Department of Health and Human Services

Centers for Disease Control and Prevention

National Institute for Occupational Safety and Health

Report to the Senate Appropriations Committee on

The Radiogenicity of Specific Cancers

Under the Energy Employees Occupational Illness

Compensation Program Act of 2000 as Amended

[Signature on file]

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December 2009

SUMMARY

In response to Senate Report (S. Rep.) 109-103 (2005), the National Institute for Occupational Safety and Health (NIOSH) examined the evidence for the radiogenicity[1] of 11 "non-presumptive cancers," which were not included in the list of 22 "specified cancers" referenced in the Energy Employees Occupational Illness Compensation Program Act of 2000 as Amended (EEOICPA)[2]. NIOSH issued an interim report on this topic in June, 2007. The interim has now been finalized, following the release of a major review of the radiogenicity of specific cancers by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Two of the other reviews NIOSH relied upon as primary references have also been updated since the issuance of NIOSH's interim report. None of the updates reviewed resulted in a change in the recommendations that NIOSH presented in the 2007 interim report. That is, NIOSH still finds consistent evidence to support the radiogenicity of basal cell carcinoma. As requested in Senate Report 109-103, this report enumerates the cases of basal cell carcinoma among classes of employees included in the Special Exposure Cohort (SEC). This final NIOSH report reflects the conclusions in these new and updated reviews.

RADIOGENICITY OF SPECIFIC CANCERS

Comprehensive reviews of the radiogenicity of various specific cancers appeared in the peer-reviewed scientific literature in the mid- and late 1990s, some of which have recently been updated (Boice et al. 2006, Mettler and Upton 2008, Ron 1998). The most extensive recent examination of this topic was published by UNSCEAR (2006). Because these four reviews reflect the weight of the available scientific evidence, they are less prone than individual epidemiologic studies to observe chance associations between radiation exposure and the development of cancer.

The current classification under EEOICPA for site-specific cancers is provided in Table 1. The table presents cancers in specific organs individually, including those that are grouped in the NIOSH Interactive Radioepidemiology Program (NIOSH-IREP) as "other respiratory," "other endocrine," and "other and ill defined sites."

Table 2 summarizes the primary conclusions of the four comprehensive reviews regarding the radiogenicity of each current non-presumptive site-specific cancer listed in Table 1. The four reviews differed in the list of cancers explicitly considered. To the extent that specific cancers were discussed, the authors were similar in concluding that little or no evidence of radiogenicity exists for chronic lymphocytic leukemia (CLL) and cancers of the connective tissue, larynx, lymphoma (Hodgkin's), male genitalia, oral cavity, prostate, and uterus.

[1] Radiogenicity refers to the causation of cancer in a given organ by exposure of that organ to ionizing radiation.

[2] The Department of Labor treats colon and rectal cancer as one type of cancer for purposes of EEOICPA, based on a National Cancer Institute advisory.

The scientific evidence for skin cancer is more complicated, depending on the specific type of skin cancer. UNSCEAR (2006) recognized a strong relationship between radiation exposure and basal cell carcinoma, but reported little evidence of an association for squamous cell carcinoma or malignant melanoma.

In a study focused on the Japanese atomic bomb survivors, Ron et al. (1998) reached conclusions similar to those of UNSCEAR. In this study, there was a pronounced decrease in the excess relative risk (ERR) per Sievert (ERR/Sv) for BCC as age increased; however, the risk remained significant at the 90% confidence interval for those who were exposed up to 39 years of age.

Shore (2001) also examined the evidence of an association between skin cancer and ionizing radiation exposure, and his conclusions are consistent with those of Ron et al. (1998) and UNSCEAR (2006). In addition to the Japanese life span study, Shore reviewed other studies that provide evidence that BCC is related to exposure to ionizing radiation. These include evaluations of radiologists, uranium miners, and patients exposed during medical treatments. Shore (2001) concludes that:

The principal epidemiological studies of ionizing radiation and skin cancer have all shown that radiation causes basal cell carcinoma but have not found dose-related excesses of squamous cell carcinoma or malignant melanoma.

A summary of the findings of the studies reviewed by Shore is provided in Table 3.

In contrast to these findings, a recent review argued for an association between radiation exposure and malignant melanoma (Fink and Bates 2005). This review employed meta-analytical techniques to examine melanoma risks relative to leukemia risks in populations that may have been exposed to ionizing radiation. The report concluded that:
People exposed to ionizing radiation may be at increased risk of developing melanoma, although alternative explanations are possible. Future epidemiological studies of ionizing radiation effects should include melanoma as an outcome of interest.

Both Mettler and Upton (2008) and Boice et al. (2006) discussed skin cancer as a single entity, with the former indicating that a number of studies show an association with radiation, and the latter concluding that skin cancer is rarely associated with radiation and effects may be limited to high doses. Ron (1998) also considered skin cancers as a group and concluded that associations have been reported but are not well quantified.

More recently, the United States National Academy of Sciences published *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2* (National Research Council 2006), which does not explicitly discuss the evidence of radiogenicity for specific cancers, but notes that nonmelanoma skin cancer has been linked clearly with radiation exposure in atomic bomb survivor data.

Taken together, NIOSH finds consistent evidence to support the radiogenicity of basal cell carcinoma, but not malignant melanoma. As previously noted, the evidence of radiogenicity of

basal cell carcinoma is much stronger for exposures received at young ages, particularly during childhood. The strength of the association declines with age, becoming statistically insignificant among most populations exposed at older ages (UNSCEAR 2006). Additionally, it is recognized that a primary cause of basal cell carcinoma is exposure to ultraviolet radiation in sunlight (UNSCEAR 2006). The nature and magnitude of the interaction between ultraviolet and ionizing radiation exposure are unknown at this time (Shore 2001, UNSCEAR 2006).

CONCLUSION

Review of the evidence of radiogenicity of specific cancers indicates that there is strong epidemiologic evidence for the radiogenicity of basal cell carcinoma and insufficient evidence for larynx, CLL, lymphoma (Hodgkin's), male genitalia, oral cavity, prostate, skin (squamous cell), uterus, and malignant melanoma.

ACKNOWLEDGEMENT: The NIOSH Office of Compensation Analysis and Support expresses its appreciation for the constructive external peer review of a draft of this report provided by: Drs. Randy Brill, Richard Hornung, Fred Mettler, Richard Wakeford, and Steve Wing. The conclusions in this report, however, are those of NIOSH.

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Table 1: Current presumption status of specific cancers under EEOICPA[a]

Cancer Site	Presumption Status
Bile ducts	Presumptive
Bone	Presumptive
Brain	Presumptive
Breast	Presumptive
Colon/rectum[b]	Presumptive
Connective tissue	Non-presumptive
Esophagus	Presumptive
Gall bladder	Presumptive
Kidney	Presumptive
Larynx	Non-presumptive
Leukemia (exc. CLL)	Presumptive
Liver	Presumptive[c]
Lung	Presumptive
Lymphoma (NHL)	Presumptive
Lymphoma (Hodgkin's)	Non-presumptive
Male genitalia	Non-presumptive
Multiple myeloma	Presumptive
Oral cavity	Non-presumptive
Ovary	Presumptive
Pancreas	Presumptive
Pharynx	Presumptive
Prostate	Non-presumptive
Salivary gland	Presumptive
Skin – BCC	Non-presumptive
Skin – SCC	Non-presumptive
Skin – melanoma	Non-presumptive
Small intestine	Presumptive
Stomach	Presumptive
Thyroid	Presumptive
Urinary bladder	Presumptive
Uterus	Non-presumptive

CLL = chronic lymphocytic leukemia
NHL = non-Hodgkin's lymphoma
BCC = basal cell carcinoma
SCC = squamous cell carcinoma

a: To qualify as presumptive under the SEC, most cancers require a minimum time period of 5 years between first exposure to radiation and cancer diagnosis. The exceptions are bone, lung, and kidney cancer (no minimum) and leukemia (minimum = 2 years).

b: The Department of Labor's Employment Standards Administration (ESA) noted that the National Cancer Institute considers rectal cancer to be the same as colon cancer based on tissue similarity, and thus groups the two together as colon/rectal cancer. Therefore rectal cancer is considered to be the same cancer as colon cancer for ESA purposes, and is treated as a specified cancer for EEOICPA purposes.

c: Liver cancer is considered presumptive except when cirrhosis or hepatitis B is indicated.

Table 2: Evaluation of radiogenicity of currently nonpresumptive cancers in comprehensive reviews

	(Mettler and Upton 2008)	(Boice et al. 2006)	(Ron 1998)	(UNSCEAR 2006)
Connective tissue	"The epidemiologic data show convincing excesses of bone p6680 and connective tissue tumors after radiation therapy and after internal contamination with large amounts of alphaemitting radionuclides. There remains an argument as to whether a practical threshold exists relative to the alpha emitters. There has been no clear excess demonstrated as a result of external occupational exposure or at low activities of internal radionuclides. There is no statistically significant excess identified in the atomic bomb survivors. Most authoritative reports give risk estimates for bone cancer although usually not at low doses."	Rarely associated with radiation with no reliable risk estimates available. Effect may be limited to high doses.	NA	(considered together with bone cancers) As in the UNSCEAR Report, studies of patients treated for childhood cancer demonstrate an increasing risk of bone and soft tissue sarcomas with dose over a range of several tens of grays (low-LET). These studies are not informative about risks at doses below a few grays…Studies of persons receiving high-LET radiation, in particular ^{226}Ra, ^{228}Ra, and ^{224}Ra, strongly suggest an exposure-related increased risk of bone tumours.
Larynx	"The oral cavity, pharynx, and larynx are generally regarded as tissues of low risk in radiation carcinogenesis.".	NA	NA	NA
Lymphoma (Hodgkin's)	"With the exception of what are thought to be statistical chance associations radiation has not been associated with the development of Hodgkin's disease".	Hodgkin's never or sporadically associated with radiation with no risk estimate. Little evidence.	"…rarely related to radiation exposure".	"There continues to be no clear indication of an excess risk of Hodgkin's disease associated with radiation exposure, but the data are very sparse, and most of the data sets lack dose-response analyses".
Male genitalia	"The epidemiologic literature shows no causal association between male	Never or sporadically associated with radiation	"…rarely related to radiation exposure". (testes)	NA

	(Mettler and Upton 2008)	(Boice et al. 2006)	(Ron 1998)	(UNSCEAR 2006)
	genital cancer and radiation exposure".	with no risk estimates. Little or no evidence.		
Oral cavity	"Epidemiologic studies show no consistent or statistically significant increase in cancer of the oral cavity or pharynx following internal or external radiation exposure".	NA	NA	NA
Prostate	"A large number of epidemiologic studies have looked for an increased risk of prostate cancer after radiation exposure. At the present time there is no clear evidence that prostate cancer is induced by radiation".	Never or sporadically associated with radiation with no risk estimates. Little evidence.	"…rarely related to radiation exposure".	"There is little indication of effects due to radiation exposure on prostate cancer risks".
Skin - BCC	"A number of studies indicate an association between skin cancer and radiation".	Rarely associated with radiation with uncertain risk estimates. Effect may be limited to high doses (or UV necessary).	"Associations between radiation and cancer…have been reported, but the relationships are not as well quantified".	"…there is strong evidence that NMSC [non-melanoma skin cancer] and specifically BCC, is inducible by ionizing radiation, with the RR [relative risk] strongly decreasing with increasing age at exposure".
Skin – SCC, malignant melanoma	"A number of studies indicate an association between skin cancer and radiation". "There is little or no consistent scientific evidence that malignant melanomas are induced by radiation".	Rarely associated with radiation with uncertain risk estimates. Effect may be limited to high doses (or UV necessary).	"Associations between radiation and cancer…have been reported, but the relationships are not as well quantified".	"To date there has been little indication of an association between ionizing radiation and SCC [squamous-cell carcinoma], but the data are sparse". "…there remains only weak evidence that cutaneous melanoma is inducible by ionizing radiation"
Uterus	"The epidemiologic literature does not support radiation induction of uterine neoplasms. While there are a few anecdotal case	Rarely associated with radiation with uncertain risk estimates. Effect may be limited to high doses.	"…rarely related to radiation exposure". (cervix)	"Available evidence indicates that there is no strong ionizing radiation dose response for uterine

	(Mettler and Upton 2008)	(Boice et al. 2006)	(Ron 1998)	(UNSCEAR 2006)
	reports in the literature, these should not be taken to prove a causal relationship. In fact, the epidemiologic literature, which is vastly stronger, cannot identify a relationship.”.			cancer. An absence of association between cervical cancer risks and radiation exposures is a consistent finding, including exposures at very high doses. The evidence is not quite so universally negative for cancer of the uterine corpus but suggests that, if there is any effect, it is largely confined to the region of very high doses.”

NA = this cancer was not explicitly considered
BCC = basal cell carcinoma
SCC = squamous cell carcinoma

Table 3: Studies of Ionizing Radiation and Skin Cancer Risk (from Shore 2001)

Study	Relative Risk (at 1 Gray or Sievert)	95% Confidence Interval
Japanese atomic bomb	2.8	1.8-4.3
Israel tinea capitas	1.7	1.3-2.4
New York tinea capitas X-ray	1.6	1.3-2.0
Enlarged thymus X-ray	2.1	1.4-3.0
Lymphoid tissue X-ray	1.2	1.1-1.7
Enlarged tonsils X-ray	1.1	1.0-1.2
Uranium miners	2.1	1.7-2.7
TB fluorospcopy	1.0	<1-1.0
Postpartum mastitis X-ray	1.1	<1-1.4

Table 4: Number of basal cell carcinoma claims at each currently-designated SEC site (as of March 18, 2009)

SEC[3] Site (and time period covered by the approved SEC class)	Number of claims with basal cell carcinoma as a listed cancer
Allied Chemical (1/1/59-12/31/76)	16
Amchitka Island Nuclear Explosion Site (before 1/1/1974)	35
Ames Laboratory (1/1/42-12/31/70)	9
General Atomics (1/1/60-12/31/69)	3
Hanford (10/43-1968)	343
Harshaw Chemical (8/14/42-11/30/49)	1
Horizons, Inc. (1952-1956)	1
Iowa Ordnance Plant (3/1949-12/1974)	58
Kellex/Pierpont (1943-1953)	1
Lawrence Livermore National Laboratory (1950-1973)	23
Linde Ceramics Plant (10/1/1942 – 10/31/1947)	5
Los Alamos National Laboratory (9/1/44-7/18/63)	51
Los Alamos National Laboratory (3/15/43-1975)	81
Mallinckrodt Chemical Works, Destrehan Street Facility (1942-1957)	25
Metallurgical Laboratory (8/13/1942-6/1946)	3
Monsanto (1/1/43-12/31/49)	3
Mound Laboratory (10/49-2/59)	4
Nevada Test Site (1/27/51-12/31/62)	78
NUMEC Apollo (1957-1983)	30
NUMEC Parks Township (1960-1980)	10
Oak Ridge Gaseous Diffusion Plant (K-25 Site) (before 2/1/1992)	479
Oak Ridge Institute for Science Education (5/15/50-12/31/63)	3
Oak Ridge S-50 Thermal Diffusion Plant (7/9/44-12/31/51)	5
Pacific Proving Ground (1946-1962)	25
Paducah Gaseous Diffusion Plant (before 2/1/1992)	547
Portsmouth Gaseous Diffusion Plant (before 2/1/1992)	317
Rocky Flats (4/1952-1966)	31
SAM Laboratories (8/13/1942-1947)	3
WR Grace (1958-1970)	6
Y-12 Plant (3/1943-12/31/1957)	290

[3] Special Exposure Cohort