Carcinogenicity of EBDCs

In 1997 we published an article in *EHP* on cytogenetic and thyroid hormonal changes in 49 heavily exposed workers applying ethylene bisdithiocarbamate (EBDC) fungicide to tomatoes, based on a collaborative study done by the U.S. National Institute for Occupational Safety and Health and the Institute of Public Health in Mexico (Steenland et al. 1997). EBDCs are a common class of fungicides (e.g., mancozeb, maneb) that are metabolized to ethylene thiourea (ETU) in workers after primarily dermal absorption. In experiments in rats, ETU caused decreased thyroid hormone [thyroxine (T_4)], increased thyroid-stimulating hormone (TSH), and thyroid tumors. We sought to determine whether workers exposed to ETU showed thyroid hormone changes compared to a nonexposed comparison group ($n = 31$). We also looked at sister chromatid exchange (SCE) and chromosomal translocations (balanced chromosomal aberrations that are not cell lethal) in the lymphocytes of exposed workers and nonexposed controls.

In this study (Steenland et al. 1997), we found a mean urinary ETU level in the exposed applicators of 58 ppb, although 34% had levels below the limit of detection (most ETU is excreted within 24 hr). All 31 nonexposed controls had levels below the limit of detection. We found a significant increase in TSH ($p = 0.05$) in applicators versus nonexposed controls, suggesting that increased TSH compensated for a thyroid hormone decrease (altered homeostasis). We also found increased SCEs ($p = 0.03$) and chromosomal translocations ($p = 0.05$) in the applicators versus the nonexposed population, suggesting cytogenetic damage due to ETU.

Subsequently, in 2001 the International Agency for Research on Cancer (IARC) downgraded ETU from group 2B (possibly carcinogenic to humans) to group 3 (not classifiable as to carcinogenicity in humans) (IARC 2001). Although IARC recognized that ETU was carcinogenic in animals, it judged that the mechanism by which cancer occurred in animals was not relevant to humans. Specifically, IARC (2001) stated that cancer occurred via a

> … nongenotoxic mechanism, which involves interference with the functioning of thyroid peroxidase resulting in a reduction of circulating thyroid hormone concentrations and increased secretion of thyroid-stimulating hormone. Consequently, ETU would not be expected to produce thyroid cancer in humans exposed to concentrations that do not alter thyroid hormone homeostasis.

The use of mechanisms as a basis for classifying or reclassifying agents as carcinogens has been controversial, sometime leading to upward classifications (ethylene oxide and TCDD), but more often to downward ones (e.g., ETU, atrazine, phthalates, saccharin) (Tomatis 2002).

The IARC ETU working group (IARC 2001) cited our article (Steenland et al. 1997) as indicating cytogenetic damage in workers "presumably" exposed to ETU (apparently discounting the urinary evidence). With regard to our findings of increased TSH, indicative of altered thyroid hormone homeostasis in ETU-exposed workers, they noted that the workers had a "marginal increase in the serum concentration of TSH but no change in that of thyroxine (T_4)." As noted above, the "marginal" increase was statistically significant, albeit not clinically important (and normal T_4 due to increased TSH might be expected). The working group chose to ignore this evidence of altered homeostasis (IARC 2001).

It seems surprising that the IARC working group downgraded ETU based on a lack of evidence that ETU alters thyroid homeostasis in humans, while the only study that has looked at this question in humans did indeed find such evidence.

I would like to bring this apparent discrepancy to the attention of the environmental health community and to sound a cautionary note regarding the possible human carcinogencity of EBDC fungicides, which are used extensively throughout the world. In the United States, the U.S. Environmental Protection Agency cancelled the use in 1992 of EBDC fungicides on 11 crops due to the evidence of animal carcinogenicity but continues to permit their use on a wide variety of nut, fruit, and vegetable crops.

The author declares he has no conflict of interest.

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Carcinogenicity of EBDCs: Response

The *IARC* (International Agency for Research on Cancer) *Monographs on the Evaluation of Carcinogenic Risks to Humans* deal with all kinds of agents and exposures in the human environment that may present a cancer hazard. As of October 2002 (Volume 84), the program has evaluated 888 agents and exposures, including ethylene thiourea (ETU) recently (IARC 2001) and some of the ethylene bisdithiocarbamate (EBDC) fungicides earlier. The monographs do not formally evaluate the carcinogenicity of metabolites or other endogenously formed substances, although evidence on the biological activity of metabolites may provide important supporting data for evaluating the carcinogenicity of parent substances. The monographs evaluated ETU as a primary environmental exposure (IARC 2001).

Monograph working groups, which are composed of independent scientific experts, must follow the criteria set forth in the "Preamble" to the monographs (IARC 1992) when making overall evaluations of carcinogenicity to humans. Those criteria are refined from time to time. In 1992 (when Lorenzo Tomatis was director of IARC) the definition of Group 3—not classifiable as to carcinogenicity to humans—was modified as follows (IARC 1992):

> This category is used most commonly for agents, mixtures and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals. *Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.* [italics added]. Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category.

This definition has not changed since it was first established in 1992. It is the responsibility of individual working groups to decide when the italicized criterion applies.

The Monographs Programme has convened several scientific workshops to address certain modes of carcinogenic action in experimental animals and to develop criteria for assessing the roles of mechanistic evidence in establishing overall evaluations of carcinogenicity. The proceedings of these workshops have been published, and the consensus reports from these publications are made available as guidance to monograph working groups and are also freely available on the monographs website (IARC 2003). Mechanisms of action of agents that cause thyroid follicular cell tumors in experimental animals have been studied extensively and include both genotoxic and nongenotoxic processes; these mechanisms have been specifically addressed in several papers in Capen et al. (1999).

Thyroid follicular cell neoplasms are commonly seen in bioassays for carcinogenicity in

rats and mice. A crucial element for assessing the predictive value of rodent thyroid tumors for human cancer hazard is whether data are adequate to exclude a genotoxic mode of action. These tumors are readily induced by many genotoxic carcinogens, but they may also be induced by virtually any nongenotoxic goitrogen in these rodent species. In this respect rodents and humans are quite different. Human thyroid cancers are not exactly comparable to the follicular cell tumors of rats and mice, and no nonradioactive chemical is known to cause these cancers in humans. The only clearly established cause of thyroid cancers in humans is ionizing radiation, especially in childhood (Ron 1996).

Occupational exposures to EBDCs cannot be simply equated to exposure to ETU. Occupational exposure to EBDCs entails exposures to the parent compound(s) plus other ingredients of the working formulations used in agriculture, as well as to endogenously formed ETU and other metabolites, and is not identical to environmental exposure to ETU per se. The 1997 study by Steenland et al. concerns a group of workers using a mixture of different pesticides, such as EBDC fungicides, organophosphates (in "a typical mixture" up to 48% by weight), plant-regulating substances, and foliar nutrients (Steenland et al. 1997). As the authors themselves indicate, this paper reported on a single field study with limited sample size; the results are limited to subclinical outcomes (all thyroid hormone data being within the normal range); and the data are of borderline statistical significance and should be interpreted with caution. The working group for IARC Monograph Volume 79 (2001) did justice to the paper by mentioning it as they did.

Steenland's assertion that mechanistic information has been used more often by monograph working groups to reach lower overall evaluations of carcinogenicity—to "downgrade" rather than "upgrade"—is incorrect. Of the 888 overall evaluations of carcinogenicity made since 1972, only a small fraction have been based on what the monographs refer to as "other relevant data," including mechanisms of carcinogenicity. "Upgrades" include 5 from Group 2A to Group 1; 38 from Group 2B to Group 2A; and 6 from Group 3 to Group 2B, a total of 49. Only 8 substances—< 1% of the total—are "downgrades" from Group 2B to Group 3 on the basis of mechanistic information, and only 3 of these substances are thyrotropic chemicals. Anyone can go to the lists of evaluations that are given on the monographs website (IARC 2003) and confirm this. Overall evaluations that rely in part on "other relevant data" bear a notation to that effect.

The authors declare they have no conflict of interest.

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Comment on "Use of A-Bomb Survivor Studies as a Basis for Nuclear Worker Compensation"

I read with interest the letter of Wing and Richardson (2002), which raised concerns about using cancer risks derived from the Life Span Study (LSS) cohort of Japanese atomic-bomb survivor data in radiation worker compensation plans. Wing and Richardson (2002) criticized the methods of dose assessment for the LSS data and implied that there is significant dose misclassification in this data set. They also stated that the atomic-bomb survivors exhibit dose- and age-related selective survival, citing recent work of Stewart and Kneale (2000). They also implied that there is inconsistency between the cancer risks observed in the LSS and their variation with age, and those observed in certain occupationally and medically exposed groups. In this letter, I will show that these criticisms of the LSS are without foundation.

There are random and systematic uncertainties in the dose estimates in the LSS, as are also found in most occupationally exposed groups. Errors in dose assignments in the LSS arise from uncertainties in the location of survivors and those associated with shielding by neighboring structures (Jablon 1971; Roesch 1987). Uncertainties in dose estimates in the worker cohorts are caused by sampling variation in measurements from film badges and thermoluminescent dosimeters, adjustments made to doses below the limit of detection, and attenuation of externally measured dose by shielding (Gilbert 1998; Gilbert and Fix 1995). The errors in the Japanese dose estimates are thought to be log-normal with a geometric standard deviation of about 30% (Jablon 1971); the dosimetric errors in the radiation workers are of the same order (Kite and Britcher 1996). The National Council on Radiation Protection and Measurements (NCRP 1997) concluded that accounting for random and systematic errors in the LSS results in reduction in the cancer mortality risk coefficient by a factor of 0.84 [90% subjective confidence interval (CI), 0.69–1.0].

Although the overall effect of dosimetric errors on cancer risk coefficients derived from the LSS is slight, it is well recognized that such errors can substantially alter the evidence for modification of the cancer dose response by acute injury status (Little 2002a; Neriishi et al. 1991). Stewart and Kneale (2000) found significant differences of excess relative risk (ERR) in the LSS for leukemia and other end points, between survivors with two or more acute injuries and survivors not having any acute injuries, but did not take into account dosimetric errors. Little (2002a) analyzed the same data and showed that the findings of Stewart and Kneale (2000) largely disappeared if proper account was taken of dosimetric errors.

Stewart and Kneale (2000) also found significant heterogeneity in ERR by age group for various disease end points, which they used to argue for the delayed effects of acute injury in "vulnerable" age groups in the LSS. Wing and Richardson (2002) also highlighted this decrease of ERR at older ages in the LSS compared with the enhanced sensitivity at older ages observed in some worker cohorts. However, these findings in the LSS are commonly observed in many medically exposed groups [United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2000]. Various mechanistic models of carcinogenesis (Little 1995, 1996; Little et al. 1992) imply a reduction of ERR with increasing age at exposure. That these patterns are observed in many different populations suggests that the hypothesis proposed by Stewart and Kneale (2000) and Wing and Richardson (2002) to account for their occurrence in the LSS is unlikely to be correct.

The risks observed in the LSS are generally statistically consistent with those observed in occupationally (Cardis et al. 1995; Muirhead et al. 1999) and medically exposed groups (Little and Boice 1999; Little et al. 1999; UNSCEAR 2000). For example, Muirhead et al. (1999) estimated that the ratio of the leukemia ERR coefficient in U.K. nuclear workers to that in the LSS is

1.18 (90% CI, < 0–3.73), and the corresponding ratio for all malignant neoplasms excluding leukemia and lung cancer is 0.89 (90% CI, < 0–3.65). The ratio of lung cancer risk coefficients in the LSS and in groups of underground miners is close to the value suggested by the latest International Commission on Radiological Protection (ICRP 1994) model of lung dosimetry (Birchall and James 1994; Little 2002b). The general consistency of risks in the LSS and in medically and occupationally exposed groups implies that there are no serious biases in the LSS dosimetry.

The author declares he has no conflict of interest.

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Wing S, Richardson D. 2002. Use of A-bomb survivor studies as a basis for nuclear worker compensation [Letter]. Environ Health Perspect 110:A739.

Re: "Use of A-Bomb Survivor Studies as a Basis for Nuclear Worker Compensation"

Wing and Richardson (2002) suggested that it is inappropriate to apply radiation risk estimates derived from the follow-up of the Japanese atomic-bomb survivors to persons exposed chronically to low doses of radiation. They referred to a paper I co-authored (Doll and Wakeford 1997) in support of their claim that a raised risk of childhood cancer was not detected among the Japanese survivors irradiated *in utero*, in contrast to the elevated risk found in case–control studies of antenatal exposure to diagnostic X rays. In fact, only just over 750 Japanese children were exposed *in utero* during the atomic bombings of Hiroshima and Nagasaki, and two cases of childhood cancer were observed in this cohort against an expected number of, at most, 0.43 (Doll and Wakeford 1997; Yoshimoto et al. 1988). These limited data do indicate an excess risk of childhood cancer following intrauterine irradiation during the bombings; the pertinent question is whether the risk coefficient (risk per unit dose) that may be derived from the Japanese cohort study is compatible with the risk estimates that may be obtained from the findings of the case–control studies of fetal exposure (Boice and Miller 1999; Doll and Wakeford 1997; Wakeford 1995).

By far the largest case–control study of childhood cancer and antenatal radiographic examinations is the Oxford Survey of Childhood Cancers (Bithell and Stewart 1975). A highly statistically significant excess relative risk (ERR) associated with a diagnostic X-ray examination of 40% was obtained from the Oxford Survey, but reliable estimates of fetal doses appropriate for this study are not easily derived (Mole 1990). Bithell (1993) obtained an ERR coefficient from the Oxford data of 51 per sievert, but he believed that the uncertainty of this estimate could be as much as an order of magnitude. Further, Wakeford and Little (In press) suggest that there are good reasons from the Oxford data for believing that this risk estimate may be a systematic overestimate by perhaps as much as a factor of four. In comparison, the Japanese data for *in utero* irradiation provide an ERR coefficient for childhood cancer of 23 per sievert, although, again, the uncertainty of this estimate is large (Delongchamp et al. 1997). The ERR coefficient derived from the Japanese cohort is only of marginal statistical significance, but the limited data available from this source must be emphasized. Once proper account has been taken of the uncertainties present in the analyses of both data sets, it cannot reasonably be concluded that risk estimates are incompatible (Wakeford and Little. In press).

The case–control studies of childhood cancer and fetal X-ray exposure are important because they demonstrate an excess risk associated with doses near 10 mSv, doses an order of magnitude below those received in other epidemiologic studies showing an excess risk of cancer following irradiation (UNSCEAR 2000). The interpretation of the findings of these case–control studies has been questioned (Boice and Miller 1999), but Doll and Wakeford (1997) believed that the available evidence provides strong grounds for a causal explanation of the association. However, the point estimates of risk obtained from a comparatively small ERR in the face of many uncertainties should not be overinterpreted, and it cannot be claimed with any confidence that the risk coefficient derived from the Oxford Survey is discrepant with that derived from the limited data from the Japanese survivors exposed *in utero* (Wakeford and Little. In press). I suspect that Wing and Richardson (2002) have been overoptimistic in the accuracy that they have assigned to two risk estimates that superficially appear to suit their argument.

Although the author is employed by British Nuclear Fuels plc (BNFL), he does not feel there is a genuine conflict of interest, because the Doll and Wakeford paper referred to by Wing and Richardson argues for a non-zero risk of cancer at low doses of radiation.

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Corrections

In the article by Wilhelm and Ritz [*Environ Health Perspect* 111:207–216 (2003)], a negative sign was omitted from the equation on page 208. The correct equation appears below. *EHP* regrets the error.

$$Y = \left(\frac{1}{0.4\sqrt{2\pi}}\right) \times \exp\left[-\left(\frac{(0.5)\left(\frac{D}{500}\right)^2}{(0.4)^2}\right)\right]$$

Li et al. [*EHP* 111:455–460 (2003)] would like to thank Arantzazu Eiguren-Fernandez and Antonio H. Miguel of the Southern California Particle Center and Supersite (Los Angeles, CA, USA) for their analyses of polycyclic aromatic hydrocarbons, elemental carbon, and organic carbon reported in "Ultrafine Particulate Pollutants Induce Oxidative Stress and Mitochondrial Damage," published in the April issue of *EHP*. Their data is a valuable contribution to the article.

In "Atrazine-Induced Hermaphroditism at 0.1 ppb in American Leopard Frogs (*Rana pipiens*): Laboratory and Field Evidence" by Hayes et al. [Environ Health Perspect 111:568–575 (2003)], Figure 8 was incorrect. The correct figure appears below:

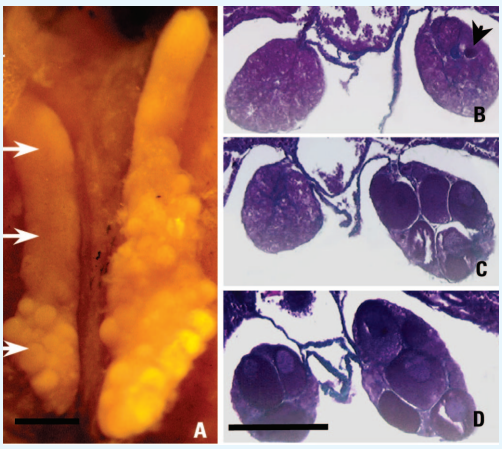

Figure 8. Gonads from a treated male *R. pipiens* (0.1 ppb atrazine) with vitellogenic testicular oocytes. (*A*) Bouin's-fixed section; bar = 250 µm. The posterior portion of the gonad is filled with oocytes that are protruding through the testicular lobules and can be seen on the surface of the gonad; white arrows show areas where transverse cross-sections were taken. (*B*) Transverse cross-sections showing that the anterior testis has poorly developed testicular lobules; the black arrowhead shows a tangentially sectioned oocyte. (*C*) and (*D*) Large vitellogenic oocytes in the posterior portion of the gonads. Bar = 250 µm for panels (*B–D*). See "Materials and Methods" for details of histological analysis.