 2002. Furthermore, SC&A ran the NIOSH-IREP model using the identical parameter values identified in Exhibit 1 above and was able to match all of the corresponding PC values. For illustration, Exhibit 3 shows the IREP input data for the 20 year-old male **never smoker** who was exposed to an acute lung dose of 50 cSv and diagnosed with lung cancer at age 40. At the 99th percentile, the **PC of 53.75%** matches the first entry, as previously shown in Exhibit 1.

Important to note, however, is that all PC values cited in Exhibit 1 (and verified in Exhibit 3) assume a lung dose of 50 cSv (or 50 rem) that was entered as a **constant** (i.e., with no uncertainty). Use of an organ dose as a **constant** is generally limited to a "maximized" and non-compensable DR. Thus, when the lung dose of 50 cSv is entered with a reasonable uncertainty (e.g., a lognormal value with a GSD of 1.52), the 99th percentile NIOSH-IREP PC value increases to 61.44%, as shown in Exhibit 4.

Exhibit 3: NIOSH-IREP PC Results with Dose Entered as a Constant Value
NIOSH-Interactive RadioEpidemiological Program
Probability of Causation Results

Uploaded file: **N/A**   DOL District Office: CL
Date of Run: 12/2/2010   NIOSH-IREP version: 5.6
Time of Run: 3:06:02 PM   Analytica/ADE version: 3.0
NIOSH ID #: 123456   DOL Case No: 123-45-6789
Claimant Name: John Q. Doe

Claimant Cancer Diagnoses:

Primary Cancer #1: N/A   Date of Diagnosis: N/A
Primary Cancer #2: N/A   Date of Diagnosis: N/A
Primary Cancer #3: N/A   Date of Diagnosis: N/A
Secondary Cancer #1: N/A   Date of Diagnosis: N/A
Secondary Cancer #2: N/A   Date of Diagnosis: N/A
Secondary Cancer #3: N/A   Date of Diagnosis: N/A

Claimant Information Used In Probability of Causation Calculation:

Gender: Male   Race (skin cancer only): N/A
Birth Year: 1940   Year of Diagnosis: 1980
Cancer Model: Lung (162)   Should alternate cancer model be run?: No

Smoking history (trachea, bronchus, or lung cancer only): Never smoked

NIOSH-IREP Assumptions and Settings:

User Defined Uncertainty Distribution: Lognormal(1,1)

Number of Iterations: 2000   Random Number Seed: 99

General Exposure Information:

#	Exp. Year	Organ Dose (cSv)	Exp. Rate	Radiation Type
1	1960	Constant (50)	acute	photons E>250keV

Radon Exposure Information:
  N/A (applies only to cases of Lung Cancer with Radon Exposures)

Probability of Causation (PC) *

1st percentile	4.93 %
5th percentile	8.63 %
50th percentile	24.03 %
95th percentile	45.67 %
99th percentile	53.75 %

* NIOSH-IREP is programmed with two different lung cancer risk models. Under current guidelines, each lung cancer claim is run separately using both risk models and the higher PC will determine the outcome of the claim. The results displayed above are derived from the **NIOSH-IREP lung model**, which is the model that produced the higher PC at the 99th percentile for this particular claim. The lower PC at the 99th percentile, derived from the NIH-IREP lung model, is 51.49 %. This lower PC value is reported here for information only and will have no bearing on the claim outcome.

NOTICE: This report has been reviewed for Privacy Act information and has been cleared for distribution. However, this report is pre-decisional and has not been reviewed by the Advisory Board on Radiation and Worker Health for factual accuracy or applicability within the requirements of 42 CFR 82.

Exhibit 4:   NIOSH-IREP PC Results with Dose Entered with a Lognormal Distribution
NIOSH-Interactive RadioEpidemiological Program
Probability of Causation Results

Uploaded file: **N/A**   DOL District Office: CL
Date of Run: 12/2/2010   NIOSH-IREP version: 5.6
Time of Run: 2:59:51 PM   Analytica/ADE version: 3.0
NIOSH ID #:   123456   DOL Case No: 123-45-6789
Claimant Name: John Q. Doe

Claimant Cancer Diagnoses:

Primary Cancer #1:   N/A   Date of Diagnosis: N/A
Primary Cancer #2:   N/A   Date of Diagnosis: N/A
Primary Cancer #3:   N/A   Date of Diagnosis: N/A
Secondary Cancer #1:   N/A   Date of Diagnosis: N/A
Secondary Cancer #2:   N/A   Date of Diagnosis: N/A
Secondary Cancer #3:   N/A   Date of Diagnosis: N/A

Claimant Information Used In Probability of Causation Calculation:

Gender: Male   Race (skin cancer only):   N/A
Birth Year: 1940   Year of Diagnosis: 1980
Cancer Model: Lung (162)   Should alternate cancer model be run?:   No
Smoking history (trachea, bronchus, or lung cancer only):   Never smoked

NIOSH-IREP Assumptions and Settings:

User Defined Uncertainty Distribution: Lognormal(1,1)
Number of Iterations: 2000   Random Number Seed: 99

General Exposure Information:

#	Exp. Year	Organ Dose (cSv)	Exp. Rate	Radiation Type
1	1960	Lognormal (50, 1.52)	acute	photons E>250keV

Radon Exposure Information:
   N/A (applies only to cases of Lung Cancer with Radon Exposures)

Probability of Causation (PC) *

1st percentile	3.72 %
5th percentile	7.93 %
50th percentile	23.97 %
95th percentile	49.97 %
99th percentile	61.44 %

* NIOSH-IREP is programmed with two different lung cancer risk models. Under current guidelines, each lung cancer claim is run separately using both risk models and the higher PC will determine the outcome of the claim. The results displayed above are derived from the **NIOSH-IREP lung model**, which is the model that produced the higher PC at the 99th percentile for this particular claim. The lower PC at the 99th percentile, derived from the NIH-IREP lung model, is 61.40 %. This lower PC value is reported here for information only and will have no bearing on the claim outcome.

NOTICE: This report has been reviewed for Privacy Act information and has been cleared for distribution. However, this report is pre-decisional and has not been reviewed by the Advisory Board on Radiation and Worker Health for factual accuracy or applicability within the requirements of 42 CFR 82.

4.2   LIMITATIONS AND ISSUES REGARDING OCAS-PER-008

A key limitation to SC&A's evaluation of OCAS-PER-008 is the fact that for this reviewer, IREP remains a "black box" with outputs that cannot be readily verified by manual computations. Thus, SC&A's ability to reproduce PC values cited by Apostosei and Trabalka (2004) provides no insight or assurance of compliance with the purported mathematical lung models and algorisms that represent NIH-IREP and NIOSH-IREP. Correspondingly, SC&A's concurrence with NIOSH's method for identifying the universe of potential claims affected by OCAS-PER-008, the final evaluation of 11 claims (see Exhibit 2 above), and attendant conclusions are **conditional**.

SC&A's conditional concurrence is further clouded by SC&A's concerns regarding the credibility of the NIOSH-IREP and, to a lesser extent, the NIH-IREP lung model for DR, as explained below.

4.3   THE FAILURE OF NIOSH-IREP AND THE LIMITED ABILITY OF NIH-IREP TO ACCOUNT FOR AGE AT EXPOSURE/ATTAINED AGE

In Section D of the Final Rule of 42 CFR Part 81 (Fed. Register/Vol. 67, No. 85, May 2, 2002), NIOSH provided the following explanation:

> *Probability of Causation is a technical term generally meaning an estimate of the percentage of cases of illness caused by a health hazard among a group of persons exposed to the hazard. . . .*
> *In this rule, the potential hazard is ionizing radiation to which U.S. nuclear weapons workers were exposed in the performance of duty; the illnesses are specific types of cancer. The probability of causation (PC) is calculated as the risk of cancer attributable to radiation exposure (RadRisk) divided by the sum of the baseline risk of cancer to the general population (BasRisk) plus the risk attributable to the radiation exposure, then multiplied by 100 percent, as follows:*

$$\frac{RadRisk}{RadRisk \ + \ BasRisk} \ x \ 100\% \ = \ PC \qquad \text{Eq. 1}$$

From this simple equation, it is clear that the PC value is not only driven by the organ dose, but also by the **baseline cancer** risk to the non-exposed general population. Thus, for a given dose of radiation, the PC increases when baseline risk decreases and decreases when baseline risk increases. While the baseline risk for a given population cohort is affected by many variables, an important risk factor for most cancers, including lung cancer, is **attained age**.

NIOSH-IREP. As demonstrated in Exhibit 1, the NIOSH-IREP lung model does not incorporate any age at exposure effect, but assumes that the relative excess risk per unit dose is a constant, which is used as a simple multiplier for a baseline risk that, nevertheless, may change drastically as a function of attained age.

As shown in Tables 2, 3, and 4 of Exhibit 1 above, a photon dose of 50 cSv yields the identical PC value of 53.75% in behalf of a never-smoking male exposed at age 20 and diagnosed 20 years later at age 40, and a male exposed at age 40 and diagnosed at age 60, even though the baseline lung cancer risk may have changed dramatically.

To assess just how much the baseline lung cancer risk shifts with attained age, SC&A evaluated SEER cancer incidence data for lung/bronchus, shown herein as Exhibit 5. Exhibit 5 shows the following baseline age-specific lung cancer incidence values:

- Individual #1 (exposed age 20 and diagnosed age 40):
  baseline risk – 10/100,000 or 1×10^{-4}

- Individual #2 (exposed age 40 and diagnosed age 60):
  baseline risk – 208.4/100,000 or 2.084×10^{-3}

By means of these two baseline cancer risks and the common PC value of 53.75% derived by NIOSH-IREP, Equation 1 can be used to derive the absolute radiation cancer risk for Individuals #1 and #2:

- <u>Individual #1</u>

  $$PC = 53.75\% = 0.5375 = \frac{RadRisk}{RadRisk + BasRisk}$$
  $$RadRisk = 0.5375 \, (RadRisk + (1 \times 10^{-4}))$$
  $$RadRisk = 1.162 \times 10^{-4} \text{ lung cancer/50 cSv}$$

- <u>Individual #2</u>

  $$PC = 53.75\% = 0.5375 = \frac{RadRisk}{RadRisk + 2.084 x 10^{-3}}$$
  $$RadRisk = 2.422 \times 10^{-3} \text{ lung cancer/50 cSv}$$

The above-derived radiation lung cancer risk of 2.422×10^{-3}/50 cSv for the older Individual #2 is **20.8-fold higher** than the lung cancer risk of 1.162×10^{-4} /50 cSv for the younger Individual #1. In essence, this would imply that the **lung cancer risk per unit dose** for a male exposed at age 40 is 20.8 times higher than that of a 20-year old male.

Based on the steep rise in baseline cancer risk as a function of attained age shown in Exhibit 5, a common PC value, as derived by NIOSH-IREP, for these two individuals is counter intuitive and raises concerns about the validity of the NIOSH-IREP model that does not address the effects of age at exposure and/or attained age.

Exhibit 5:   SEER Incidence Data for Lung and Bronchus
Source: Table 15.9 Reproduced from NCI 2009

Table 15.9
Cancer of the Lung and Bronchus (Invasive)

SEER Incidence[a] and U.S. Death[b] Rates, Age-Adjusted and Age-Specific Rates, by Race and Sex

	All Races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
SEER Incidence									
Age at Diagnosis									
Age-Adjusted Rates, 2002-2006									
All ages	63.1	77.7	52.5	64.4	77.6	54.8	74.7	104.3	54.7
Under 65	20.5	23.1	18.2	20.4	22.2	18.7	30.3	39.4	22.9
65 and over	357.3	455.1	289.5	368.4	460.6	304.5	381.5	552.7	274.6
All ages (IARC world std)[c]	39.8	47.7	33.6	40.6	47.4	35.2	49.4	67.6	36.2
Age-Specific Rates, 2002-2006									
<1	-	-	-	-	-	-	-	-	-
1-4	-	-	-	-	-	-	-	-	-
5-9	-	-	-	-	-	-	-	-	-
10-14	-	-	-	-	-	-	-	-	-
15-19	0.1	-	0.1	0.1	-	-	-	-	-
20-24	0.3	0.3	0.3	0.3	0.3	0.4	-	-	-
25-29	0.6	0.6	0.6	0.6	0.5	0.7	0.6	-	-
30-34	1.2	1.1	1.3	1.1	1.0	1.2	1.5	1.6	1.3
35-39	3.4	3.2	3.6	3.3	3.0	3.6	3.9	3.7	4.0
40-44	10.4	10.0	10.9	10.1	9.5	10.8	16.0	16.3	15.7
45-49	25.5	26.3	24.7	24.6	24.6	24.7	42.9	50.0	36.7
50-54	50.6	56.7	44.8	48.6	53.1	44.2	85.2	105.9	67.6
55-59	97.2	111.3	83.9	96.2	106.0	86.7	146.9	202.7	100.5
60-64	178.8	208.4	151.7	182.6	206.6	160.1	235.7	322.8	166.5
65-69	278.4	329.3	234.3	288.6	332.6	249.6	327.5	452.8	232.3
70-74	374.4	455.7	309.0	388.6	461.8	328.6	398.3	558.2	286.0
75-79	434.5	556.2	347.3	449.2	564.6	365.5	451.0	643.6	331.9
80-84	413.4	554.5	324.8	422.6	560.3	336.3	422.0	645.2	299.1
85+	297.6	441.7	230.1	300.6	445.6	233.7	298.6	497.4	216.5

NIH-IREP. As previously described, the NIH-IREP lung model does take into consideration the **age at exposure** as well as **attained age**. However, due to the limited available epidemiologic data, these two variables received only **restricted** consideration as modifiers in the NIH-IREP lung model, as noted by the National Research Council in their recent BEIR VII Report (NAS 2006):

From page 299 of BEIR VII (NAS 2006):

> *The following general linear dose-response function was used to model the ERR or EAR:*
>
> $$ERR\ (D, s, e, a)\ or\ EAR\ (D, s, e, a) =$$
> $$\beta_s\ D\ exp\ [h(e, a)], \qquad\qquad (12B\text{-}4)$$
>
> *where D is dose in sieverts, β_M and β_F are sex-specific estimates of ERR/Sv, e is age at exposure in years, and a is attained age in years. The function h includes parameters to be estimated. Most commonly, h is of the form*
>
> $$h(e, a) = \gamma\ f(e) + \eta\ g(a). \qquad\qquad (12B\text{-}5)$$
>
> *As noted above, recent analyses by RERF investigators of A-bomb survivor solid cancer mortality (Preston and others 2003) and incidence data have taken f(e) = e and g(a) = log a; note that exp (η log a) = a^η. Others (Kellerer and Barclay 1992) have developed models with g(a) = a. Some post risk assessments (BEIR V) have taken h to be a function of sex, age at exposure, and time since exposure (t). Note that any two of the variables e, a, and t determine the third (t = a – e) so models based on e and t are included in the equation (12B-4) specification.*
>
> *In recent analyses conducted for the purpose of updating radioepidemiologic tables (**NIH 2003**), the NIH evaluated models of the form indicated above, but the ERR was allowed to **vary over only a limited range of exposure ages or attained ages**. . . .* [Emphasis added.]

Thus, the NIH-IREP model allowed the ERR values to vary with age at exposure only over the narrow age range of 15 to 30 years and the attained age of only up to 50 years.

Given the likelihood that a significant fraction of EEOICPA workers were exposed above the age of 30 years and attained ages well above 50 years, and the dramatic rise in baseline lung cancer incidence above the age of 50 years (see Exhibit 5), the NIH-IREP lung model is only able to partially address the critical impacts of age at exposure and attained age in the derivation of PC. For illustration, the **NIH-IREP** PC values of 52.94% for the aforementioned never smoker exposed at age 20 and the PC value of 28.79% for the never smoker exposed at age 40 (see Exhibit 1 above), the respective lung cancer radiation risks per 50 cSv of 1.11×10^{-4} and 8.42×10^{-4} still suggests that the exposed 40-year old is nearly 8 times higher at risk per unit dose than the 20 year old.

In the 2006 BEIR VII Report, the NAS Committee reviewed and evaluated a total of 17 cancer models that included the model used by NIH-IREP (see Table 12B-2, page 300 of BEIR VII, NAS 2006). The NAS, however, concluded that model #4 (i.e., the BEIR VII ERR model) provided the best fit of data. This model allows for the variation in the ERR with age at exposure only over the range of 0 to 30 years, but allows for variation in attained age over the **full range**. By means of the BEIR VII ERR model, the NAS Committee derived **lifetime cancer incidence risks in Table 12D-1 of the BEIR VII Report as a function of age at exposure** for a single dose of 0.1 Gy (i.e., 10 rads).

As a convenience to the reader, Table 12D-1 of the BEIR VII Report is reproduced herein as Exhibit 6. The BEIR VII model suggests a steady decline in the lifetime lung cancer risk as a function of age at exposure.

Exhibit 6:   Lifetime Attributable Risk of Cancer Incidence
Table 12D-1 Reproduced from BEIR VII (NAS 2006)

TABLE 12D-1 Lifetime Attributable Risk of Cancer Incidence[a]

Cancer Site	Age at Exposure (years)										
	0	5	10	15	20	30	40	50	60	70	80
Males											
Stomach	76	65	55	46	40	28	27	25	20	14	7
Colon	336	285	241	204	173	125	122	113	94	65	30
Liver	61	50	43	36	30	22	21	19	14	8	3
Lung	314	261	216	180	149	105	104	101	89	65	34
Prostate	93	80	67	57	48	35	35	33	26	14	5
Bladder	209	177	150	127	108	79	79	76	66	47	23
Other	1123	672	503	394	312	198	172	140	98	57	23
Thyroid	115	76	50	33	21	9	3	1	0.3	0.1	0.0
All solid	2326	1667	1325	1076	881	602	564	507	407	270	126
Leukemia	237	149	120	105	96	84	84	84	82	73	48
All cancers	2563	1816	1445	1182	977	686	648	591	489	343	174
Females											
Stomach	101	85	72	61	52	36	35	32	27	19	11
Colon	220	187	158	134	114	82	79	73	62	45	23
Liver	28	23	20	16	14	10	10	9	7	5	2
Lung	733	608	504	417	346	242	240	230	201	147	77
Breast	1171	914	712	553	429	253	141	70	31	12	4
Uterus	50	42	36	30	26	18	16	13	9	5	2
Ovary	104	87	73	60	50	34	31	25	18	11	5
Bladder	212	180	152	129	109	79	78	74	64	47	24
Other	1339	719	523	409	323	207	181	148	109	68	30
Thyroid	634	419	275	178	113	41	14	4	1	0.3	0.0
All solid	4592	3265	2525	1988	1575	1002	824	678	529	358	177
Leukemia	185	112	86	76	71	63	62	62	57	51	37
All cancers	4777	3377	2611	2064	1646	1065	886	740	586	409	214

NOTE: Number of cases per 100,000 persons exposed to a single dose of 0.1 Gy.

[a]These estimates are obtained as combined estimates based on relative and absolute risk transport and have been adjusted by a DDREF of 1.5, except for leukemia, which is based on a linear-quadratic model.

4.4   SUMMARY CONCLUSIONS

SC&A's comparative evaluation of outputs generated by the two IREP lung models suggests the following:

- NIOSH-IREP lung model generates excessively high PC values due to the model's failure to account for the age at exposure, as well as the attained age of the exposed individual at the time of cancer diagnosis. As shown in our example, it is inconceivable that an identical acute lung dose received at age 40 is more than 20 times as likely to induce a lung cancer as the same dose received at age 20. Our preliminary assessment suggests that NIOSH-IREP PC values derived in behalf of persons exposed above the age of 30 with attained ages above 50 are progressively and excessively too high.

- NIH-IREP lung model adjusts on a limited basis the effects of age at exposure and attained age. A potentially significant shortcoming of this model is that there is no further adjustment for attained age greater than age 50 years. As shown in Exhibit 5 above, there is an exponential rise in baseline lung cancers above the age of 50, which is not accounted for and is a likely contribution to PC values that are still excessive for claimants with attained age at time of cancer diagnosis greater than 50 years. (As noted above, the BEIR VII model does account for attained ages >50 years.)

SC&A's concern regarding the concurrent use of NIOSH-IREP and NIH-IREP as dictated by OCAS-PER-008 and their potential contribution to unrealistically high PCs/compensable lung cancers parallel concerns raised in the November 2010 draft report entitled, *Ten Year Review – Phase I Report Dose Reconstruction.*

In Topical Subsection 7, "Individual Dose Reconstruction Compensation Results Based on the Cancer Model Used" (Wade and Adams 2010), the authors of the draft report raised the following question:

> *One question that comes to mind when reviewing the data in Table 9, is whether or not this rank by compensation rate "**makes sense**."* [Emphasis added.]

Table 9, as referenced above, is reproduced herein as Exhibit 7. Exhibit 7 shows the following:

- At 3,438 claims, lung cancer (162) represented by far the highest number of total cancer claims.

- Of the 3,428 lung cancer claims, a total of 2,413 claims (or 70.2%) were compensated. The compensation rate of 70.2% stands in contrast with the collective compensation rate of 28.5 for all cancer claims.

Although NIOSH provided some compelling reasons that may have contributed to the differentially high compensation rate for lung cancer, the potential contribution of the IREP lung models and their inherent limitations were not mentioned.

SC&A concludes that further discussion by the Subcommittee on Procedures Review regarding the use of and appropriateness of both IREP lung models is warranted.

Exhibit 7:   Rank by Compensation Rate for Ten NIOSH-IREP Cancer Models
Table 9 Reproduced from Wade and Adam (2010)

Table 9: Rank by Compensation Rate for Ten NIOSH-IREP Cancer Models

Rank by Compensation Rate	NIOSH-IREP Cancer Model (ICD-9 Code)	Percent Compensated (PC greater than or equal to 50%)	Percent Not Compensated (PC less than 50%)	Number of Claims with this ICD-9 Code	Percent of Claims with this ICD-9 Code of the Total Number Of Claims
1	Lung (162)	70.2	29.8	3438	22.5
2	Chronic Myeloid Leukemia (205.1)	59.7	40.3	67	0.4
3	Non-melanoma Skin Basal Cell (173)	57.8	42.2	1108	7.3
4	Acute Lymphocytic Leukemia (204.0)	56.9	43.1	65	0.4
5	Liver (155.0)	48.2	51.8	112	0.7
6	Acute Myeloid Leukemia (205.0)	41.6	58.4	149	1.0
7	Malignant Melanoma (172)	38.8	61.2	405	2.7
8	Lymphoma & Multiple Myeloma(200-203)	38.1	61.9	1161	7.6
9	Leukemia, excl. CLL (204-208, excl 204.1)	35.4	64.6	99	0.6
10	Other respiratory (160,161,163-165)	34.9	65.1	436	2.9

5.0   SUBTASK 4: SELECTION CRITERIA FOR A SAMPLE SET OF DRS

Selection of a sample of DRs affected by OCAS-PER-008 for audit by SC&A may at this time be premature and may have to await potential discussion/resolution by the Subcommittee on Procedures Review regarding concerns raised by SC&A in Section 4.3 above.

On the assumption that the Subcommittee may dismiss SC&A's concerns and accept OCAS-PER-008 in its present state, the selection of DRs for audit is limited to the following eight claims identified in Table 2 of OCAS-PER-008 (and included herein in Exhibit 2): Claims #1, #2, #4, #5, #6, #8, #10, and #11).

Given the limited number of DRs that may require audit, one option may be to audit all eight claims. If the Subcommittee were to select only a subset of DRs, priority should be given to those DRs with the highest "Interim Claim PC" values, as given in Column 5 of Table 2 in Exhibit 2. Claims with the highest re-evaluated PC (but less than 50%) include Claim #5 (49.15%), Claim #6 (48.93%), and Claim #8 (47.44%).

Since all eight claims that may be selected for audit were originally DRs that represent an "overestimate" of lung (152) dose, our audit of these claims would entail a full-blown best-estimate assessment of assigned doses from all sources of external and internal lung doses.

6.0   REFERENCES

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