Cancer Risks in Naval Divers with Multiple Exposures to Carcinogens

Elihu D. Richter,[1] Lee S. Friedman,[1] Yuval Tamir,[2] Tamar Berman,[1] Or Levy,[1] Jerome B. Westin,[1] and Tamar Peretz[3]

[1]Unit of Occupational and Environmental Medicine, Hebrew University-Hadassah, Jerusalem, Israel; [2]Israel Defense Forces (Retired); [3]Department of Oncology, Hebrew University-Hadassah, Jerusalem, Israel

We investigated risks for cancer and the case for a cause–effect relationship in five successive cohorts of naval commando divers (n = 682) with prolonged underwater exposures (skin, gastrointestinal tract, and airways) to many toxic compounds in the Kishon River, Israel's most polluted waterway, from 1948 to 1995. Releases of industrial, ship, and agricultural effluents in the river increased substantially, fish yields decreased, and toxic damage to marine organisms increased. Among the divers (16,343 person-years follow-up from 18 years of age to year 2000), the observed/expected ratio for all tumors was 2.29 ($p < 0.01$). Risks increased in cohorts first diving after 1960 compared to risks in earlier cohorts, notably for hematolymphopoietic, central nervous system, gastrointestinal, and skin cancer; induction periods were often brief. The findings suggest that the increases in risk for cancer and short induction periods resulted from direct contact with and absorption of multiple toxic compounds. Early toxic effects in marine life predicted later risks for cancer in divers. *Key words:* **cancer, diving, heavy metals, multiple exposures, naval divers, petroleum derivatives, solvents, water pollution.** *Environ Health Perspect* **111:609–617 (2003). doi:10.1289/ehp.5901 available via *http://dx.doi.org/* [Online 1 November 2002]**

In 2000, we received reports of a suspect cancer cluster in Israeli naval divers who trained in the Kishon River, its estuary, and in Haifa Bay (Richter et al. 2000b). Since the late 1940s, the Kishon River and Haifa Bay served as a training site for recruits and naval commandos, an elite and highly select group in the Israeli military (Figure 1). In the past 50 years, pollution in the Kishon had progressively worsened, reaching levels close to those found in the world's most polluted rivers (e.g., Reine, Alba, Po) [Government of Israel Commission of Inquiry (GICI) 2001]. The major sources of pollution were industrial effluents, dredging of sediments, and dumping of waste from ships in the Haifa Harbor.

As early as 1953, government reports documented isolated fish kills from fertilizer runoff, odors of oil from the fish and loss of edibility, and, later, in the 1970s, repeated episodes of acidity, pollution, and fish kills (GICI 2001). Thereafter, an array of anecdotal reports, site visits, governmental reports, and research projects cited in the GICI document confirmed these observations as well as the presence of numerous toxic compounds and effects on marine life. For example, one report from the 1970s (Library Archival Files on Kishon River, Israel Ministry of Health, Jerusalem, Israel) states that

> Fertilizers began to pose a problem in 1953 … and fish kills began. Before 1953, many species of fish lived.… [T]oday the only fish are "buri," which are especially resistant to pollution, and even from them there is a sharp smell of oil and they are inedible.

Another report stated that

> … during the years 1971–[1972] a number of "disasters" occurred in the river; some of these caused major fish kills, for example, the death of the fish species *Sardina pilchardus* in May 1971, as a result of increased pollution combined with acidic conditions.…

(Library Archival Files on Kishon River, Israel Ministry of Health, Jerusalem, Israel) (Figure 2). In 2000, veteran fishermen recalled the progressive decrease in fish yield from "abundant" in the 1950s to "reduced" in the 1960s, to "poor" in the 1970s, to "disastrous" in the 1980s, to "catastrophic" in the 1990s (Richter ED. Unpublished data).

The first two divers with cancer presented in the late 1960s, (one with brain cancer, one with bowel cancer), and nine more divers presented with diverse cancers in the 1970s. By 1989, the cumulative number had increased to 26. Between 1990 and 1999, there were 24 additional cancers. Although there have been population-based surveys of cancer risks in naval personnel (Garland et al. 1988, 1990a, 1990b; Hoiberg 1981; Robinette et al. 1980), reports on carcinogenic risks from toxic exposures in water among professional naval divers are not available. We report the results of our investigation of exposures and risks for cancer incidence among a cohort of naval divers exposed to heavily polluted waters and examine the case for a cause–effect relationship. This investigation (Richter et al. 2001a, 2001b) triggered the establishment of a Governmental Commission of Inquiry, the "Kishon Commission," into the history, circumstances, and determinants of what came to be called the "Kishon disaster."

Methods

Exposure data and individual estimates of exposure. We collected and analyzed data regarding sources, daily industrial effluents, indicators of water quality, and toxic compounds in the water from investigations cited in the Kishon Commission's report (Cohen et al. 1993; Greenpeace Research Laboratories. Unpublished data; Kronfeld and Navrot 1974; Krumgalz et al. 1989; Saliternik 1973). In most cases the Kishon Commission reported average levels but did not include information on the number of individual measurements. Therefore, we did not calculate weighted means but treated each figure as an individual sample. Samples of water quality and contaminants were sporadic. First reported samples were taken in 1953, but the majority was drawn in the 1970s and afterward. Samples were taken along the length of the river from its source to the Haifa Bay. Most were taken along the estuary and Kishon Harbor, the location of heaviest industry. We converted reported water levels of contaminants to parts per million of water and compared the results to 1999 Israeli standards for fresh water (GICI 2001). Information on effects of pollution on mollusks and fish came from another investigation (Bresler et al. 1999).

Population at risk and follow-up. We defined the cohort as all members of the Naval Commando Diving Unit who were full-time undersea divers, starting from those first diving in 1948 to those first diving in 1993. The Israeli Navy uses highly demanding physical and psychological criteria for

Address correspondence to E.D. Richter, P.O. Box 12272, Ein Kerem Medical Campus, Hebrew University-Hadassah, Jerusalem 91010, Israel. Telephone: 972–2–6758147. Fax: 972–2–6784010. E-mail: elir@huji.ac.il

This work was preceded by a preliminary report presented at the Collegium Ramazzini in Carpi, Italy (October 2000), by testimony to the Governmental of Israel Commission of Inquiry on the Kishon (January 2001), and as an abstract presented at the Conference of the International Society for Environmental Epidemiology, Garmisch, Germany (September 2001).

We thank the divers and their families, T. Tamir, D. Brunner, H. Rosenthal, A. Tel-shir, Z. Yehezkeli, R. Laster, M. Bar-Chana, and Y. Aviram for their untiring help. We thank S. Linn, K. Cantor, D. Davis, and O. Manor for advice, critiques, and suggestions on methodologic issues. We also thank H. Maibach for reviewing statements on the physiology of dermal absorption, and M. Molchin and S. Barsky for comments on the work conditions of professional divers. The responsibility for the work is exclusively that of the authors.

Partial support for this work came from the International Student Fund, the Amuta for Education and Health, and a fund for the Divers.

Received 22 July 2002; accepted 8 October 2002.

recruiting diver candidates, who undergo arduous training before selection. Training for the naval commando unit begins at age 18 and includes a year of strenuous daily underwater exercises. Divers spent an additional 3 years in the unit, and 3 weeks (18 work days) a year in reserve duty for the next 15 years.

Our definition of the cohort at risk of full-time undersea divers (n = 682) came from written materials we received from one retired senior officer and from in-depth interviews with other senior officers in the unit. We cross-checked our tallies of the size of the cohort with information published by the Investigation Commission. The commission reported that 4,248 trainees passed through the unit (GICI 2001). Of these, 1,046 (24.6.2%) dived at least once in the Kishon River, its estuary, and Haifa Bay. From the interviews with the senior officers, we estimated that 682 of the 1,046 individuals were full-time divers, including 12 recruited as the first divers in 1948–1950, when the unit was created. These 12 used snorkeling equipment and had limited exposures. The remaining 364 were exposed as divers for brief periods (< 20 hr total) and served mostly in support activities such as rowing boats, maintenance, and shore work.

From 1950 to 1975, the unit recruited and trained 10 full-time commando divers per year, and thereafter 20 per year. From the interviews with senior officers from the unit, we ascertained that there was little to no deviation from this annual recruitment quota for full-time divers. Our estimate of the denominator and person-years follow-up did not take into account losses from deaths, dropouts, and attrition from work injuries, a statistic that is not publicly available. There was close agreement between the estimate of the denominator we derived separately from information provided by the Kishon Commission and from numbers provided by the senior officers.

The divers reported spending an average 15–20 hr/week under water in the Kishon and other adjacent sites during their first year of training, and thereafter 10 hr/week for the next 3 years of their service, for a total of 45 weeks/year. Thereafter, they spent 10 hr/week for 4 weeks/year under water during reserve service for another 15 years. Total exposure during the first year totaled some 675 hr, an additional 1,350 hr during the next 3 years, and another 450 hr over the next 15 years, with an estimated cumulative total of some 2,475 hr/diver.

Data collection. The Kishon Commission reported that there were 88 persons with cancer among 4,248 soldiers who ever received training in naval diving in the Kishon from 1948 to 1993. Fifty-one of these 88 persons with cancer came from the subgroup of full-time naval commando divers from 1948 onward (n = 682). The remaining 37 cases came from the 3,566 others, but at the time of writing, information was not available on how many cases came from nondiving members of the naval unit and how many came from divers with brief or episodic immersions in the Kishon. We restricted our analysis to the 51 cases from this group of full-time divers. We subdivided the 51 cases into 5 subgroups by the decade they began diving: before 1950, 1950–1959, 1960–1969, 1970–1979, and 1980–1995.

A small volunteer group of divers interviewed their colleagues by mail, telephone, e-mail, and in person. Proxy interviews of family were used in the 21 (41%) of the divers with cancer who had died. The questionnaire covered year of birth, dates of entry and end of service in the diving unit, date of diagnosis, current status (dead/alive on 31 December 2000), and best available information on the type of tumor.

For 49 of the 51 cases, there was complete agreement between diagnoses reported during interviews and those listed in the Israel Cancer Registry (ICR). Two of the cases were diagnosed in 2000 and were not yet listed in the registry, which has a 2-year lag period in reporting new cases (Bar-Chana M. Personal communication). The list of 51 cases excludes new cases after 31 December 2000 and excludes 8 individuals with basal cell carcinoma, 4 among commandoes who first dived before 1960 and 4 who dived after 1960.

Risk estimates and statistical analysis. We carried out two analyses. The first compared risks for cancer (all combined and specific organ systems) among divers first diving before 1960 and those first diving after 1960. The second analysis compared risks in five cohorts defined by decade of first diving: 1948–1949, 1950–1959, 1960–1969, 1970–1979, and 1980–1995. In both cases, we calculated the average age of diagnosis and the observed cancer risk per person-years of risk within the cohort. Because nearly all the cases were Israeli born, we used 1993 age-specific morbidity incidence rates for the equivalent age of Jewish males born in Israel as reported by the Israel Cancer Registry (ICR 1996) to calculate observed/expected (obs/exp) ratios. We also calculated risks and obs/exp ratios for specific tumor sites. Because the numbers were much smaller, we restricted ourselves to a comparison of risks for specific tumor sites among those first diving before and after 1960.

Figure 1. Naval commando diver (courtesy of Yediot Aharonot).

Figure 2. Warning sign, Kishon River.

Because rates for malignant lymphoma were unavailable for 1993, we used 1995 age-specific incidence to calculate obs/exp ratios (ICR 1998). We matched mean age of diagnosis for each subgroup with the age-specific incidence rates reported by the ICR.

We used the *z*-test approximation method $\{z = [a - (m)(p)]/\sqrt{[mpq]}\}$ to test statistical significance for obs/exp ratios, using two-sided tests at a significance level of 0.05. We derived induction periods from age of onset of tumor minus age 18, when divers first began their underwater training.

Results

Exposures. **Sources.** The oil refinery, the factory discharging the largest amount of effluent into the Kishon, has been active since the 1930s, when it was built by British Mandatory Authorities. Most of the other factories discharging large amounts of effluent into the Kishon River and bay started operations in the late 1950s and early 1960s (Table 1). During this period, the refinery was the major source of effluent. Other major polluters were petrochemical and fertilizer plants and a sewage treatment plant whose effluent is discharged directly to the Kishon River, estuary, and bay. Concentration of waste effluent from all these sources was increased by diversion of the headwaters of the river and estuary and by depleted water flow (Cohen et al. 1993; Kronfeld and Navrot 1974; Krumgalz et al. 1989).

Indicators of water quality. Reports from 1950 onward documented gray-brown-black discoloration of the water, a surface film of oil and foam, deposition of black oil and tar on the Kishon's banks, and strong odors of sewage, acids, and petroleum-containing agents. Throughout 1955–1999, measures of water quality indicated extreme deviations in pH, reaching levels as low as 0.5 pH. Thirty-eight percent of the measurements were highly acidic, and mean levels of biochemical oxygen demand and total suspended solids exceeded standards of the Ministry of Environment by 20- to 30-fold (Table 2). Low pH levels inhibit precipitation and settling of metals in sediment and sludge, thereby increasing their suspension in water (Cohen et al. 1993; Greenpeace Research Laboratories. Unpublished data; Kronfeld and Navrot 1974; Krumgalz et al. 1989).

Escherichia coli levels in the water indicated severe pollution in the 1970s and exceeded American Public Health Association (APHA) guideline levels (< 50 organisms/100 mL) for freshwater bathing by 75,000-fold (mean = 3,730,563 organisms/100 mL water; range = 100–18,000,000) (APHA 1985).

Contaminants. The riverside industries discharged effluent containing many toxic agents with and without prior neutralization. The agents detected in both water and sediment included petrol effluents, including many polycyclic aromatic hydrocarbons (PAHs), benzene, toluene, and xylene, long-chain and branched hydrocarbons, phenols, alcohols, chlorinated alkylbenzenes, trichlorethylene, trichlorophenol,

Table 1. Industries contributing waste to the Kishon water system: commercial product, years of production, known pollutants in waste, and mean daily effluents.

Company	Product	Years of production	Known pollutants	Mean daily effluents (m^3/day; 1993–1999)
Primary sources of pollution				
Haifa Petroleum Refineries	Petroleum refinery process includes removal of salts from the petroleum, petroleum refining, hydrosulfurization, rinsing petroleum by-products, production of lubricants, waxes, asphalts, liquids, and gases; 9 million tons of petroleum refined in 1999; 5.5 million tons refined in 1975	1938–present	Aliphatics, aromatics, long-chain and branched hydocarbons, 2,4,5 - trichlorophenol, ammonia, mineral oils, detergents, phenols, oil by-products	12,400
Municipal sewage treatment plant (Haifa)	Processing of residential waste; by 1975 it was working 75% above its original design capacity.	1961–present	Chlorinated benzenes (di- and tri-chloro), ammonia, chlorides, Fe, Mn, Cd, Cu, Zn, Ni, Pb	50,480
Haifa Chemicals	Potassium nitrate fertilizers and various potassium-based food, ceramic, glass, and firework products; including Mn-, S-, Fe-, B-, Zn-, Cu-, Mo-, and Ca-enriched fertilizers	1960s	KNO_3 fertilizers, K, Na, Ca, Mg, B, Fe, Zn, Cr, Cd, Cu, Pb, Hg, Mo, N, P, chromium, P_2O_5, HNO_3, H_3PO_4, KMg, KB, KCl, KNO_3, $CaNO_3$, $C_5H_{12}O$, chlorides, nitrates, phosphates, sulfates, fluorides, sulfide, butyl phosphate, ammonia, tribromomethane, brominated trimethylbenzenes, chlorinated naphthalene derivatives, alpha-HCH, mono-ammonia phosphate, sodium tripolyphosphate, various alcohols, mineral oils	5,714
Deshenim Chemicals and Phosphates	Fertilizers and various other chemicals, including H_3PO_4	1953–present	H_3PO_4, H_2SO_4, ammonia, HNO_3, chlorides, fluorides, sulfates, nitrates, Ca, Cu, Ba, lime, P, ammonia, mineral oils, detergents, chlorine, nitrogen by-products, nitrates, heavy metals, chlorides	1,267
Gadot Biochemical	Lemon acid production	1959–present	Various organic compounds including cycloalkanes, alcohols, aldehydes, ketones, and organic acids, derivative of 4-chloro-benzenesulfonic acid, ammonia, mineral oils, nitrogen, sulfides, iron	1,100
Petrochemical Industries	Ethylene, polyethylene, asphalts, polystyrene, rubber	Data unavailable	Organic matter, carbon by-products from petrol production, polystyrene solids, ethlylene, phenols	250
Other sources of pollution[a]	Cement, dyeing of textiles, commercial detergent production, processing and coating metal pieces, aromatic compounds, petrol products, ship assembly, automobile assembly, agriculture compost, leather manufacturer, cooking oils, fish packaging, run-off from agricultural pesticides, residential waste and water used for cooling purposes only	Varying	NaCl, Na_2SO_4, Na_2CO_3, Na_2S, NaSH, CH_2O_2, NH_4NO_3, amyls, branched hyrdrocarbons, polyurethanes, diisocyanats, alkylbenzenes, pesticides, complex hydrocarbon mixtures, vinyl chlorides, detergents, ammonia, sulfides, chlorides, N, B, Cr, Cu, Hg, Fe, Ni, Zn, chromium, lime, acidic salts, organic and inorganic acids, basic compounds (pH 11–12), petrols, ship paints, mineral oils, organic residential waste, primarily salts from cooling process, dust and cement powder	Data incomplete

HCH, hexachlorocyclohexane. Data from GICI (2001), Greenpeace Research Laboratories (2000).
[a]Nesher, Atta Kordani, Kibbutz Yagor, Witco Chemicals, Soltam, Frutarom, Gadiv, Carmel Olefins, Sonol, Paz Oils and Equipment, Miles Chemicals, Kaiser Eileen, Til (formerly Kaiser Eileen), Israel Shipping and Drydocks, domestic waste (1,000 people; residential), Israel Electric Company, Matmar, compost factories, tannery and leather hides, Shemen Soap and Cosmetic Products, Tnuva Fish Products.

cresols, cycloalkanes, aldehydes, ketones, many brominated and chlorinated aromatic organic compounds, di-(2-ethylhexyl)phthalate, diphenyl, hexachlorocyclohexanes, methylene chloride, styrenes, organic and inorganic acids, fertilizers and their by-products, nitrogen by-products, vinyl chlorides, salts, dust, and cement in powder form, as well as radionuclides of uranium, radium, and radon.

Studies from the 1970s report the presence of toxic metals including arsenic, cadmium, chrome, chromium, cobalt, copper, mercury, nickel, lead, vanadium, and zinc at mean levels 100 to more than 5,000 times greater than 1999 Israeli standards for fresh water. Sediment levels of toxic metals were in most cases higher than water levels. However, in the late 1980s and early 1990s the floor of the Kishon Water System frequently underwent dredging that resulted in recirculation of toxic compounds.

In Table 3, we report on the mean water levels of a shortened list of contaminants found in the Kishon River, its estuary, and Haifa Bay from 1953 onward. In all cases mean water levels of these toxics exceeded the 1999 standards. There were no available data on polychlorinated biphenyls or dioxins.

Time trends in effluents. Effluents increased steadily from the 1950s onward, with weak enforcement of restrictions on output and few requirements for purification (Figure 3). The data indicate that release of industrial waste to the Kishon water system during the 1980s was more than 10 times greater than release during the 1960s.

Effects on marine life. In the 1950s, fishermen reported an oily smell from the fishes and episodic fish kills. As noted, fish yields began falling in the 1960s and reached virtual extinction in the 1990s. Field studies showed significant reductions in the number of mollusks, bivalve fauna, and gastropods in the 1980s and 1990s and enzyme changes, organ swelling, and DNA nicks in marine mollusks and fish in the Kishon area (Bresler et al. 1999). Two *in vitro* studies using the alkaline comet assay, a sensitive method for detecting DNA strand breaks and alkali labile sites in individual cells, showed significantly higher genotoxic values for fish hepatic cell lines treated with Kishon water samples through 2001 (Avishai et al. 2002; Kamer and Rinkevich 2002). These studies provided evidence confirming the impressions and findings from many of the reports that the GICI cited.

Potential for exposure and absorption via dermal, gastrointestinal, and airway routes. The divers dove in wet suits, not dry suits, a fact that underscores the potential for skin contact, occlusion, and absorption. There was prolonged skin contact with PAHs, benzene and derivatives, and other agents that have partition coefficients that predict a high degree of skin penetration (Wester and Maibach 2000a). Furthermore, because these agents do not volatilize in water, they remain available in high concentrations under conditions of high hydrostatic pressure at the interface between water and the skin surface and may produce body burdens far exceeding those from inhalation and ingestion (Boman and Maibach 2000; Kalnas and Teitelbaum 2000; Wester and Maibach 2000a, 2000b).

Exposure to the agents via the skin was enhanced by the production of a layer of crust, which often remained on the skin for hours afterward. Divers reported taking 30–40 min to scrub down the residue on their skin after diving, a practice that may have enhanced absorption via the production of abrasions and wounds.

The divers reported swallowing large amounts of water. Their complaints of indigestion and nausea after dives suggest the importance of direct gastrointestinal contact and absorption. The divers also reported odors from volatile organics and irritants at the

Table 2. Indicators of water quality of the Kishon water system: 1955–2000 (mean levels and 1999 Israeli water and sediment standards).

Water quality	No. of reported findings[a]	Mean[a]	Range	Standard[b]
Temperature (°C)	8	32	13.5–60	< 40
pH	129	6.87	0.5–12.3	pH 7–8.5
Percent < 7.0 (38%)	49	4.72	0.5–6.9	
Percent > 8.5 (9%)	11	10.4	8.8–12.3	
Turbidity (Jackson units)	29	34.69	0–98	
Dissolved oxygen	63	24.52	0–200	
Biochemical oxygen demand	120	293.85	0–4,800	< 10 mg/L
Chemical oxygen demand	90	1093.3	0–33,920	
Total suspended solids	60	1301.97	19–25,000	< 60 mg/L
Total dissolved solids	25	10856.84	280–53,563	
Chlorides	71	4253.82	279–80,000	(Current levels)
Salinity (%)	4	15.9	0–39	
Chlorine	4	497.84	8.445–1,527	

Values shown are milligrams per liter unless otherwise specified.
[a]Because the number of individual measurements per reported findings was in most cases unknown, we did not use weighted means; the Kishon Report (GICI 2001) used reported annual means, in most cases omitting the number of measurements per reported mean. [b]Israeli standards for water and sediment levels for 1999 and Israeli standard level for water total suspended solids for 1978 (fresh waters, < 60 mg/L) from GICI (2001).

Table 3. Toxics found in the Kishon water system: 1953–2000 (mean levels, 1999 Israeli fresh water standards).

Exposure	No. of reported findings[a]	Mean (ppm)[a]	Range (ppm)	Standard (ppm)[b]	Ratio of mean contaminant levels to standards	EDI (mg/kg/24 hr)[c,d]
Elements (water)						
Cd	29	5.59	0–56.3	0.005	1,117	34.87
Cr	19	77.28	0.305–462	0.01	7,728	482.37
Chromium	6	0.08	0.0017–0.22			0.48
Fe	7	3974.43	56–10,000			24806.11
Hg	24	2.02	0.00002–14.87	0.0005	4,031	12.58
Ni	25	10.16	0.005–33.5	0.05	203	63.39
Pb	24	43.22	0.0002–252	0.01	4,322	269.79
Chemical compounds (water)						
Oil	43	455.41	1.2–10,000	1.00	455.41	2842.41
Mineral oil	6	4.82	3.41–6.23	1.00	4.82	30.08
Detergents	104	10.50	0–620	0.50	21.00	65.54
Ammonia	78	108.91	0.08–1788.5			
NO_3	9	513.39	4.74–3,000	10.00	51.34	3204.29
PO_4	8	1770.90	3.58–4,500	0.10	17709.00	11052.95
SO_4	16	1229.70	175–2,750			7675.08
Phenols	7	0.07	0–0.132	0.05	1.40	0.44

[a]Because the number of individual measurements per reported findings was in most cases unknown, we did not use weighted means; the Kishon Report (GICI 2001) used reported annual means, in most cases omitting the number of measurements per reported mean. All reported water levels were converted to parts per million of water. [b]Israeli standards for fresh water, for 1999 from GICI (2001). [c]Per 24-hr exposure based on mean contaminant levels. Formula for absorption through skin from contaminated water is EDI = ($C \times P \times SA \times ET \times EF \times .0001$)/BW, where C = concentration of contaminant in water (mg/L, ppm; based on mean water levels, 1953–2000); P = permeability constant, conservative measure of 1.0 cm/hr used; SA = surface area of exposed skin (average body of male > 20 years of age = 18,200 cm^2); ET = exposure time (24 hr); EF = exposure factor (how often an individual was exposed; we used 1.0 to keep units per 24 hr; 0.001 to convert liters to cm^3); BW = body weight (average body weight of male > 20 years of age is 70 kg. Formula for water ingestion exposures of contaminated water is EDI = ($C \times IR \times EF$)/BW, where C = concentration of contaminant in water (mg/L, ppm; based on mean water levels between 1953–2000); IR = ingestion rate (L/day; we used the conservative assumption that a diver ingests 0.1 L per 24 hr of diving); EF = how often an individual was exposed over a lifetime (we used 1.0 to keep units per 24 hr); and BW = body weight (average body weight of male> 20 years of age is 70 kg. [d]See "Correction," p. 616.

water–air interface, especially in warm weather. They experienced frequent headaches and burning of the eyes, nasal passages, and throat. These complaints confirmed reports of odors and visible pollutants in the river by nondiving observers (GICI 2001).

Estimates of risk for cancer. **Risks in cohorts first diving before and after 1960.** The obs/exp ratio for all tumor types combined was 2.29 ($p < 0.01$) and increased from 1.58 ($p < 0.03$) in all divers first diving before 1960 to 3.72 ($p < 0.01$) in those first diving after 1960 (Table 4).

Risks in cohorts defined by decade first diving. There was a lower than expected obs/exp ratio (0.69) for the small 1948–1949 cohort of 12 divers, in which there were 3 victims of cancer, all with induction periods > 10 years (Figure 4). The obs/exp ratio in the 1950–1959 cohort, in which there were 16 divers with cancer, was more than twice that of the 1948 cohort (1.67 compared to 0.69). The obs/exp ratio increased again to 6.58 in the 1960–1969 cohort, in which there were 18 divers with cancer. Thereafter, the obs/exp ratio fell to 1.79 in the 1970–1979 cohort, in which there were 5 divers with cancer, and then rose again to 6.62 in the 1980–1995 cohort, in which there were 9 divers with cancer.

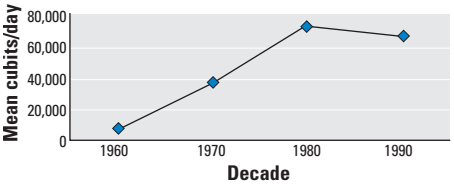

Figure 3. Total reported industrial waste released daily into the Kishon water system and Haifa Bay [mean daily waste (cubits/day) by decade, 1960s to 1990s]. Data from GICI (2001). 1960s, data for 1962: waste from 7 companies, cumulative daily waste = 6019.7 mean cubits/day; 1970s, data for 1972 and 1975: waste from 17 measurements (14 companies), cumulative daily waste = 22,115 for 1972 and 51,218 for 1975; 1980s, data for 1984: waste from 9 companies, cumulative daily waste = 72,990; 1990s, data for 1993, 1996, 1998, and 1999: waste for 36 measurements (10 companies), cumulative daily waste = 99,650 for 1993, 55,361 for 1996, 57,644 for 1997, 76,327 for 1998, and 40,373 1999.

Case mix and case fatality. The most frequent cancers were gastrointestinal tract (n = 10; 7 fatal), brain and central nervous system (CNS; n = 8; 2 fatal), hematolymphopoietic (n = 8; 3 fatal), skin (n = 7; 1 fatal), and lung (n = 5; 4 fatal). Two divers each had three primary tumors: melanoma, gastrointestinal tumors, and benign tumor of the hypophysis. In addition, there were two divers with testicular cancer, two with prostatic cancer, and one each with cancer of the salivary gland, pancreas, thyroid, and angiosarcoma, and three tumors of unknown type. One diver with lung cancer (fatal) was a heavy smoker who dived in the 1950s and died at age 51. These data show that case fatality was highest among those with gastrointestinal and lung tumors.

Risks by tumor type: before and after 1960. Examination of the obs/exp ratios by tumor type and cohort indicated increased risks within cohorts first diving before 1960 for colon (6.48), leukemia (5.74), brain and CNS (12.5), and prostate (3.89). Obs/exp ratios in the cohorts first diving after 1960 were higher than for those first diving before 1960 for melanoma (7.26 vs. 0.66), stomach (5.71 vs. 0.99), lymphomas (3.98 vs. 0.40), brain and CNS (19.18 vs. 12.50), lung (6.63 vs. 1.33), and testicular cancer (3.51 vs. 0) (Table 5).

In a group of 15–20 men reported as carrying out dredging in 1989, 4 developed tumors, all in the head and neck; 3 were brain tumors, including 1 hypophyseal tumor, and 1 was a thyroid cancer.

Cancer in divers: trends in age of onset and induction periods. The age range of diagnosis of cancer in three persons from the first cohort of snorkel divers was 43–58 years, but all nine patients presenting with cancer before 1980 from later cohorts, starting in 1950 and after, were young (age range: 23–46, median: 26 years). The mean age of all 51 divers with malignant tumors was 39.5 years. Twenty-one (41.2%) reported onset of tumor before age 40, and 21 (41.2%) died at ages ranging from 26 to 62 (mean: 42.5 years).

Overall, 21 (18.8%) of 112 persons diving before 1960 and 37 (6.5%) of the 570 persons first diving from 1960 were diagnosed with cancer. Among those first diving after 1960, the youngest as well as mean ages of first diagnosis fell for nearly all tumor types compared with the group first diving before 1960. The youngest ages of diagnosis after 1960 compared to before 1960 are as follows: brain/CNS, 19 versus 27; skin, 23 versus 29; stomach, 35 versus 58; leukemia, 40 versus 47; lymphomas, 32.8 versus 56; lung, 38 versus 54.7; and other, 31 versus 48.5.

There were no individuals with induction periods less than 25 years between onset of exposure and first appearance of tumors in the 1948–1949 cohort of snorkel divers. But induction periods between first exposure and onset of cancer in many individuals in all cohorts first exposed from 1950 and thereafter were extremely short (Figure 4, Tables 4 and 5).

Induction periods and case mix. Over the years the case mix of tumors with induction periods < 10 years was large bowel (n = 2), lung (n = 1), skin cancer (n = 1), brain, (n = 1), thyroid/thymus (n = 1), lymphoma (n = 2), and testicular cancer (n = 2). There were no cases of leukemia with induction periods < 10 years, the earliest sentinel event associated with exposures to ionizing radiation and benzene. (Rinsky et al. 1987; Upton 1984). In contrast to groups exposed to ionizing radiation and benzene, tumors at surfaces in direct contact with waters of Kishon were sentinel events in the divers.

Discussion

The case for causality. The case for a cause–effect relationship comes from the findings on high and increasing levels of contamination and their effects on marine life, the high risks for many cancers, the time trends in increased risks for many types of cancer, and the short induction periods and early ages of presentation of tumors. In addition, there were plausible relationships between

Table 4. Cancer risks in naval divers with multiple exposures to carcinogens by initial diving period, person-years of follow-up, mean latency (range), and obs/exp ratios.

Diver group by decade of first exposure	Person-years of follow-up[a]	Mean latency (years)[b]	Obs[c]	Exp	Obs/exp	p-Value[d]
Cohort by decade						
Before 1950	1,166	33 (32–40)	3	4.34	0.69	0.26
1950–1959	4,550	28.9 (8–46)	16	9.56	1.67	0.02
1960–1969	3,550	21.9 (5–36)	18	2.73	6.58	< 0.01
1970–1979	3,625	18.6 (3–25)	5	2.79	1.79	0.10
1980–1995	4,000	7.7 (1–18)	9	1.36	6.62	< 0.01
Cohort by period						
IDF Before 1960	5,716	30.4 (8–46)	19	12.02	1.58	0.03
After 1960	11,175	17.7 (1–36)	32	8.60	3.72	< 0.01
All groups combined	16,343	22.4 (1–46)	51	22.24	2.29	< 0.01

IDF, Israel Defense Forces. Data for morbidity for malignant neoplasms in Jewish males born in Israel from the Israel Cancer Registry (1996).
[a]Person-years follow-up is the mean years in a subgroup from initial exposure to end of follow-up (31 December 2000) multiplied by the number of divers in each subgroup. [b]Latency was determined by subtracting 18 years of age, the age divers began service, from the age at diagnosis. [c]Incidence rates are crude age-specific rates. [d]p-Values were calculated using an approximation method for estimating risk based on person-years.

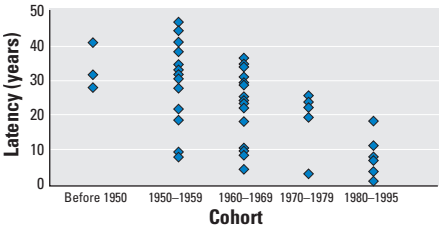

Figure 4. Induction periods for cancer in naval divers (n = 51) in five cohorts.

case mix of tumor types and multiple routes of exposure-absorption and target organs. The risks in the 1950–1959 cohort of divers were already greater than those in the 1948–1949 group of divers, and the grouped risks after 1960 were much greater than those in the 1950–1959 cohort.

The increases in obs/exp ratios for cancer in later cohorts exposed to higher effluent levels provide evidence for dose response, which supports the case for a cause–effect relationship. The fact that 2 of the 51 individuals with cancer had 3 primary tumors at the same target sites is also of note and raises the question of whether individuals with multiple primary tumors serve as sentinels of increased group-risk from environmental exposures. The one individual reported as having angiosarcoma, a tumor indicative of exposure to vinyl chloride, corresponds with reports of emissions of vinyl chlorides from a plant making polyvinyl chloride from these reagents. Time trends in damage to marine life and decreases in fish yields anticipated increased risks for cancer in the divers.

The lower than expected risks for cancer in the 1948–1949 group of snorkel divers suggests a healthy-worker effect in this group, although we cannot exclude the role of underreporting from loss to follow-up. The fact that risks for all cancers combined increased by 58% in the 1950–1959 cohort corresponds with the abundant information on increases in exposures going back to this decade. From 1950–1959 onward, the long-term trend in increases in risks overrode the protective benefit associated with the possible healthy-worker effect.

Increased risks for cancer were associated with organ sites having the highest contact with water or in tissues with known affinities of many of the reported toxicants in the water: from direct exposure via skin (melanoma), gastrointestinal route (stomach and bowel cancer, salivary gland), inhalation of heavy metals and volatiles (lung), and absorption and deposition of carcinogens in fat-soluble target tissues (blood-forming organs and CNS).

If the average exposure of each diver reached some 2,500 hr, and risks increased by approximately 60 and 270%, respectively, for the cohorts first diving before and after 1960, then each 10 hr of diving increased risks for all tumors combined by 0.24% and 1.08%, respectively, with correspondingly higher increases for specific tumors.

In the 1960s and the 1970s, among the divers, the case mix of tumors first appearing in "real time" were brain (n = 2), bowel (n = 4), lung (n = 1), lymphoma (n = 1), prostate (n = 1), skin (n = 1), and unknown (n = 1), all in persons 25–50 years of age. This list shows that by 1980, there were sentinel clinical events indicating a cluster of many different tumor types rather than one or two types. We suggest that the relatively short induction periods of the first tumors in "epidemiologic time" and the young ages of the victims were the first indications of later increase in risk for the later cohorts. But the diverse case mix of low numbers of different tumors with induction periods < 10 years may have been one reason that medical surveillance missed these early signals.

We have no explanation for the fact that risks in the 1970–1979 group were lower than those for the cohorts of preceding and following decades. It was during this decade that larger classes were recruited. Selective underreporting, lower exposures, or too short follow-up are all possible explanations; we have no information on changes in type of diving suits or diving regimens during this decade.

Induction periods and current and future risk. Decreasing ages of diagnosis and short induction periods in individuals are recognized indicators of high exposure and predictors of increased risks in the exposed groups from which they come (Armenian and Lilienfeld 1974; Smith and Doll 1982; Weinberg 1982; Whittemore 1977). The young age at diagnosis and extremely short induction periods for many of these divers go together with increased risks for many tumor subtypes. As noted, even in the early cohorts after 1950, there were persons with tumors with induction period < 10 years. The fact that there were substantial drops in the lowest age of diagnosis within nearly all tumor subtypes in those diving after 1960 compared to those diving before 1960 indicates that the drops were not merely a consequence of truncated follow-up of later cohorts.

The finding that earlier cohorts that had subjects with tumors with short induction periods also had subjects with tumors with longer induction periods implies that there will be more cases in the later cohorts with the passage of time. So far, the findings on induction periods and case mix provide no indication of risks from underwater exposure to penetrating ionizing radiation because leukemias with induction periods < 10 years did not appear among the divers.

Modifiers and confounders. **Prior exposures.** We were unable to examine the possibility of prior individual childhood agricultural exposures to pesticides, but there are several reasons for discounting their role as either a major or important contributory cause for the high risks for cancer in the Kishon divers. First, many of the victims came from urban nonfarming as well as from farming backgrounds. Second, in Israel, during the 1950s, 1960s, and 1970s, spraying of cows in dairy farms resulted in nationwide exposure to organochlorines via dietary ingestion of a massively contaminated milk supply, which was not restricted to agricultural or rural populations. This nationwide exposure began declining in the mid- to late 1970s (Ben-Michael et al. 1999; Westin and Richter 1990). Because organochlorines appear to act as promoters (Westin and Richter 1990), this

Table 5. Cancer risks in naval divers with multiple exposures to carcinogens by tumor site and first year diving [mean latency (induction periods) and obs/exp ratios].

	First dived before 1960					First dived 1960–1993				
Cancer type[a]	Mean latency (years)	Obs	Exp	Obs/exp	p-Value	Mean latency (years)	Obs	Exp	Obs/exp	p-Value
Skin	46	1	1.53	0.66	0.34	21.8 (5-32)	6	0.83	7.26	< 0.01
Colon	19.5 (8–31)	2	0.31	6.48	0.0047	19.5 (8-36)	4	0.60	6.63	< 0.01
Stomach	40	1	1.01	0.99	0.496	17 (8-25)	3	0.53	5.71	< 0.01
Leukemia	29 (28–30)	2	0.35	5.74	0.0078	22	1	0.76	1.32	0.4
Malignant lymphoma[b]	38	1	2.52	0.40	0.1736	14.8 (3-28)	4	1.01	3.98	< 0.01
Brain and CNS	15.5 (9–22)	2	0.16	12.50	< 0.01	15.5 (1-29)	6	0.31	19.18	< 0.01
Lung	36.7(31–43)	3	2.26	1.33	0.32	20 (5-35)	2	0.30	6.63	< 0.01
Testicular	NA	0	NA	NA	NA	4	2	0.57	3.51	0.054
Prostate	30.5 (28–33)	2	0.51	3.89	0.0307	34	1	2.29	0.44	0.2
Other[c]	30.5 (30–31)	4	NA	NA	NA	13 (4-22)	2	NA	NA	NA
Unknown	19	1	NA	NA	NA	22	1	NA	NA	NA

NA, not applicable. Values shown in parentheses are range. Expected cases based on data on morbidity for malignant neoplasms in Jewish males (standardized rates per 100,000) from the Israel Cancer Registry (1996). Person-years follow-up is the mean years in subgroup from initial exposure to end of follow-up (31 December 2000) multiplied by the number of divers in each subgroup; the mean person-years follow-up was 5,716 for divers initially exposed before 1960 and 11,175 for divers initially exposed after 1960.
[a]Cases include two women (1 leukemia, 1 lymphoma). [b]Data for morbidity for malignant neoplasms in Jewish males for 1995 from the Israel Cancer Registry (1998). Data for 1993 malignant lymphoma were unavailable (standardized rates per 100,000). [c]Other tumors include one case each of liver, pancreas, salivary, and thymus cancer for divers who first dived before 1960.

later drop in exposure should have resulted in a protective effect occurring relatively rapidly and in decreased risks in later cohorts, a trend opposite to what actually occurred in the 1980 cohort.

In the 1950s and 1960s, radiation of the scalp for ringworm, a recognized cause of increased cancer risks in Israel, was restricted to childhood immigrants from North Africa, Iraq, and Yemen (Ron and Modan 1980), groups from whom there were no recruits to the unit.

Current other possible exposures. Divers trained at a naval base containing radar units, and some had episodic work on missile and patrol boats equipped with radar. We cannot rule out the possibility that risks for cancer may have been enhanced by such exposures to radiofrequency/microwave radiation from radar in light of reports noting this association (Garland et al. 1990a, 1990b; Goldsmith 1997; Grayson and Lyons 1996a, 1996b; Richter et al. 2000a, 2002; Robinette et al. 1980; Szmigielski et al. 2001; Zaret 1977) and experimental evidence of genotoxic effects (Lai and Singh 1996).

An update of the study by Robinette et al. (1980) reports an increase in risks for leukemia alone in certain naval radar occupational subgroups, not for other cancers in the entire cohort (Groves et al. 2002). The fact that the work histories for most of the cohort did not include major or prolonged exposures to radar argues against a substantial role for these exposures for increasing the group risks.

There is a need to consider the possible role of sunlight in interacting with solvents, metals, liquid asphalt, and grease on the skin to increase risks for skin cancer, notably melanoma. Garland et al. (1990b) have shown that risks for skin cancer from sunlight can be enhanced or promoted by dermal contact with cutting oils, greases, and other derivatives of raw petroleum used for machine work, repair, and maintenance by naval mechanics. But the strength of the case for a dose–response relationship between the progressive increase in contamination in the Kishon estuary and port and increased risks for cancer in later cohorts indicates that additional risks from other sources, if present, may have added to the toxic risks from diving and do not provide an alternative explanation for this relationship.

In divers who smoked, there may have been an additional risk. But the increase in risks for lung cancer, the cancer type most increased by smoking, was less than that for melanoma and hematolymphopoietic tumors. Where occupational exposures to carcinogens are severe, the risks are generally far greater than those from the contribution of smoking. The hypothesis that smoking does not appear to account for the relationship in this situation, any more than it does with other occupational exposures (Blair et al. 1988), is suggested by the lowest ages, 49 and 23, respectively, of divers presenting with lung cancer in cohorts first diving before and after 1960. There is a need to investigate suggestions that other groups such as members of the unit who did not dive for prolonged periods of time, naval divers from other countries who dived in Haifa Bay, and fishermen are also significantly at risk (Linn S. Personal communication).

Environment–gene interactions. Time trends in increasing exposure and increase in risk, such as those seen in the successive cohorts, argue for a dominant role of environmental determinants and a minimal role for individual susceptibility for past risks. In any case, twin studies show an approximate 75 to 25 ratio of environmental to genetic determinants (Lichtenstein et al. 2000). More fundamentally, we suggest that emphasis on searching for individual susceptibles should not divert attention from the need for reduction of exposure in the entire group of divers as a whole (Richter and Peretz 2002).

Limitations. It is possible that the true number in the cohort of divers with prolonged cumulative exposures may be larger or smaller than the numbers we received. In addition, the data we received were limited to military exposures. Furthermore, the abundant exposure data did not definitely rule out the presence of all dioxins or polychlorinated biphenyls, although polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans were reported as being below levels of detection (GICI 2001). We were unable to investigate the role of prior or concurrent individual nonmilitary exposures.

Another limitation of this study is that we used cross-sectional incidence data on tumor types by age, sex, and country of birth from the ICR, as opposed to cohorts comparable with respect to date and country of birth. Because overall cancer risks have risen in the male comparison group since 1970 (ICR 1996; Richter and Chlamtoc 2002), our use of population-based data for cancer risks for the mean age of specific cancers in the male Israeli-born population may have produced underestimates of obs/exp ratios for all cancers combined. However, the fact that 40 (78%) of the 51 cases presented in the 1980s (n = 14) and 1990s (n = 26) suggests that the distortions in estimates of risk, if at all, are restricted to the remaining 11 cases appearing in the 1960s (n = 2) and 1970s (n = 9).

ICR data for 1970–1995 (males, Israel) show per annum increases in risks of 0.8% for all cancers combined, 0.5% for Hodgkin's lymphoma, 0.7% for brain/CNS, 1.3% for non-Hodgkin's lymphoma, 2.5% for testes, 3.8% for colon, and 4.2% for melanoma for Israeli males. There were per annum decreases in risks for the following tumors appearing before 1980: 2.4% for stomach, 1.3% for leukemia, and 0.4% for lung. For those tumors in the diver cohorts for which population-wide risks were increasing in Israeli males, our calculations of risk may be too low. For those tumors for which population-wide risks were decreasing, these calculations may be too high. Therefore, we surmise that the risks we report may underestimate hematolymphopoietic (n = 1), brain/CNS (n = 2), colon (n = 4), and melanoma cancer (n = 1)—a total of 8 out of 12 cases before 1980—but overestimate lung (n = 1) and stomach cancer (n = 0).

Because we used a population-based control and not an occupational cohort matched for age or sex, we were not able to assess the role of the healthy worker effect in this highly select occupational group. The lower than expected risks in the 1948–1949 cohort of divers suggest that the healthy worker effect was substantial. We suggest that the calculations in Appendix 1, which provide estimates of the risks among personnel with brief or sporadic exposures, provide some support for this hypothesis.

We have good reason to believe that our list of 51 cases of cancer among the divers is incomplete. We were advised of new cases of cancer from the 1970 cohort, notably after January 2002, following a television program on the naval commandoes in late June 2002, but at the time of writing, we did not have access to details.

We were unable to provide quantitative estimates of dermal absorption. The evidence for the plausibility of high internal doses from multiple exposures and multiple routes derives from the circumstances of exposure and, in the case of skin, the *a priori* evidence for dermal exposure (Maibach H. Personal communication) under conditions of high hydrostatic pressure.

Data on biological markers of internal dose in divers were not available. Because we carried out the entire investigation long after exposures ended and cancer appeared, it is uncertain how useful or valid such information would be. In any case, the abundant evidence of toxicity from *in situ* biomarker damage in marine life may be sufficient to indicate similar effects in human divers with the same exposures.

The major limitation of this study is that we were unable to examine risks for noncarcinogenic outcomes, for which there were many anecdotal reports. These outcomes included poorly characterized autoimmune and allergic syndromes of bowel, lung, liver, and nervous system. Preliminary estimates are that many divers have had such problems.

Cluster or cohort? In testimony before the Kishon Commission (Richter et al. 2001a), we addressed the objection that this investigation was an exercise in cluster investigation, and therefore not a true test of a hypothesis of

excess risk. A cluster is defined as a group of diseases of a similar kind grouped together in space or time (Last 1983) or a numerator without a readily definable denominator. The Kishon cases involved many kinds of cancer and were spread out over some 40 years, first presenting as two sentinel cases in the 1960s, and then as a cluster of many different kinds of cancer in the1970s, without a recognized denominator. Because there were many different kinds of cases, it was more difficult to recognize the cluster. More than two decades elapsed before the suspicion emerged that the cluster of different kinds of cancer belonged to an occupational cohort exposed to agents with high risks for both cancer and other health effects.

Conclusion

This is the first report on increased risks for cancer in naval divers with occupational exposures to a mixture of petrochemicals, solvents, metals, and other chemical and biological toxics from mixed exposures via multiple routes of absorption. In retrospect, the indications of damage to marine life in the 1950s and the first episodic fish kills predicted the later risks to naval divers. Malignant tumors of the gastrointestinal tract, brain/CNS, skin, and lung were the most frequent diagnoses. We suspect there were increased risks for other medical outcomes as well. Given the rise in incidence of cancer with age, we can expect more tumors in the divers, especially in the later cohorts, although it is not necessarily certain that relative risks will rise. New calculations (available on request) suggest that following termination of exposure, age-specific risks for incidence fall in older divers.

If 20 pack-years, or some 6,000 packs of cigarettes increase cancer risks by 1,400% (Doll 1978), and 2,500 hr of diving increase risks by 270%, then risks from < 1 hr of diving were equal to smoking some 2 packs of cigarettes. Conversely, preliminary calculations at this stage suggest that the group risks for cancer for those with casual, brief underwater exposures to the Kishon appear to be less than those of 1/10 pack-year of cigarettes and are outweighed by reduction in risk of the order of 30% afforded by a healthy worker effect. These calculations do not rule out the possibility of risks for cancer and other adverse health outcomes from brief underwater exposures in susceptible individuals.

Our findings confirm that routine training in contaminated areas creates unacceptable health risks for divers in wet suits. Furthermore, because exposures involve mixtures, routes of exposure are multiple, absorption rates may be slow, and effects are many, we warn that short-term experiments to search for a safe standard for dermal absorption for individual pollutants raise troublesome questions, both scientific and ethical (Richter ED. Unpublished data). For tasks that must be carried out in contaminated waters, Barsky's manual, which includes case studies, checklists, protocols, spreadsheets listing the effectiveness of protective materials in experimental tests, classification of protective gear, diving techniques, procedures for decontamination, and references, is a useful source of information concerning diving in contaminated environments (Barsky 2001). This reference warns against guarantees of absolute safety and presents information suggesting that no single material provides absolute protection against dermal contact of all toxics. Our past reports to the GICI suggested the use of chromosome aberrations and other epidemiologic markers of early group risk in new divers and the use of these markers to monitor adequacy of protective measures of failure (Richter et al. 2001a), but there is no assurance that these measures will ensure detection of hazard before risk is produced.

If early toxic effects in fish predicted later cancer risks in the divers, then the subsequent history of delay in acting on early warnings recalls similar episodes from around the world (European Environmental Agency 2001) concerning other environmental and occupational disasters. In the case of the Kishon divers, the findings in the 1960s and 1970s stated the case for a precautionary policy that would have prevented the overwhelming majority of cancer cases. We have suggested (Richter et al. 2001a, 2001b) that the findings on adverse health effects in humans and concurrent ecotoxic effects state the case for a proactive policy of zero emissions from sources of pollution for the river and estuary—and elsewhere.

The first report released by the Kishon Commission recommended a stop to all diving activities in the river, cessation of all pollution discharges, and comprehensive cleanup. We suggest that evidence of emissions and ecosystem toxicity serve as contraindications to use of the Kishon River as a site for routine training for underwater naval divers.

Correction

The authors have noted a need to clarify calculations of the EDI in Table 3. These clarifications will be presented in a forthcoming letter to the editor.

References

APHA. 1985. Standard Methods for the Examination of Water and Waste Water. Washington, DC:American Public Health Association.

Armenian HK, Lilienfeld AM. 1974. Distribution of incubation periods of neoplastic diseases. Am J Epidemiol 99:92–100.

Avishai N, Rabinowitz C, Moiseeva E, Rinkevich B. 2002. Genotoxicity of the Kishon River, Israel: the application of an in vitro cellular assay. Mutat Res 518:1:21–37.

Barsky S. 2001. Diving in High Risk Environments. Santa Barbara, CA:Hammerhead Press.

Ben-Michael E, Grauer F, Raphael H, Zahm Z, Westin JB, Richter ED. 1999. Residues of organochlorine insecticides and PCB's in fat tissues of autopsied trauma victims in Israel: 1984 to 1986. J Environ Pathol Toxicol Oncol 18:4:297–303.

Blair A, Steenland K, Shy C, O'Berg M, Halperin W, Thomas T. 1988. Control of smoking in occupational epidemiologic studies: methods and needs. Am J Ind Med 13:1:3–4.

Bland M. 1995. An Introduction to Medical Statistics. 2nd ed. New York:Oxford University Press.

Boman A, Maibach H. 2000. Percutaneous absorption of organic solvents. Int J Occup Environ Health 6:2:93–95.

Bresler V, Bissinger V, Abelson A, Dizer H, Sturm A, Kratke R, et al. 1999. Marine mollusks and fish as biomarkers of pollution stress in littoral regions of the Red Sea, Mediterranean Sea and North Sea. Mar Res 53:219–243.

Cohen Y, Kress N, Horning H. 1993. Organic and trace metal pollution in the sediments of the Kishon River (Israel) and possible influence on the marine environment. Water Sci Technol 27:7–8.

Doll R. 1978. An epidemiologic perspective of the biology of cancer. Cancer Res 38:3573–3583.

European Environmental Agency. 2001. Late Lessons from Early Warnings: The Precautionary Principle 1896–2000. Luxembourg:European Communities.

Garland FC, Gorham ED, Garland CF, Ferns JA.1988. Non-Hodgkin's lymphomas in U.S. Navy personnel. Arch Environ Health 43(6):425–429.

Garland FC, Shaw E, Gorham ED, Garland CF, White MR, Sinsheimer PJ. 1990a. Incidence of leukemia in occupations with potential electromagnetic field exposure in United States Navy personnel. Am J Epidemiol 132:2:293–303.

Garland FC, White MR, Garland CF, Shaw E, Gorham ED. 1990b. Occupational sunlight exposure and melanoma in the U.S. Navy. Arch Environ Health 45:5:261–267.

Goldsmith JR. 1997. Epidemiologic evidence relevant to radar (microwave) effects. Environ Health Perspect 105(suppl 6):1579–1587.

Government of Israel Commission of Inquiry. 2001. 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. Report Part 1. Tel Aviv, Israel:Government of Israel. Available: http://www.tau.ac.il/~bhkishon/ [accessed 1 October 2002].

Grayson JK, Lyons TJ. 1996a. Cancer incidence in the United States Air Force. Aviat Space Environ Med 67:2:101–104.

———. 1996b. Brain cancer, flying and socioeconomic status: a nested case-control study of USAF aircrew. Aviat Space Environ Med 67:12:1152–1154.

Groves FD, Page WF, Gridley G, Lisimaque L, Stewart P, Tarone R, et al. 2002. Cancer in Korean War Navy technicians: mortality survey after 40 years. Am J Epidemiol 155:810–818.

Hoiberg A. 1981. Cancer among Navy personnel: occupational comparisons. Mili Med 146:8:556–561.

Israel Cancer Registry.1996. Cancer Trends 1993. Jerusalem, Israel:Ministry of Health.

———. 1998 Trends in Morbidity and Mortality from Cancer in Israel: 1970–1995. Jerusalem, Israel:Ministry of Health.

Kalnas J, Teitelbaum D. 2000. Dermal absorption of benzene: implications of work practices and regulations. Int J Occup Environ Health 6:114–121.

Kamer I, Rinkevich B. 2002. In vitro application of the comet assay for aquatic genotoxicity: considering a primary culture versus a cell line. Toxicol In Vitro 16:2:177–184.

Kronfeld J, Navrot J. 1974. Transition metal contamination in the Qishon river system Israel. Environ Pollut 6:281–288.

Krumgalz BS, Fainshtein G, Gorfunkel L, Nathan Y. 1989. The Kishon River as a Trap for Heavy Metal Pollution of Haifa Bay. Environmental Quality and Ecosystem Stability, Vol IV-A, Environmental Quality b. Jerusalem:Israel Society for Environmental Quality and Ecosystem Stability.

Lai H, Singh NP. 1996. Single and double strand DNA breaks in rat brain cells after acute exposure to radiofrequency electromagnetic radiation. Int J Radiat Biol 69:513–521.

Last J, ed. 1983. A Dictionary of Epidemiology. Oxford, UK:Oxford University Press.

Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. 2000. Environmental and heritable factors in the causation of cancer. N Engl J Med 343:78–85.

Richter ED, Ben-Michael E, Berman T, Laster R, Westin JB.

2000a. Cancer in radar technicians exposed to RF/MW: sentinel episodes. Int J Occup Environ Health 75:187–193.
Richter ED, Berman T, Ben-Michael E, Levy O, Westin JB, Peretz T. 2001a. Cancer risks in naval divers with multiple exposures to carcinogens. Expert Testimony to Government Commission of Inquiry, 21 January 2001, Tel Aviv, Israel.
____.2001b. Cancer and other exposures in naval divers with multiple exposures to carcinogens [Abstract]. Epidemiology (suppl):A77.
Richter ED, Berman T, Ben-Michael E, Westin JB, Peretz T. 2000b. Cancer in naval divers and fishermen and DNA breaks in fish: a preliminary report [Abstract]. In: Collegium Ramazzini Annual Meetings, 27 October 2000, Carpi, Italy. Bentivoglio, Italy:Collegium Ramazzini, 9.
Richter ED, Berman T, Levy O. 2002. Brain cancer with induction periods of less than 10 years in young military radar workers. Arch Environ Health 57:270–272.
Richter ED, Chlamtoc N. 2002. Ames, pesticides, and cancer revisited. Int J Occup Environ Health 6:63–72.
Richter ED, Peretz T. 2002. Ethical issues in molecular epidemiology. Epimarker Bull 6:1–5.
Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, et al. 1987. Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med 316:17:1044–1050.
Robinette CD, Silverman C, Jablon S. 1980. Effects upon health of occupational exposure to microwave radiation (radar). Am J Epidemiol 1121:39–53.
Ron E, Modan B. 1980. Benign and malignant thyroid neoplasms after childhood irradiation for tinea capitis. J Natl Cancer Inst 65:1:7–11.
Saliternik H. 1973. Sources of Pollution for The Kishon, in Water Quality in Israel. Report of the Committee for Research of Water Quality in Israel. Jerusalem:Israel National Committee for Biosphere and Environmental Quality, Internal Report.
Smith PG, Doll R. 1982. Mortality among patients with ankylosing spondylitis after a single treatment course with X-rays. Br Med J 284:449–460.
Szmigielski S, Sobiczewska E, Kubacki R. 2001. Carcinogenic potency of microwave radiation: overview of the problem and results of epidemiologic studies on Polish military personnel. Eur J Oncol 6:2:193–199.
Upton AC. 1984. Hiroshima and Nagasaki: forty years later. Am J Ind Med 6:75–85.
Weinberg JA. 1982. Current approaches to the experimental investigation of chemicals in relation to cancer of the brain. Ann NY Acad Sci 381:43–45.
Wester RC, Maibach H. 2000a. Understanding percutaneous absorption for occupational health and safety. Int J Occup Environ Health 6:2:87–92.
___. 2000b. Benzene percutaneous absorption: dermal exposure relative to other benzene sources. Int J Occup Environ Health 6(2):122–126.
Westin JB, Richter ED. 1990. The Israeli breast-cancer anomaly. Ann NY Acad Sci 609:269–279.
Whittemore AS. 1977. Age distribution of human cancer from carcinogenic exposure of various intensities. Am J Epidemiol 106:418–432.
Zaret MM. 1977. Potential hazards of Hertzian radiation and tumors. NY State J Med 1:146–147.

Appendix

Estimated Interim Risks in Personnel Who Were Not Full-Time Divers with Prolonged Exposures

We carried out a provisional estimate of interim risks in personnel who were not full-time divers, based on data published by the Kishon Commission (GICI 2001). The commission reported a total of 88 cases in 4,248 persons as having ever been exposed to the Kishon. Fifty-one of these 81 occurred in divers with past heavy exposures.

Within the naval diving unit, there were those who dived a great deal ("all divers," n = 682), and members of the unit who mostly rowed boats (n = 364), who were not part of this study, for a total of 1,046. A total of 4,248 recruits, including this subgroup of 1,046 individuals, passed through the Kishon Naval Diver Unit, but this far larger number reportedly had exposures usually no longer than several days at the most, with a small subgroup having exposures lasting weeks in a small number. The calculations below provide crude estimates of risks in the divers compared to the others and suggest an overall RR much greater than the obs/exp values we report.

Relative Risks/Prospective Studies

Methods. We used Taylor and Delta methods for calculating the variance of estimated relative risks (RR) (Bland 1995).

	Dis +	Dis –		
Exp +	A	B	$a + b = m_1$	$Pa = a/m_1$
Exp –	C	D	$c + d = m_2$	$Pb = c/m_2$
				N = denominator = m_1 or m_2

where Exp = exposure, Dis = disease, A = individuals with exposure and with disease outcome, B = individuals with exposure history and without disease, C = individuals without exposure and with disease, D = individuals without exposure and without disease, m_1 = sum of cells A and B, m_2 = sum of cells C and D, $Na = m_1$, and $Nb = m_2$.

$$\text{Var}(\ln \text{RR}) = \{[(1 - Pa) \div Pa] \div Na\} + \{[(1 - Pb) \div Pb] \div Nb\}$$

95% confidence interval (CI): RR

$$\ln(\text{RR}) \pm 1.96\sqrt{\{[(1 - Pa) \div Pa] \div Na\} + \{[(1 - Pb) \div Pb] \div Nb\}}$$

or

$$\ln(\text{RR}) \pm 1.96\sqrt{[(1 - Pw) \div Pw] \div (1 \div Na) + (1 \div Nb)}$$

Results.

	Dis +	Dis –	
Exp +	51	631	682
Exp –	37	3,529	3,566
	88		4,248

Pa = 0.0748
Pb = 0.0104
Estimated RR = 7.19 (95% CI, 4.76 – 10.91)

These interim calculations have several implications:

1. The high relative risks in the divers relative to the larger group—not "all divers" but also a select group receiving a short training course, and no more—suggest risks in the latter large group so far appear to be far less than that of the general population of Israeli-born males, which indicates a healthy worker effect.
2. The above finding fits with the suggestion of a healthy worker effect suggested by the obs/exp ratio of 0.69 in the first cohort of Kishon divers, the 1948–1949 snorkelers. The case for the validity of this inference is suggested by the following calculation: if 1 hr of diving is equal to risks from smoking a pack of cigarettes and the immersion exposures did not exceed, say, 10–20 hr at the most, then the cumulative increase in risk is equivalent to 20–40 packs of cigarettes, or < 10% of 1 pack year—a risk far outweighed by the reduction in risk from a healthy worker-type effect—some 30%.
3. The findings suggest that the risks we report for the full-time divers are underestimates because we obtain higher risks when we compare these divers to a group more closely similar to it than the general population.
4. The lower than expected risks in the larger group as a whole may conceal pockets of excess risk in certain individuals or small groups who in fact did have prolonged exposures and may be misclassified.
6. More up-to-date data will require revision of these estimates.
7. These estimates do not rule out a no-threshold effect for both carcinogenic and other noncarcinogenic individuals in susceptible individuals.