**Localized Irradiation of the Skin: Estimation of Dose, Excess Cancer Risk, and Probability of Causation/Assigned Share of Skin Cancer**

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A recent report by Mauro and Behling (2013) raised concerns about use of the Interactive RadioEpidemiological Program (IREP) to estimate the probability of causation/assigned share (PC/AS) of diagnosed skin cancers when irradiation of the skin is localized. Such a scenario would occur, for example, when the dose to skin is due to deposition of radioactive particles on the hands, face, or neck. Mauro and Behling (2013) also raised concerns about methods used by the National Institute for Occupational Safety and Health (NIOSH) to estimate the dose to skin due to localized deposition of radioactive particles on the body surface.

The purpose of this report is twofold. First, we discuss the use of IREP to estimate PC/AS of diagnosed skin cancers when irradiation of the skin is localized. Second, we discuss the approach used by NIOSH to estimate the dose to skin and its uncertainty in cases of localized deposition of radioactive particles on the body surface (ORAUT, 2005).

### 1. Use of IREP to Estimate PC/AS in Cases of Localized Irradiation of Skin

PC/AS of a diagnosed cancer in an individual due to exposure to ionizing radiation is defined as:

$$PC/AS = EAR/(EAR + B) ,$$

where EAR is the excess absolute risk (probability) of the cancer type of concern due only to that individual's radiation exposure and B is the baseline risk (probability) of that cancer due to all other causes. This is the representation of PC/AS discussed by Mauro and Behling (2013).

In IREP, PC/AS of a diagnosed cancer in an exposed individual is calculated on the basis of an estimate of the excess relative risk (ERR) due to radiation, rather than EAR (Land et al., 2003; Kocher et al., 2008). ERR, which is not a probability, is defined as RR – 1, where RR is the relative risk (i.e., the total risk of the cancer type of concern in an exposed individual relative to the baseline risk) given by (EAR + B)/B. The relationship between ERR and EAR then is

$$ERR = EAR/B ,$$

and PC/AS is calculated in IREP as

$$PC/AS = ERR/(ERR + 1) .$$

In IREP, ERR for skin cancer (and many other cancer types) is assumed to be a linear function of dose and is estimated as the product of a risk coefficient (ERR per Sv), denoted by ERR/Sv, and the dose to skin (Sv). The assumed risk coefficients for skin cancer as a function of an individual's age at the time of exposure and attained age (age at diagnosis) are based on data in Japanese atomic-bomb survivors, who received uniform exposures of the whole body.

The basic issue with using IREP to calculate PC/AS of a diagnosed skin cancer when irradiation of the skin is localized that was raised in Section 6.0 of the report by Mauro and Behling (2013) can be stated as follows:

> Given that estimates of ERR/Sv for skin cancer in IREP are based on estimates of excess risks of skin cancer, regardless of their location on the body surface, due to uniform exposure of the whole body and estimates of baseline risks of skin cancer, also regardless of location, can those risk coefficients be used to calculated PC/AS when irradiation of the skin is localized? Or, is some adjustment of the ERR/Sv for skin cancer in IREP required to give a proper estimate of PC/AS in cases of localized irradiation?

The following argument suggests that estimates of ERR/Sv for skin cancer in IREP can be used to estimate PC/AS in cases of localized irradiation of the skin or, more generally, in cases of non-uniform irradiation. If the area of the skin in which a localized irradiation occurs is a fraction $f_{skin}$ of the total area of the skin, estimates of EAR and B for skin cancers at all locations, which are used to estimate ERR/Sv for skin cancer in IREP, can be reduced by the fraction $f_{skin}$ to give estimates appropriate to the location of interest; i.e., in cases of localized irradiation, $EAR_{local} = f_{skin} \times EAR$ and $B_{local} = f_{skin} \times B$. From these relationships, it follows that $ERR_{loc} = EAR_{loc}/B_{loc} = EAR/B$ is independent of $f_{skin}$ and, therefore, estimates of ERR/Sv in IREP can be applied to any localized or non-uniform irradiation of the skin.

This conclusion comes with a potentially important caveat. An assumption that estimates of ERR/Sv for skin cancer in IREP can be used to estimate PC/AS of a diagnosed skin cancer for any localized or non-uniform irradiations of the skin is strictly correct only if either of the following two conditions is met: (1) EAR and B are uniform over the body surface; or (2) EAR and B vary with location in the same way, i.e., the ratio of EAR to B is the same at all locations. In either case, ERR = EAR/B would be the same at any location.

It is doubtful, however, that either condition described above is met. The first condition (EAR and B are uniform over the body surface) clearly is not met in Caucasians for whom baseline rates of skin cancer on the face, head, and neck, which comprise a small fraction of the total area of the body surface, are much higher than baseline rates in all other regions combined (Scotto et al., 1996). The non-uniformity of baseline rates of skin cancer over the body surface in Caucasians is due to the primary importance of ultraviolet (UV) radiation in causing skin cancer and the effect of clothing in shielding much of the body surface from UV radiation.

In regard to the second condition (EAR and B are not uniform over the body surface but EAR/B is independent of location), unless there is a strong multiplicative interaction between ionizing and UV radiation in causing skin cancer (i.e., EAR due to radiation is roughly proportional to B), the distribution of EAR for skin cancer over the body surface presumably

would be more uniform than the distribution of B, in which case ERR = EAR/B would be lower in skin of the face, head, or neck than elsewhere.  This difference would be substantial if, for example, EAR due to radiation were approximately uniform over the body surface.

The relationship between excess risks of skin cancer due to radiation and baseline risks in different regions of the body in Japanese atomic-bomb survivors was investigated by Ron et al. (1998); see also Kishikawa et al. (2005) and Preston et al. (2007).  For non-melanoma skin cancers including basal cell carcinomas (BCCs), which are the most common in Caucasians (Scotto et al., 1996), EARs in atomic-bomb survivors were rather similar in UV-exposed and UV-shielded regions and, thus, ERRs were significantly higher in shielded regions.

Current data on induction of non-melanoma skin cancers in Japanese atomic-bomb survivors appear to be inadequate to investigate in detail the relationship between EAR due to radiation and the baseline risk in different regions of the body surface.  Given that the estimated number of excess non-melanoma skin cancers in Japanese atomic-bomb survivors is only about 12% of the total number of cases (Preston et al., 2007), we believe that it would be difficult to evaluate the dependence of EAR on location on the body surface with a meaningful degree of confidence, even if the locations of all such skin cancers in exposed and unexposed groups of survivors were known.

Given the difficulties in estimating the relationship between EAR and B for skin cancers over the body surface, we believe that the only reasonable option at the present time is to assume that ERR = EAR/B does not vary substantially over the body surface and can be used to estimate PC/AS of skin cancer in cases of localized or non-uniform irradiation of the skin.  To the extent that EAR is independent of B (i.e., the interaction between ionizing and UV radiation in causing skin cancer is additive), as suggested in studies of atomic-bomb survivors, this assumption should result in overestimates of ERR = EAR/B and PC/AS in regions, such as the hands, face, or neck, that usually are not covered by clothing and where baseline risks are the highest.  These are the regions where localized irradiation due to deposition of radioactive particles on the body surface is most likely to occur.  Therefore, although estimates of ERR/Sv for skin cancer in IREP are not biased (i.e., they are based on estimates of EAR for uniform whole-body exposure and B for all skin cancers regardless of location), we believe that use of IREP to calculate PC/AS for skin cancer in cases of localized irradiation of the hands, face, or neck as prescribed by NIOSH (ORAUT, 2005) is claimant-favorable.

We caution, however, that use of estimates of ERR/Sv for skin cancer in IREP to calculate PC/AS in cases of localized irradiation of skin in regions of the body surface that usually are covered by clothing probably is not claimant-favorable.  This situation would occur, for example, when radioactive particles are deposited and retained on clothing.  If, as indicated in studies of atomic-bomb survivors, EAR due to radiation is more uniform over the body surface than the baseline risk, ERR/Sv in regions of the body surface that normally are covered should be greater than estimates in IREP and, therefore, PC/AS of diagnosed skin cancers in those regions should be underestimated.  We also note, however, that doses to skin from contamination of clothing should be less than doses from the same level of contamination on bare skin, due to

such factors as the frequent changing and washing of clothing and the shielding effect of clothing in reducing dose rates from beta particles.[1]

## 2. Estimation of Dose in Cases of Localized Irradiation of Skin

The approaches used by NIOSH to estimate radiation doses to skin in cases of localized deposition of radioactive particles on the body surface or other partial-body irradiations are described in Section 3.0 of ORAUT (2005). Three different scenarios are considered:

- it is known that a diagnosed skin cancer occurred within an area of contamination or partial-body irradiation;
- it is known that a diagnosed skin cancer did not occur within an area of contamination or partial-body irradiation;
- it is not known whether or not a diagnosed skin cancer occurred within an area of contamination or partial-body irradiation.

The approaches to estimating doses to skin in the first two scenarios are straightforward. In the first, the dose to skin at the location of a skin cancer is calculated as prescribed by NIOSH and entered into IREP, without adjusting for the area of the skin of interest relative to the total area of the skin over the entire body. As described in the previous section, estimates of ERR/Sv in IREP are considered appropriate for use in estimating PC/AS in such cases and should be claimant-favorable when the area of contamination or partial-body irradiation usually is not covered by clothing. In the second scenario, the assigned dose in the area where a diagnosed skin cancer occurred due to contamination or partial-body irradiation in another area is zero.[2]

The third scenario is more challenging, because the "true" dose is either the dose within the area of contamination or partial-body irradiation or it is zero (or a lower dose due, for example, to an additional uniform whole-body exposure), but it is not known which of the two doses is correct. In such cases, an estimate that best represents the state of knowledge of the true but unknown dose is the dose to skin averaged over the whole body. The "correct" representation of this average dose is a binomial probability distribution with a weight $f_{skin}$ given to the dose $D_{local}$, where $D_{local}$ is the dose to skin in the irradiated region and $f_{skin}$ again is the fraction of the total area of the skin in that region, and a weight $(1 - f_{skin})$ given to the dose in all other regions, $D_{other}$. The mean of this distribution is a dose of $f_{skin}D_{local} + (1 - f_{skin})D_{other}$.

A binomial probability distribution to represent an uncertain dose cannot be entered into IREP at the present time.[3] The approach used by NIOSH is to assume an equivalent lognormal

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[1] Irradiation of the basal layer of the skin due to deposition of alpha-emitting radionuclides on the body surface also could be important, depending on the thickness of the epidermis in the contaminated area and the energies of alpha particles. Models and data that can be used to estimate dose to skin due to deposition of alpha-emitting radionuclides on the body surface are discussed in Section 4.1.5 of NCRP Report No. 163 (NCRP, 2009).

[2] The assigned dose of zero assumes that a radiation-induced skin cancer can occur only in areas that are irradiated, i.e., that abscopal effects do not occur.

[3] IREP could be modified to accept a binomial probability distribution of dose or any other distribution that would better represent the state of knowledge of an uncertain dose than currently available options.

probability distribution of the dose (ORAUT, 2005). The mean of the binomial probability distribution calculated as indicated above is assumed to be the median (50th percentile) of a lognormal probability distribution. The geometric standard deviation (GSD) of that distribution is defined such that the $100(1 - f_{skin})$-th percentile is approximately at the dose $D_{local}$; i.e., the probability that the dose is $D_{local}$ or greater is assumed to be approximately $f_{skin}$.

For example, if we assume, as in a case discussed by Mauro and Behling (2013), that (1) the dose to skin on the head, face, and hands is 16 mrem, (2) the skin in those regions comprises 14% of the total area of the skin, and (3) the dose in other regions is zero, the *mean* dose to the skin is (0.14)(16 mrem) = 2.2 mrem, and this dose is assumed to be the *median* of a lognormal probability distribution. The GSD then is defined by setting the dose of 16 mrem at the 86th percentile of the lognormal distribution, which gives a GSD of 6.3.

Rather than estimate the GSD of an assumed lognormal probability distribution of the dose for each case on the basis of the appropriate fraction of the total area of the skin that is irradiated, NIOSH simplifies the method by defining ranges of the ratio of the non-irradiated (other) area of the skin to the irradiated (localized) area [the ratio $(1 - f_{skin})/f_{skin}$] over which the GSD is assigned integer values that approximate the condition described above (ORAUT, 2005). For example, if the ratio of the non-irradiated area of the skin to the irradiated area is in the range of 1 to 10, a GSD of 6 is assumed, and if that ratio is in the range of 10 to 100, a GSD of 8 is assumed. We verified by example calculations that the integer values of the GSD assigned by NIOSH for defined ranges of the ratio $(1 - f_{skin})/f_{skin}$ are approximately equal to or greater than the GSD that would be calculated by setting the $100(1 - f_{skin})$-th percentile of the assumed lognormal probability distribution at approximately the dose $D_{local}$.[4]

In agreement with a conclusion in the ORAUT (2005) report, we believe that the lognormal probability distributions of dose used by NIOSH when the location of a skin cancer in relation to the area of a localized irradiation is not known are claimant-favorable; i.e., they are more likely than not to result in overestimates of PC/AS of diagnosed skin cancers. One source of conservatism in the lognormal probability distributions of dose used by NIOSH is that the mean dose, which is the expectation value, is always greater than the median; i.e., the mean of an assumed lognormal probability distribution of dose is always greater than the mean of the "correct" binomial distribution.

A second source of conservatism is a result of the assumption used by NIOSH to define the GSD of the equivalent lognormal probability distribution of dose. In the example discussed by Mauro and Behling (2013) and described above, the probability distribution used by NIOSH assumes that there is a probability of about 14% that the dose to skin in the irradiated region is greater than 16 mrem. In that case, for which NIOSH assumes a GSD of 6, the upper tail of the

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[4] In the example discussed by Mauro and Behling (2013) and described above, in which the irradiated area comprises 14% of the total area of the skin, the calculated GSD of 6.3 is slightly greater than the integer value of 6 assigned by NIOSH. However, we do not believe that the difference between the two GSDs is significant, given that there is uncertainty in the fraction of the total area of the skin that is irradiated ($f_{skin}$) and the dose to skin in that region ($D_{local}$). When the ratio $(1 - f_{skin})/f_{skin}$ is 10 or higher, we found that the integer value of the GSD assigned by NIOSH is always greater than the value that would be calculated using that ratio.

assumed lognormal probability distribution extends well above 16 mrem; e.g., the 95th percentile is about 40 mrem. This assumption clearly is conservative if the estimated dose of 16 mrem in the irradiated region is accurate, and it would result in an increase in the 99th percentile of the probability distribution of PC/AS used in adjudicating claims for compensation.

In general, the degree of conservatism in the mean dose using the NIOSH approach (i.e., the ratio of the mean of an assumed lognormal probability distribution to the "true" mean of a "correct" binomial probability distribution when the latter is assigned as the median of the lognormal distribution) increases as the assumed GSD of the lognormal distribution (i.e., the ratio of the non-irradiated area to the irradiated area) increases. However, the degree of conservatism embodied in the upper tail of the assumed lognormal probability distribution (i.e., the fraction of the probability distribution that extends beyond the dose $D_{local}$) decreases as the assumed GSD increases (i.e., as the irradiated area decreases).

On the basis of these considerations, we conclude that the approach used by NIOSH to estimate the dose to skin and its uncertainty when it is not known whether or not a diagnosed skin cancer occurred within an area of contamination or partial-body irradiation is reasonable and is unlikely to result in underestimates of PC/AS at the 99th percentile.

### 3.  Conclusions

Discussions in this report have led to two conclusions, which are summarized as follows.

- The assumption by NIOSH that estimates of ERR/Sv for skin cancer in IREP can be used to calculate PC/AS of diagnosed skin cancers in cases of localized irradiation of skin on the hands, face, or neck (ORAUT, 2005) should be claimant-favorable.

This conclusion is based on two considerations: (1) estimates of ERR/Sv for skin cancer in IREP are based on data on excess risks due to uniform whole-body exposure and baseline risks regardless of location; and (2) data in atomic-bomb survivors indicate that EAR for skin cancer due to radiation is more uniform over the whole body than the baseline risk, which is due primarily to exposure to UV radiation in areas of the skin that normally are uncovered. Consequently, ERR = EAR/B in regions of the body surface that normally are uncovered should be less than estimates obtained using IREP, and PC/AS should not be underestimated.

We caution, however, that the conclusion stated above probably is not valid when a diagnosed skin cancer occurs in a region of the body surface that normally is covered by clothing. In such cases, ERR = EAR/B should be greater than estimates obtained using IREP, and PC/AS should be underestimated.

- In cases of localized deposition of radioactive particles on the body surface or other partial-body irradiations, the approach used by NIOSH to estimate the median dose to skin and its uncertainty when it is not known whether or not a diagnosed skin cancer occurred within the irradiated area should be claimant-favorable.

This conclusion is based on three considerations: (1) the "true" mean dose to skin should be overestimated; (2) the extent to which the dose to skin in an irradiated area could be exceeded should be overestimated; and (3) the assigned integer values of the GSD of an assumed lognormal probability distribution should be approximately equal to or greater than values that would be calculated by assuming that the $100(1 - f_{skin})$-th percentile of the distribution is approximately at the dose in the irradiated area.

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