Cancer Risk to Naval Divers Questioned

In the report by Richter et al. (2003) on increased risk for cancer in naval commando divers in the Kishon River in Israel, there are three systematic errors in estimating the degree of exposure to environmental water contaminants (their Table 3).

First, Richter et al.'s report on the concentrations of heavy metals in water (Table 3; Richter et al. 2003) is misleading and is not supported by references within the Kishon Commission's report (Investigation Committee for the Effects of Military Activities in the Kishon River 2001). The concentrations reported by Richter et al. (2003) are in fact a meaningless mixture of values, most of which were measured in the river sediment [several of their maximal values were reported by Herut et al. (1993)]. Thus, the values of water contaminant concentration used by Richter et al. in Fick's equation, describing the molar diffusion flux related to a concentration gradient, were derived from averaged data obtained from two completely different phases, water and sediment, assuming a simple and homogenous system. In fact, the system is very complicated, consisting of four interlinked reservoirs of chemicals: water, sediment, suspended particles, and interstitial water. The partitioning of each of the individual chemicals between the water and the sediment compartments is governed by many factors, including aqueous solubility, sediment binding, pH, and temperature. For most environmental contaminants, at steady state the sediment/water ratio is about 2–4 and up to 6 orders of magnitude for hydrophobic compounds. This explains the very wide range of reported values presented in Table 3 (Richter et al. 2003). For instance, the range of lead concentrations is 0.0002–252 ppm (mg/L) and of that of chromium is 0.305–462 ppm (mg/L). To reduce the uncertainty in estimating the bioavailable chemical concentration, it is recommended to use unfiltered water samples with minimum turbidity [U.S. Environmental Protection Agency (EPA) 1995]. In fact, the observed concentrations of suspended particulate matter and particulate heavy metals in the Kishon River (Herut and Kress 1997) were 2–4 orders of magnitude lower than those reported by Richter et al. (2003). Furthermore, the mean values calculated by Richter et al. are much higher (e.g., 5-fold for cadmium and 10-fold for Cr) than the metal concentrations measured in the effluents discharged by the fertilizer plants from which nearly all metals were introduced (Herut et al. 1993). The level of exposure reported by Richter et al. was also higher than the actual exposure, because the vast majority of diving activities of the naval divers were in the Kishon Harbor sea water, rather then in the river itself.

Second, the particulate-bound chemicals in aqueous medium are much less bioavailable for dermal absorption because of inefficient adsorption of suspended particles to the skin surface and a slower rate of absorption into the skin. Richter et al. (2003) used a "conservative" value of 1 cm/hr to describe the permeability constant of all chemical contaminants presented in their Table 3. In fact, for a given skin, the permeability constant describes "dermaphilicity" and strongly depends on the physicochemical properties of the individual compounds such as the oil/water partition coefficient (K_{ow}) and molecular weight. A detailed list of permeability coefficients has been published elsewhere (U.S. EPA 2001). For the heavy metals presented by Richter et al. in their Table 3, the values are 3–4 orders of magnitude lower.

Third, Richter et al. (2003) used a bioavailability factor of 1.0 to estimate the oral absorption of water swallowed while diving. Absorption values for the heavy metals presented in their Table 3 were recently reported (U.S. EPA 2001) and are markedly lower than unity (0.025, 0.013, 0.07, 0.04, and 0.05 for Cd, Cr, mercury, nickel, and Pb, respectively).

In keeping with the recommendations and guidelines for assessment of dermal and oral absorption (U.S. EPA 1995), it is our understanding that Richter et al. (2003) overestimated the dose intake by a factor of $\geq 10^5$. To support this conclusion, the estimates for Cd and Pb calculated by Richter et al. were 34.87 and 269.79 mg/kg/24 hr, respectively. According to their calculations, the intake of these metals during 20 hr of diving in 1 week for a person weighing 70 kg would be 2,034 mg Cd and 15,738 mg Pb. The cumulative intake in 2,475 hr of diving would be 252 g Cd and 1.95 kg Pb. These amounts would have caused severe and potentially fatal acute and chronic toxicity. In fact, none of the naval divers developed overt symptoms of heavy metal toxicity. Furthermore, in June 2001, blood Pb and Cd levels were measured in 70 naval divers, of whom 6 were diving regularly in the Kishon Harbor during the 1980s through 1993. Their blood Pb levels were 2–5 µg/dL, and Cd in blood was below detection limits in all 6. Because Pb and Cd have elimination half-lives of several years following chronic exposure, these findings rule out exposure to the levels suggested by Richter et al. (2003).

The authors declare they have no conflict of interest.

Yona Amitai
Ministry of Health
Jerusalem, Israel
E-mail: yona.amitai@moh.health.gov.il
Shlomo Almog
Institute of Toxicology and
Clinical Pharmacology
Sheba Medical Center
Tel Hashomer, Israel
Barak Herut
Israel Oceanographic and
Limnological Research Ltd.
Haifa, Israel

References

Herut B, Kress N. 1997. Particulate metals contamination in the Kishon River Estuary, Israel. Mar Poll Bull 34:706–711.

Herut B, Shirav M, Kress N, Hornung H, Illani S, Olga Y. 1993. Sediments Composition and Pollution Levels along the Kishon River and Its Drainage Basin. Report H25/93 GSI/23/93. Haifa, Israel:Israel Oceanographic and Limnological Research and Geological Survey of Israel.

Investigation Committee for the Effects of Military Activities in the Kishon River. 2001. Report of the Investigation Committee for the Effects of Military Activities in the Kishon River and the Region's Water on the Health of IDF Soldiers Activated There [in Hebrew]. Part 1. Available: http://www.tau.ac.il/~bhkishon/ [accessed 28 July 2003].

Richter ED, Friedman LS, Tamir Y, Berman T, Levy O, Westin JB, et al. 2003. Cancer risks in naval divers with multiple exposures to carcinogens. Environ Health Perspect 111:609–617.

U.S. EPA. 1995. Groundwater Sampling Workshop – A Workshop Summary. EPA/600/r-94/205. Dallas, TX:U.S. Environmental Protection Agency.

———. 2001. Risk Assessment Guidance for Superfund. Vol 1. Human Health Evaluation Manual. EPA/540/R/99/005. Washington, DC:U.S. Environmental Protection Agency.

Cancer Risk to Naval Divers: Response

We would like to address the epidemiologic implications of Amitai et al.'s comments on the validity of our estimates of exposure, dermal contact and absorption, internal doses, and permeability coefficients that we reported in our article published in the April 2003 issue of *EHP* (Richter et al. 2003)

We now know that excessive skin contact occurred in the 1950s and 1960s when divers used defective and torn skin suits and applied skin greases [Governmental Commission of Inquiry (GICI) 2003]. Strikingly, all cases of melanoma occurred among those who began diving before 1970, and no melanoma was found in those who began diving after 1970 (Richter et al. 2003). The fact that seven of the eight divers with melanoma belonged to the 1960 cohort accounts for the sharp peak in observed/expected ratio (6.58) for all cancers combined in the 1960–1969 cohort.

Our calculations (Richter et al. 2003) were based on data from the GICI (2003). Both the Kishon Harbor and Haifa Bay were severely polluted, and dilution of effluents

did not occur until well past the mouth of the Kishon River. Many samples were taken near apertures of effluent drains, where concentrations would be substantially higher before downstream dilution. Most diving took place at the mouth of the Kishon River, Haifa Bay, and Kishon Harbor, close to and downstream from these apertures.

Furthermore, divers frequently descended to sediment depths. Frequent dredging resulted in recirculation of sediment. Therefore, the data on toxics were probably reasonable indicators of the conditions of exposure.

For determining estimated potential exposure dose intake, we used reported water levels only, not substantially higher sediment levels (Richter et al. 2003). Measures such as biological oxygen demand, total suspended solids, and sediment levels for observed pollutants state the case for severe contamination, even if dose estimates based on concentrated water samples are too high.

Regulatory agencies have used a permeability constant of 1.0 cm/hr and a bioavailability factor of 1.0 rather than measured or estimated values (Great Lakes Health Effects Division 1993). Correcting for the permeability coefficient and bioavailability factor suggests an overestimate of daily intakes by 1.5–3.0, not 5, as stated by Amitai et al. Even so, we are currently addressing the potential for high rates of intake from high concentrations of toxics in subsurface water and still higher concentrations in surface films of petroleum. Solvents, of course, have permeability constants and bioavailability factors higher than those for metals, and many exceed 1.0 (e.g., ethanol, toluene).

In our paper (Richter et al. 2003), we presented estimates normalized to 24 diving hours, not daily exposure, which was 3–4 hr/day for the first year and 2 hr/day for the remaining 3 years of full-time service (Table 3; Richter et al. 2003). Therefore, an estimate of absorption per workday should be approximately one order of magnitude less than the 24-hr value.

Our calculations based on the classical models of exposure and equations (Richter et al. 2003) probably provide substantial underestimates of exposure hazards under real-life conditions.

Several real-life conditions increased the hazard from exposure. First, wet suits acted as occlusive pressure dressings on the skin. Second, abrasions and open cuts facilitate higher penetration (ATSDR 1999b). Third, the divers used abrasive soaps (intended for cleaning horses) and turpentine-containing thinners to clean thick crusts off their skin. Fourth, the soaps, together with detergents in the Kishon waters, produced additional abrasions and surface injury to the skin. Fifth, the thinners removed the protective fat layer on the skin and served as carriers of contaminants in crusts deposited on the skin.

Current blood cadmium and lead levels do not indicate past absorption and exposure. For both Cd and Pb, skin exposure can pose a risk for absorption when contact continues for prolonged periods (several hours) or at very high levels, and when skin is abraded or injured (i.e., common conditions for the divers) (ATSDR 1999a, 1999b). Short-term studies underestimate these risks.

Measurements of blood levels of two heavy metals ≥ 8 years after the last exposure certainly do not serve as indicators of occupational exposures to these agents, and certainly not to many lipophilic toxics in the Kishon River. Neither blood Cd nor Pb levels reflect long-time cumulative body burdens or exposures that terminated years ago. The major portion of the Cd body burden is in the liver, kidney, and other tissues; for Pb, it is in bone. In humans, the half-life of Cd in blood is approximately 75–128 days for the fast component and 7.4–16.0 years for a residual slower component (Jarup et al. 1983). The half-life of Pb in blood is only 28–36 days (ATSDR 1999b). Blood presumably contains Pb that is transferring in and out of other compartments.

Figure 1 presents cumulative risks for all cancers combined in terms of years lapsed from first exposure to diving. Short induction periods follow the onset of exposure, and reversibility reaches unity at 42 years after the first exposure (after full-time exposure is terminated), a strong argument for causation.

We question the validity of estimating risks for long-term exposures from toxicokinetic models derived from short-term controlled experimental settings. If we have overestimated dermal exposure and absorption, then internal doses far lower than our original estimates were sufficient to produce the increase in risks, and removal of these exposures reversed the increase.

The authors declare they have no conflict of interest. One author, Y. Tamir, a diver with cancer, played a key role in the process of data collection.

Elihu D. Richter
Lee S. Friedman
Hebrew University-Hadassah
Jerusalem, Israel
E-mail: elir@huji.ac.il

Yuval Tamir
Israel Defense Forces (Retired)

Tamar Berman
Maya Sadeh
Or Levy
Jerome B. Westin
Tamar Peretz
Hebrew University-Hadassah
Jerusalem, Israel

Irene Lipshitz
Micha Bar-Chana
Ministry of Health
Jerusalem, Israel

References

ATSDR. 1999a. Toxicological Profile for Cadmium (Update). Atlanta, GA:Agency for Toxic Substances and Disease Registry.

———. 1999b. Toxicological Profile for Lead (Update). Atlanta, GA:Agency for Toxic Substances and Disease Registry.

Governmental Commission of Inquiry (GICI). 2003. The Investigation Committee for the Effects of Military Activity in the Kishon River and the Region's Waters on the Health of IDF Soldiers Activated There [in Hebrew]. Final Report. Available: http://www.tau.ac.il/~bhkishon [accessed 6 May 2003].

Great Lakes Health Effects Division. 1993. Investigating Human Exposure to Contaminants in the Environment: A Handbook for Exposure Calculations. Ottowa, Ontario, Canada:Health Protection Branch, Health Canada.

Jarup L, Rogenfelt A, Elinder C-G, Nogawa K, Kjellstrom T. 1983. Biological half-time of cadmium in the blood of workers after cessation of exposure. Scand J Work Environ Health 9:327–331

Richter ED, Friedman LS, Tamir Y, Berman T, Levy O, Westin JB, Peretz T. 2003. Cancer risks in naval divers with multiple exposures to carcinogens. Environ Health Perspect 111:609–617

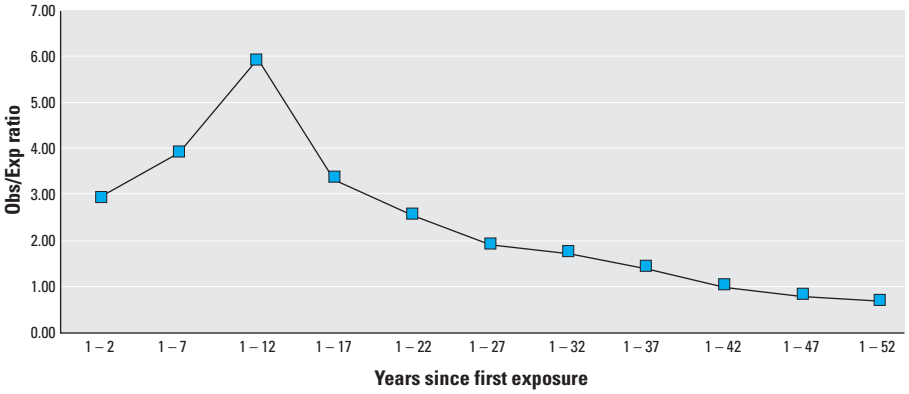

Figure 1. Observed/expected (Obs/Exp) ratios for all cancers in naval divers in relation to years since first exposure.

Bisphenol A: Findings of a Multigenerational Rat Study

I read with great interest John Heinze's letter (2003) about the article by Schönfelder et. al. (2002) titled "Parent Bisphenol A Accumulation in the Human Maternal–Fetal–Placental Unit" and the response to Heinz by Ibrahim Chahoud (2003). I am the study director and first author of the multigenerational study of dietary bisphenol A (BPA) in CD (Sprague-Dawley) rats (Tyl et al. 2002) Chahoud referred to when he mentioned "the problem of the interpretation of the so-called negative studies." Specifically, he referred to our interpretation of our finding of reduced absolute and relative ovarian weights observed in F_0, F_1, and F_2 (but not F_3) adult females at 500 mg/kg/day BPA (7,500 ppm) and the reduced ovarian weights observed only in the F_2 females at 1 (0.0015 ppm) and 300 µg/kg/day (4.5 ppm), but not at 20 µg/kg/day (0.3 ppm), 5 mg/kg/day (75 ppm), or 50 mg/kg/day (750 ppm). In our multigenerational study, we used six BPA dose groups (0.0015–7,500 ppm) and a concurrent vehicle control group, 30 animals per sex per group per generation, with the F_3 animals raised to adulthood. In such a study, the F_1, F_2, and F_3 generations are essentially replicates (although the F_3 animals were not bred), so the findings observed in the multiple generations (e.g., ovarian effects at 500 mg/kg/day) can be compared in context with the findings observed only in one generation (e.g., ovarian effects at 1 and 300 µg/kg/day). In the latter example, an effect in only one generation, with no dose–response pattern, is most likely not treatment or dose related but is most likely due to biologic variation. In the former example, the reduced F_0, F_1, and F_2 maternal ovarian weights and the reduced F_1, F_2, and F_3 litter sizes at birth at 500 mg/kg/day BPA were clearly related to treatment and dose. However, there was a clear indication at this high dietary dose (7,500 ppm) of profound systemic toxicity in both sexes in all four generations; therefore, the effects on the ovaries and litters are confounded by the toxicity at this dose, which exceeded the maximum tolerated dose.

I agree with Chahoud that "investigators are in the position to interpret the adversity of their own data …" We are not only in position to, but are scientifically and morally responsible to interpret our data. In our paper (Tyl et al. 2002), we concluded that there was systemic toxicity in the form of decreases in body weight gain at the 50- and 500-mg/kg/day doses (750 and 7,500 ppm); therefore, the NOAEL (no-observed-adverse-effect level) for adult systemic toxicity of BPA was 5 mg/kg/day (75 mg/kg/day). Because reproductive toxicity occurred only at 500 mg/kg/day, the NOAEL for reproductive toxicity of BPA was 50 mg/kg/day. These conclusions are fully supported by our data (Tyl et al. 2002); this opinion was also held by the statistics subcommittee of the National Toxicology Program (NTP)/U.S. Environmental Protection Agency Endocrine Disruptors Low-Dose Workshop (NTP 2001), who reviewed all of our data on this study and concurred with all of our results and interpretations.

The fact that our statistically powerful study, compliant with good laboratory practices (and the study by Ema et al. 2001 and others), could not confirm the low-dose effects of BPA was also acknowledged by the Statistics Subpanel of the Endocrine Disruptors Low-Dose Workshop as follows:

> There is credible evidence that low doses of BPA can cause effects on specific endpoints. However, due to the inability of other credible studies in several different laboratories to observe low dose effects of BPA, and the consistency of these negative studies, the Subpanel is not persuaded that a low dose effect of BPA has been conclusively established as a general or reproducible finding. In addition, for those studies in which low dose effects have been observed, the mechanism(s) is uncertain (i.e., hormone related or otherwise) and the biological relevance is unclear.

The absence of effects of BPA at low dietary doses in rats (Ema et al. 2001; Tyl et al 2002) and mice (Ashby et al. 1999; Tyl et al. Unpublished data) and the absence of any consistent or persistent adverse effects exhibiting a "nonmonotonic inverted-U dose–response curve" mitigate against any "need for mechanistic experimental studies as well as follow-up studies in humans regarding low-dose effects" (Chahoud 2003). One cannot and should not perform mechanistic studies on nonreproducible findings. My laboratory has shown (Tyl et al. Unpublished data) that CD-1 mice can tolerate 5,000 (0.5%; BPA intake ~850 mg/kg/day) and 10,000 (1.0%; BPA intake ~1,700 mg/kg/day) ppm BPA in the diet, with dose-related systemic toxicity in parental livers and kidneys and reduced litter size at birth found only at 10,000 ppm. Our data confirm and extend those of Reel et al. (1985). The conclusion by the NTP Low-Dose Review and the detailed analyses published in individual articles provide strong support for the absence of reproducible, convincing effects after exposure to low doses of BPA. Also, my laboratory (Tyl et al. 2002) showed that *a*) dietary BPA < 500 mg/kg/day does not produce reproductive, fertility, or developmental effects, and *b*) BPA is not a selective reproductive toxicant in any generation in either sex at doses < 500 mg/kg/day. It is my understanding that workplace and consumer exposures are orders of magnitude below these doses.

The author declares she has no conflict of interest.

Rochelle W. Tyl
Center for Life Sciences and Toxicology
Research Triangle Institute
Research Triangle Park, North Carolina
E-mail: rwt@rti.org

References

Ashby J, Tinwell H, Haseman J. 1999. Lack of effects for low dose levels of bisphenol A and diethylstilbestrol on the prostate gland of CF1 mice exposed *in utero*. Regul Toxicol Pharmacol 30:156–166.

Chahoud I. 2003. Adverse health effects of bisphenol A: Chahoud's response. Environ Health Perspect 111:A383.

Ema M, Fujii S, Furukawa M, Kiguchi M, Ikka T, Harazono A. 2001. Rat two-generation reproduction study of bisphenol A. Reprod Toxicol 15:505-–523.

Heinze JE. 2003. Adverse health effects of bisphenol A in early life. Environ Health Perspect 111:A382–A383.

NTP. 2001. National Toxicology Program's Endocrine Disruptors Low-Dose Peer Review. Research Triangle Park, NC:National Toxicology Program. Available: http://ntp-server.niehs.nih.gov/htdocs/liason/LowDosePeerFinalRpt.pdf [accessed 23 April 2002].

Reel JR, George JD, Myers CB, Lawton AD, Lamb JC. 1985. Reproduction and Fertility Assessment in CD-1 Mice when Administered in the Feed. Final Study Report. Research Triangle Park, NC:National Toxicology Program.

Schönfelder G, Wittfoht W, Hopp H, Talsness CE, Paul M, Chahoud I. 2002. Parent bisphenol A accumulation in the human maternal–fetal–placental unit. Environ Health Perspect 110:A703–A707.

Tyl RW, Myers CB, Marr MC, Thomas BF, Keimowitz AR, Brine DR, et al. 2002. Three-generation reproductive toxicity study of dietary bisphenol A (BPA) in CD (Sprague-Dawley) rats. Toxicol Sci 68:121–146.

Correction

In Table 3 of "Renal Effects of Uranium in Drinking Water" by Kurttio et al. [*EHP* 110:337–342 (2002)], the unit for uranium in urine should be nanograms per liter instead of micrograms per liter. *EHP* regrets the error.