

**Cancer Risks in Naval Divers  
with  
Multiple Exposures to Carcinogens**

Elihu D Richter,<sup>\*a</sup> Lee S Friedman\*, Yuval Tamir, Tamar Berman,\*  
Or Levy,\* Jerome B Westin,\* Tamar Peretz\*\*  
Unit of Occupational and Environmental Medicine\*  
Department of Oncology\*\*

POB 12272  
Street: Ein Kerem Medical Campus  
Hebrew University-Hadassah  
Jerusalem ISRAEL 91010  
Telephone: 972-2-6758147  
Fax: 972-2-6784010 attention Dr Richter

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

Funding: Partial support from the International Student Fund and the Amuta for Education and Health and a Fund for the Divers

No part of this report may be used, quoted or cited without permission of the investigators. None of the investigators have any financial interest connected with the findings of this investigation

Word Count: text: 6555; abstract150; refs 1,137; Appendix 606

<sup>a</sup>Correspondence and proofs to [elir@huji.ac.il](mailto:elir@huji.ac.il)

**tanya3.rtf**

**Running title:** Cancer in naval divers

**Key words:** cancer, heavy metals, multiple exposures, naval divers, petroleum derivatives, solvents, Richter

**Acknowledgements:** We thank the divers and their families, Tal Tamir, Daniel Brunner, Dr Hans Rosenthal; Anat Tel-sher and Zadok Yekezkeli of the newspaper Yediot Ahronot, Maya Sadeh, Dr Dan Gilon, Dr Richard Laster (Society For Education and Health), Dr Micha Bar-Hana of the Cancer Registry and Mr Yoram Aviram for their untiring help and Prof Shai Linn (Epidemiology) of Rambam Hospital (Haifa), Dr Ken Cantor of the National Cancer Institute, Dr Devra Davis of Carnegie-Mellon and Dr Orly Manor of Hebrew University for advice, critiques and suggestions on methodological issues, Dr Howard Maibach of the University of California School of Medicine (San Francisco) for reviewing statements on the physiology of dermal absorption and Marianne Molchan and Steven Barsky for comments on the work conditions of professional divers. The responsibility for the work is exclusively that of the authors.

**Abbreviations used:**

BOD, Biochemical Oxygen Demand

CNS, Central Nervous System

G-I, Gastrointestinal

GICI, Government of Israel Commission of Inquiry

ICR, Israel Cancer Registry

Obs/Exp, Observed/Expected

PAH, Polycyclic Aromatic Hydrocarbons

PCB's, Polychlorinated Biphenyls

Ppm, Parts per million

PVC, Poly(vinyl chloride)

TSS, Total Suspended Solids

## Outline of Section Headers:

Abstract

Introduction

Methods

- Exposure Data and Individual Estimates of Exposure

- Population-at-Risk and Follow-up: the cohort

- Cases: Data Collection

- Risk Estimates and Statistical Analysis

Results

- Exposures

- Sources

- Indicators of Water Quality

- Contaminants

- Time trends in effluents

- Effects on Marine Life

- Potential for Exposure and Absorption via dermal, G-I and Airway routes

- Combined exposure: Heavy metals

- Estimates of Risk for Cancer

- Risks in cohorts first diving before and after 1960

- Risks in Cohorts defined by decade first diving

- Case Mix and Case Fatality

- Risks by tumor type: Before and after 1960

- Cancer in Divers: Trends in Age of Onset and Induction Periods

- Induction Periods and Case Mix

Discussion

- The case for causality

- Induction periods and Current and Future Risk

- Modifiers and Confounders

- Prior Exposures

- Concurrent other Possible Exposures

- Environment-Gene Interactions

- Limitations

- Cluster or Cohort?

Conclusion

References

Appendix 1: Estimated interim risks in personnel who were not full time divers with prolonged exposures.

Five tables and four figures

---

**Abstract**

We investigated risks for cancer (n=51) 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 toxics in the Kishon River, Israel's most polluted waterway in years 1948-1995. Releases of industrial, ship and agricultural effluents increased substantially, fish yields fell and toxic damage to marine organisms increased. Among the divers (16,343 person-years follow-up from age 18 to year 2000), the Obs/Exp ratio for all tumors was 2.29 (p<01). Risks increased in cohorts first diving after 1960 compared to risks in earlier cohorts, notably for hematolymphopietic, CNS, gastrointestinal and skin cancer, and 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 toxics. Early toxic effects in marine life predicted later risks for cancer in divers.

## Introduction

In 2000, we received reports of a suspect “cancer cluster” in Israeli naval divers who trained in the Kishon River, Estuary and Haifa Bay (Richter et al. 2000b).

Since the late 1940's, the Kishon River and Bay served as a training site for recruits and naval commandos, an elite and highly select group in the Israeli military (Fig 1). In the past 50 years, pollution in the Kishon had progressively worsened, reaching "...similar levels found in rivers currently described as the most polluted in the world (e.g. Reine, Alba, Po)" (Government of Israel Commission of Inquiry, 2001, hereafter GICI 2001). The major sources were industrial effluents, dredging of sediments, and dumping of waste from ships in the Haifa Harbor. As early as 1953, government reports documented isolated fishkills from fertilizer runoff, smells of oil from the fish and loss of edibility, and later, in the 1970's, 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 over and over again confirmed these observations, the presence of numerous toxics, and effects on marine life.

For example, one report from the 1970's states that “Fertilizers began to pose a problem in 1953...and fish kills began. Before 1953, many species of fish lived...today 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 1971-2 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” (Israel Ministry of Health Library Archival Files on Kishon River, Jerusalem) (Fig 2). In 2000, veteran fishermen recalled the progressive fall in fish yield from “abundant” in the 1950’s to “reduced” in the 1960’s, to “poor” in the 1970’s, to “disastrous” in the 1980’s, to “catastrophic” in the 1990’s (Fishermen Work Committee Members, Interview by ED Richter, Site visit to Fishermen’s Wharf, Kishon River, July 2000).

The first two divers with cancer presented in the late 1960’s, (1 brain, 1 bowel) and nine more divers presented with diverse cancers in the 1970’s. 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; Garland et al. 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 toxics in the water from investigations cited in the Kishon Commission's report (Cohen et al. 1993; Greenpeace Research Laboratories 2000; 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 afterwards. 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 (ppm) 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).

For certain heavy metals, we calculated the estimated daily dose intake via skin and ingestion per kilogram of body weight, using methods and equations presented elsewhere (Great Lakes Health Effects Division, Health Protection Branch, Health Canada, 1993). These equations are presented in footnote d in Table 3.

**Population-at-risk and follow-up: the cohort:**

We defined the cohort as all those 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 recruiting diver candidates, who undergo arduous training prior to 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 three weeks (18 work days) a year in reserve duty for the following 15 years.

Our definition of the cohort at risk (n=682) of full time undersea divers 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. Of these, 1,046 (24.6.2%) dived at least once in the Kishon River, Estuary and Haifa Bay. From the interviews with the senior officers, we estimated that 682 of the 1046 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 very brief periods (less than 20 hours total), and served mostly in supportive 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 hrs/week underwater in the Kishon and other adjacent sites during their first year of training, and thereafter 10 hrs/week for the next three years of their service, for a total of 45 weeks per year. Thereafter, they spent 10 hours/week for four weeks a year underwater during reserve service for another 15 years. Total exposure during the first year totaled some 675 hours, an additional 1350 hours during the next 3 years, and another 450 hours over the next 15 years, with an estimated cumulative total of some 2475 hours/diver.

**Cases: 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 non-diving members of the naval unit and how came from divers with very brief or episodic immersions in the Kishon.

We restrict ourselves 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: prior to 1950, 1950-59, 1960-69, 1970-79 and 1980-95.

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 Dec 31, 2000) and best available information on the type of tumor.

For 49 of the 51 cases, there was total 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 two-year lag period in reporting of new cases (Dr Micha Bar Hana, Director of Cancer Registry, Israel Ministry of Health. Personal communication). The list of 51 cases excludes new cases after Dec 31 2000 and 8 individuals with basal cell carcinoma, four among commandoes who first dived before 1960 and four 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: 1948-49, 1950-59, 1960-69, 1970-79 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. Since nearly all the cases were Israeli born, we used 1993 age-specific morbidity incidence rates for Jewish males born in Israel as reported by the Israel Cancer Registry (ICR,

1996) to calculate Obs/Exp ratios. We 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.

Since 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 ( $z = [a - (m)(p)] / \text{square root of } [m \cdot p \cdot q]$ ) to test statistical significance for Obs/Exp ratios, using two-sided tests at a 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 putting out the largest amount of effluent into the Kishon, has been active since the 1930's, when it was built by British Mandatory Authorities. Most of the other factories putting out 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 the period of 1955 to 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 (BOD) and Total Suspended Solids (TSS) exceeded standards of the Ministry of Environment by twenty to thirty fold (Table 2). Low pH's inhibit precipitation and settling of metals in sediment and sludge, thereby increasing their suspension in water (Cohen et al. 1993; Greenpeace Research Laboratories 2000; Kronfeld and Navrot 1974; Krumgalz et al. 1989).

E. Coli levels in the water indicated severe pollution in the 1970s and exceeded American Public Health Association guideline levels (<50 organisms/100 ml; p.44) for freshwater bathing by 75,000 fold (mean=3,730,563 organisms/100ml of H<sub>2</sub>O, range=100 to 18,000,000).

**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, benzene, toluene and xylene, long-chain and branched hydrocarbons, phenols, alcohols, chlorinated alkylbenzenes, trichlorethyene,

trichlorophenol, 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 bi-products, nitrogen bi-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 (VI), copper, mercury, nickel, lead, vanadium and zinc at mean levels 100 to more than 5000 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 re-circulation of toxics.

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

**Time trends in effluents:** Effluents increased steadily from the 1950's 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 1950's, 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 1990's. 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 making use of the alkaline comet assay, a sensitive method for detecting DNA strand breaks, and alkali labile site detection in individual cells, showed significantly higher genotoxic values for fish hepatica 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 GICI cited.

**Potential for exposure and absorption via dermal, G-I and airway routes:**

The divers dove in wet suits, not dry suits, a fact that underscores the potential for skin contact and absorption. There was prolonged skin contact with PAH's, benzene and derivatives and other agents that have partition coefficients which predict for 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, 2000 b).

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 minutes to scrub down the residue on their skin after diving, a practice that itself 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 following dives suggest the importance of direct gastro-intestinal contact and absorption.

The divers reported odors from volatile organics and irritants at the 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 from external observers (GICI 2001).

**Combined exposure: heavy metals;** The estimated dose intakes in mg/kg from skin and swallowing per 24 hours of exposure were cadmium, 34.9, chrome, 482.4; mercury 12.6; and lead, 269.8. Estimates are based on mean contaminant levels (Table 3).

#### **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 prior to 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 greater than 25 y. (See below and Fig 4). The Obs/Exp ratio in the 1950-59 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 1970-1979 cohort, in which there were 5 divers with cancer, and then rose again to 6.6.2 in the 1980-1995 cohort , in which there were 9 divers with cancer.

**Case mix and case fatality:** The most frequent cancers were gastrointestinal tract (n=10; 7 fatal), brain and 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 3 primaries: 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 3 tumors of unknown type. One diver with lung cancer (fatal) was a heavy smoker who dived in the 1950's 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 to 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 year 1989, four developed tumors, all in the head and neck: 3 were brain tumors, including one 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 3 persons from the first cohort of snorkel divers was 43 to 58. But all nine patients presenting with cancer prior to 1980 from later cohorts, starting in 1950 and after, were extremely young (age range: 23-46, median: 26). The mean age of all fifty-one divers with malignant tumors was 39.5. Twenty-one (41.2%) reported onset of tumor under the age 40, and 21 (41.2%) died at ages ranging from 26 to 62 (mean: 42.5).

Overall, twenty-one (18.8%) of 112 persons diving prior to 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 as 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 compared to 27; skin, 23 compared to 29; stomach, 35 compared to 58; leukemia, 40 compared to 47; lymphomas, 32.8 compared to 56; lung, 38 compared to 54.7; and other, 31 compared to 48.5.

In the 1848-1949 cohort of snorkel divers, there were no individuals with induction periods less than 25 years between onset of exposure and first appearance of tumors. 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) as well as lymphoma (n=2), and testicular cancer (n=2). There were no cases of leukemia with induction periods less than 10 y--the earliest sentinel event associated with exposures to ionizing radiation and benzene. (Rinsky 1987; Upton 1983). 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 case mix of tumor types and multiple routes of exposure-absorption and target organs. The risks in the 1950-59 cohort of divers were already greater than those in the 1948-49 group of divers, and the grouped risks for all cohorts first diving after 1960 were much greater than those in the 1950-59 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 two of the 51 individuals with

cancer had three primaries at the same target sites is also of note, and raises the question of whether individuals with multiple primaries serve as sentinel indicators of increased group risk from environmental exposures. The one individual reported as having angiosarcoma, a signal tumor for vinyl chloride, corresponds with reports of emissions of vinyl chlorides from a plant making PVC from these reagents. Time trends in damage to marine life and falls 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 toxics 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 average exposure of each diver reached some 2500 hours, and risks increased by approximately 60% and 270% respectively for the cohorts first

diving before and after 1960, then each 10 hours of diving increased risks for all tumors combined by 0.24% and 1.08% respectively, with correspondingly higher increases for specific tumors.

In the 1960's and the 1970's, 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) and skin (n=1), and unknown (n=1), all in persons in age range 25-50. 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 ("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 y may be one reason why 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:** Falling 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 risks  $> 5.0$  for many tumor subtypes. As noted, even in the early cohorts after 1950, there were persons with tumors with induction period less than 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 having cases with short induction periods later had additional cases 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, since leukemias with induction periods  $< 10$  y 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 non-farming as well as farming backgrounds. Second, in Israel, during the 1950's, 60's and 70's, spraying of cows in dairy farms resulted in nationwide exposure to organochlorines via dietary ingestion of a massively contaminated milk supply -- not restricted to agricultural or rural populations. This nationwide exposure began declining in the mid to late 1970's (Ben-Michael et al. 1999;

Westin and Richter 1990). Since organochlorines appear to act as promoters (Westin and Richter 1990), this later drop in exposure should have resulted in a protective effect occurring relatively rapidly and falling risks in later cohorts—i.e. a trend opposite to what actually occurred in the 1980 cohort.

In the 1950's and 1960's, 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 in 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 RF-MW from radar, in the light of reports noting this association (Garland et al. 1990a, 1990b; Goldsmith 1997; Grayson and Lyons 1996a, 1996b; Richter et al. 2000a, 2003; 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 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 explain the relationship in this situation, any more than it does with other occupational exposures (Blair and Steenland 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 the need to investigate suggestions that other groups—i.e. 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 were also at risk (Professor Shai Linn. 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 2003).

**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. But the abundant exposure data did not include measurements ruling out the presence of dioxins, PCB's or active radionuclides. We were unable to investigate the role of prior or concurrent individual non-military exposures.

Another limitation of this study is that we used cross sectional incidence data on tumor types by age sex-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 (Israel Ministry of Health Cancer Registry, 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 39 (76%) of the 51 cases

presented in the 1980's (n=16) and 1990's (n=23) suggests that the distortions in estimates of risk, if at all, are restricted to the remaining 12 cases appearing in the 1960's (n=2) and 1970's (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 rising in Israeli males, our calculations of risk may be too low. For those tumors for which population wide risks were falling, these calculations may be too high. Therefore, we surmise that the risks we report may be underestimates for hematolymphopoietic, (n=1) brain/CNS,(n=2) colon (n=4) and melanoma cancer (n=1) (a total of 8 out of 12 cases prior to 1980) but overestimates for 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 directly able to assess the role of the healthy worker effect in this highly select occupational group. However, the lower than expected risks in the 1948-49 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 case for 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. 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 damage to biomarkers and marine life states the case for similar effects in human divers with the same exposures.

The major limitation of this study is that we were unable to examine risks for non-carcinogenic 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, we addressed the objection that our findings were 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 1960's, and then as a cluster of many different kinds of cancer in the 1970's, 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 having 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 1950's and the first episodic fishkills 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.

If 20 pack-years, or some 6000 packs of smoking increase cancer risks by 1400% (Doll 1978), and 2500 hours of diving increase risks by 270%, then risks

from less than one hour of diving for the later cohorts were equal to smoking some 2 packs of cigarettes. If our risks are underestimates resulting from a healthy worker effect, as the calculations in Appendix 1 imply, then these risk equivalents may be slightly higher. 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 under 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, since 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. (ED Richter, Memorandum to GICI via Yuval Tamir, June 23 2001). For tasks which 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 1960's and 1970's stated the case for a precautionary policy that would have prevented the overwhelming majority of the later 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 pro-active 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 clean-up. 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.

## References

- 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. *Mutation Research* 518:1:21-37.
- Barsky S. 2001. *Diving in High Risk Environments*. Santa Barbara: Hammerhead Press. 197 pp
- 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. *Journ of 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.
- 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. *Marine Research* 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, Science and Technology* 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* 43:6:425-9.

- 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* 45:5:261-67.
- 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 Kishon Commission") Implications of Military Activities in Kishon River and Adjacent Waters on Health of Soldiers in Israel Defense Forces. Report Part 1. Tel Aviv, 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.
- . 1996. Brain cancer, flying and socioeconomic status: a nested case-control study of USAF aircrew. *Aviat Space Environ Med* 67:12:1152-1154.
- Great Lakes Health Effects Division, Health Protection Branch, Health Canada. 1993. Investigating Human Exposure to Contaminants in the Environment: A Handbook for Exposure Calculations.
- Greenpeace Research Laboratories. 2000. Letter from Dr. David Santillo, Senior Scientist Report.
- 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. *Military Medicine* 146:8:556-61.
- Israel Ministry of Health Library Archival Files on Kishon River. Jerusalem, Israel.
- Israel Cancer Registry. 1996. Cancer Trends 1993, Ministry of Health. Jerusalem, Israel.

- Israel Cancer Registry. 1998 Trends in Morbidity and Mortality from Cancer in Israel: 1970-1995. Ministry of Health, Jerusalem
- 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* 16:2:177-84.
- Kalnas J, Teitelbaum D. 2000. Dermal absorption of benzene: implications of work practices and regulations. *Int J Occup Environ Health* 6:114-121.
- Kronfeld J, Navrot J. 1974. Transition metal contamination in the Qishon river system Israel. *Environmental Pollution* 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*.
- Last J, ed. 1983. *A Dictionary of Epidemiology*. International Epidemiology Assoc. Oxford University Press, Oxford.
- 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* 69:513-21.
- 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, Westin JB, Peretz T. 2000b. Cancer in naval divers and fishermen and DNA breaks in fish: a preliminary report [Abstract]. Collegium Ramazzini Annual Meetings, Italy.
- 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*.
- .2001b. Cancer and other exposures in naval divers with multiple exposures to carcinogens. *Epidemiology (suppl): ISEE-380, A77*.
- Richter ED, Berman T, Levy O. In press. Brain cancer with induction periods < 10 Years in young radar workers and possible implications for cell phone use. *Arch Environ Health* 2003.

- Richter ED, Peretz T. In press. Ethical issues in Molecular Epidemiology, Epimarker Bulletin 2003.
- Richter ED, Chlamtoc N. 2002. Ames, pesticides, and cancer revisited. *Int J Occup Environ Health* 6:63-72.
- 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* 316:17:1044-50.
- 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. 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-(Clin-Res-Ed)* 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* 6:2:193-99.
- Upton AC. 1983. Hiroshima and Nagasaki: forty years later. In: Proceedings of the First International Symposium of the Arch Collegium Ramazzini, 17-18 Oct 1983, Carpi, Italy. 75-92.
- 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 vs. other sources. *Int J Occup Environ Health* 6:2:122-126.
- Weinberg JA. 1982. Current approaches to the experimental investigation of chemicals in relation to cancer of the brain. *Ann NY Acad Sci* 381:43-5.

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* 1:146-7.

### Appendix 1: Estimated interim risks in personnel who were not full time divers with prolonged exposures. (Prepared by L Friedman)

We have carried out a provisional estimate of interim risks in personnel who were not full time divers, based on data published by the GICI (The “Kishon Commission”). The Commission reported a total of 88 cases in 4248 persons reported as having ever been exposed to the Kishon. 51 of these 81 occurred in divers with past heavy exposures.

Within the Unit, there were those who dived a great deal (“All divers” $n=682$ —nicknamed the “heavy smokers” by the divers themselves), and members of the unit who mostly rowed boats—( $n=364$ )—who were not part of this study. The two together totaled 1046. A total of 4248 recruits, including this subgroup of 1046 individuals, passed through the Kishon Naval Diver Unit, but this far larger number (“the ritually immersed”) reportedly had cumulative exposures usually no longer than several days at the most, with a small subgroup having exposures lasting weeks. The calculations below provide crude estimates of risks in the divers compared to the others, and suggest an overall RR much greater than the O/E’s we report.

#### Methods: Relative Risks / Prospective Studies

We used Taylor and Delta methods for calculating the variance of estimated RR

	Dis +	Dis -		
Exp +	A	B	a+b=m1	Pa=a/m1
Exp -	C	D	c+d=m2	Pb=c/m2
				N=denominator=m1 or m2

$$\text{Var}(\text{LN RR}) = \left\{ \frac{(1-Pa)}{Pa} / Na \right\} + \left\{ \frac{(1-Pb)}{Pb} / Nb \right\}$$

95%CI: RR

$$\ln(\text{RR}) \pm 1.96 \sqrt{\left\{ \frac{(1-Pa)}{Pa} / Na \right\} + \left\{ \frac{(1-Pb)}{Pb} / Nb \right\}}$$

OR

$$\ln(\text{RR}) \pm 1.96 \sqrt{\frac{\left\{ \frac{(1-Pw)}{Pw} / (1/Na) + (1/Nb) \right\}}{1}}$$

We normalized the above using the  $\exp^x$ .

$$\text{CI}_{95\%} \ln(\text{RR}) = 1.23, 2.3$$

Convert to (Using  $e^x$ ),

$$\text{CI}_{95\%} \text{RR} = 3.42, 9.97$$

#### Results:

	Dis +	Dis -	
Exp +	51	631	682
Exp -	37	3529	3566
	88		4248

Pa=0.0748  
Pb=0.0104  
ERR=7.19 (CI95%: 4.76 – 10.91)

These interim calculations have several implications.

1. The high RR's in the full time divers relative to the larger group of non-divers, including a select group receiving a short training course, suggest that the risks in the latter large group so far appear to be far less than that of the general population of Israeli born males, --a healthy worker effect.
2. The above finding fits with a healthy worker effect shown by the O/E ratio of 0.69 in the very first cohort of Kishon Divers, the 1948-49 snorkelers. The case for the validity of this inference is suggested by the following calculation: if one hour of diving is equal to risks from smoking a pack of cigarettes, and the immersion exposures did not exceed 10-20 hours at the most, then the cumulative increase in risk is equivalent to 20-40 packs of cigarettes, or less than to 10% of one 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.
5. The findings suggest that the risks for cancer that we report for the full time divers may be underestimates, because we obtain higher risks when we compare these divers to a group more closely similar to it than the general population.
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 non-carcinogenic individuals in susceptible individuals.

Table 1: Industries Contributing Waste to the Kishon Water System: Commercial Product, Years of Production, Known Pollutants in Waste and Mean Daily Effluents

Table 2: Indicators of Water Quality of Kishon Water System: 1955-2000 Mean Levels and 1999 Israeli Water and Sediment Standards

Table 3: Toxics found in Kishon Water System: 1953-2000: Mean Levels, 1999 Israeli Fresh Water Standards and Estimated Dose Intake

Table 4: Cancer Risks in Naval Divers with Multiple Exposures to Carcinogens by Initial Diving Period: Person-Years of Follow-up, Mean Latency and Obs/Exp Ratios

Table 5: Cancer Risks in Naval Divers with Multiple Exposures to Carcinogens by Tumor Site and Year First Diving: Mean Latency and Obs/Exp Ratios

Fig 1: Naval Commando Diver (courtesy of Yediot Aharonot)

Fig 2: Warning Sign: Kishon River

Fig 3: Total Reported Industrial Waste Released Daily Into Kishon Water System and Haifa Bay: Mean Daily Waste (cubits/day) by Decade: 1960's to 1990's

Fig 4: Latency Periods For Cancer in Naval Divers (n=51) in Five Cohorts

<p align="center"><b>Table 1</b>  <b>Industries Contributing Waste to the Kishon Water System</b>  <b>Commercial Product, Years of Production, Known Pollutants in Waste and Mean Daily Effluents</b></p>				
<b>Company</b>	<b>Product</b>	<b>Years of Production</b>	<b>Known pollutants</b>	<b>Mean Daily Effluents (m<sup>3</sup>/day; 1993-99)</b>
Primary Sources of Pollution				
Haifa Refinery	Petrol refinery process includes removal of salts from the petrol, petrol refining, hydrosulfurization, rinsing petrol bi-products, production of lubricants, waxes, asphalts, liquids and gases. 9 million tons of petrol refined in 1999. 5.5 million tons of petrol were refined in 1975.	1938 - present	Aliphatics, aromatics, long-chain and branched hydrocarbons, 2,4,5 - trichlorophenol, Ammonia, mineral oils, detergents, phenols, oil bi-products	12400
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	50480
Haifa Chemicals	Potassium nitrate fertilizers and various K-based food, ceramic, glass and firework products. Including Mn, S, Fe, B, Zn, Cu, Mo, Ca enriched fertilizers.	1960s	KNO3 fertilizers, K, Na, Ca, Mg, B, Fe, Zn, Cr, Cd, Cu, Pb, Hg, Mo, N, P, chromium, P2O5, HNO3, H3PO4, KMg, KB, KCl, KNO3, CaNO3, C5H12O, 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	5714
Deshenim (name)	Fertilizers and various other chemicals	1953 - present	H3PO4, H2SO4, Amonia, HNO3,	1267

Chemicals and Phosphates)	including H3PO4			chlorides, Fluorides, sulfates, nitrates, Ca, Cu, Ba, lime, P, Ammonia, mineral oils, detergents, chlorine, Nitrogen biproducts, Nitrates, Heavy metals, chlorides	
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	1100
Petrochemical Industries	Ethylene, polyethylene, asphalts, polystyrene, rubber	Data Unavailable		Organic matter, carbon byproducts from petrol production, polystyrene solids, ethylene, phenols	250
Other Sources of Pollution 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 (1000 people; residential), Israel Electric Company, Matmar, Compost Factories, Tannery and Leather Hides, Shemen Soap and Cosmetic Products, Tnuva Fish Products	Cement, Dying 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, Na2SO4, Na2CO3, Na2S, NaSH, CH2O2, NH4NO3, amyls, branched hydrocarbons, 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

Source: Industrial products and pollutants: p20-104 of Kishon Commission Report (GI, 2001)  
Greenpeace research laboratories, data on waste water samples from discharges to the Kishon River (22.2.2000)

---

Standards as reported in by the Kishon Commission: 1960 (p.42), 1978 (p. 64), 1980s (p.76; metals), 1999 (p. 292)  
Daily Effluents released: Kishon Report p.48, 71, 81, 290-1

<b>Table 2</b>				
<b>Indicators of Water Quality of Kishon Water System: 1955 - 2000</b>				
<b>Mean Levels and 1999 Israeli Water and Sediment Standards</b>				
<b>Water Quality</b>	<b>Number of reported findings<sup>a</sup></b>	<b>Mean (mg/L unless otherwise specified)<sup>a</sup></b>	<b>Range (mg/L unless otherwise specified)</b>	<b>Standard<sup>b</sup></b>
Temperature (celsius)	8	32	13.5 - 60	<40 degrees
pH	129	6.87	0.5 - 12.3	pH 7 - 8.5
% below 7.0 (38%)	49	4.72	0.5 - 6.9	
% above 8.5 (9%)	11	10.4	8.8 - 12.3	
Color (pt-co units)	21	132.24	22 - 340	
Turbidity (Jackson Units)	29	34.69	0 - 98	
DO (Dissolved Oxygen)	63	24.52	0 - 200	
BOD (Biochemical Oxygen Demand)	120	293.85	0 - 4800	<10 mg/L
COD (Chemical Oxygen Demand)	90	1093.3	0 - 33920	
TSS (Total Suspended Solids)	60	1301.97	19 - 25000	<60 mg/L
TDS (Total Dissolved Solids)	25	10856.84	280 - 53563	
Chlorides	71	4253.82	279 - 80000	Current Levels
Salinity (%)	4	15.9%	0 - 39%	
Chlorine	4	497.84	8.445 - 1527	

<sup>a</sup>Because number of individual measurements per reported findings was in most cases unknown, we do not use weighted means

<sup>b</sup>Kishon Report used reported annual means in most cases omitting number of measurements per reported mean

<sup>c</sup>Israeli standards for water and sediment levels, 1999; source: Kishon Commission (GICI, 2001 p.292)

Israeli standard level for water TSS, 1978 (fresh waters): <60 mg/L ; Source: Kishon Commission (GICI, 2001p.64)

Table 3

**Toxics Found in Kishon Water System: 1953 - 2000**  
**Mean Levels, 1999 Israeli Fresh Water Standards and Estimated Dose Intake**

Exposure	Number of reported findings <sup>a</sup>	Mean (ppm) <sup>a,b</sup>	Range (ppm)	Standard (ppm) <sup>c</sup>	Ratio of mean contaminant levels to standards	Estimated Dose Intake per 24 hours of exposure based on mean contaminant levels: (mg/kg/24hrs) <sup>d</sup>
<b>Elements (water)</b>						
Cd	29	5.59	0 - 56.3	0.005	1117	34.87
Cr	19	77.28	0.305 - 462	0.01	7728	482.37
Chromium	6	0.08	0.0017 - 0.22			0.48
Fe	7	3974.43	56 - 10000			24806.11
Hg	24	2.02	0.00002 - 14.87	0.0005	4031	12.58
Ni	25	10.16	0.005 - 33.5	0.05	203	63.39
Pb	24	43.22	0.0002 - 252	0.01	4322	269.79
<b>Chemical Compounds (water)</b>						
Oil	43	455.41	1.2 - 10000	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 <sub>3</sub> (Nitrate)	9	513.39	4.74 - 3000	10.00	51.34	3204.29
PO <sub>4</sub> (Phosphate)	8	1770.90	3.58 - 4500	0.10	17709.00	11052.95
SO <sub>4</sub> (Sulfate)	16	1229.70	175 - 2750			7675.08
Phenols	7	0.07	0 - 0.132	0.05	1.40	0.44

<sup>a</sup>Because number of individual measurements per reported findings was in most cases unknown, we do not use weighted means  
 Kishon Report used reported annual means in most cases omitting number of measurements per reported mean

<sup>b</sup>All reported water levels were converted to ppm (parts per million of water)

<sup>c</sup>Israeli standards for fresh water, 1999; source: as reported in Kishon report p.292

---

<sup>d</sup>Estimated Dose Intake: formula for absorption through skin from contaminated water is  $EDI = (C \cdot P \cdot SA \cdot ET \cdot EF \cdot .001) / BW$ , where

C=concentration of contaminant in water (mg/L, ppm; based on mean water levels between 1953 -2000),

P=permeability constant, conservative measure of 1.0cm/hour used; SA=surface area of exposed skin, average body of 20+year old male is 18200cm<sup>2</sup>; ET=exposure time, 24 hours used; Exposure Factor=how often an individual was exposed, used 1.0 to keep units per 24 hrs; Used .001 to convert Liters to cm<sup>3</sup>; BW=body weight, average body weight of 20+ year old male is 70kg

\*Estimated Dose Intake: formula for water ingestion exposures of contaminated water is  $EDI = (C \cdot IR \cdot EF) / BW$ , where

C=concentration of contaminant in water (mg/L, ppm; based on mean water levels between 1953 -2000),

IR=Ingestion rate (L/Day); conservative assumption that a diver ingests 0.1L per 24 hours of diving

Exposure Factor=how often an individual was exposed over a lifetime, used 1.0 to keep units per 24 hrs;

BW=body weight, average body weight of 20+ year old male is 70kg

Source for EDI: Investigating Human Exposure to Contaminants in the Environment: A Handbook for Exposure Calculations.

Prepared by The Great Lakes Health Effects Division, Health Protection Branch, Health Canada. 1993.

**Table 4**

**Cancer Risks in Naval Divers with Multiple Exposures to Carcinogens by Initial Diving Period  
Person-Years of Follow-up, Mean latency and Obs/Exp Ratios**

Diver Group by Decade of First Exposure	PYR Follow-up	Mean Latency (years)	Obs	Exp	O/E	p-value
Cohort by Decade						
Before 1950	1166	33 (32-40)	3	4.34	0.69	0.26
1950-59	4550	28.9 (8-46)	16	9.56	1.67	0.02
1960-69	3550	21.9 (5-36)	18	2.73	6.58	P<.01
1970-79	3625	18.6 (3-25)	5	2.79	1.79	0.10
1980-95	4000	7.7 (1-18)	9	1.36	6.62	P<.01
Cohort by Period						
IDF Before 1960	5716	30.4 (8-46)	19	12.02	1.58	0.03
After 1960	11175	17.7 (1-36)	32	8.60	3.72	P<.01
All Groups Combined	16343	22.4 (1-46)	51	22.24	2.29	P<.01

\*\*\*\*PYR follow-up: the mean average years in subgroup from initial exposure to end of follow-up (Dec 31, 2000) multiplied by the number of divers in each subgroup

\*Ref: Morbidity for malignant neoplasms, Jews, Males born in Israel, Israel Cancer Registry, Trends in Cancer in Israel 1993 (published in 1996)

Incidence rates are crude age-specific rates

Stat method for calculating p-value: approximation method for estimating risk based on PYR

Mean latency: eighteen (age divers began service) subtracted from age of diagnosis

**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**

Cancer Type <sup>a</sup>	First Dived: Before 1960					1960-1993				
	Mean Latency (Years)	Obs	Exp	O/E	p-value	Mean Latency (Years)	Obs	Exp	O/E	p-value
Skin	46	1	1.53	0.66	0.34	21.8 (5-32)	6	0.83	7.26	P<0.01
Colon	19.5 (8-31)	2	0.31	6.48	0.0047	19.5 (8-36)	4	0.60	6.63	P<0.01
Stomach	40	1	1.01	0.99	0.496	17 (8-25)	3	0.53	5.71	P<0.01
Leukaemia	29 (28-30)	2	0.35	5.74	0.0078	22	1	0.76	1.32	0.4
Malignant Lymphoma <sup>b</sup>	38	1	2.52	0.40	0.1736	14.8 (3-28)	4	1.01	3.98	P<0.01
Brain and CNS	15.5 (9-22)	2	0.16	12.50	P<0.01	15.5 (1-29)	6	0.31	19.18	P<0.01
Lung	36.7(31-43)	3	2.26	1.33	0.32	20 (5-35)	2	0.30	6.63	P<0.01
Testicular	n/a	0	n/a	n/a	n/a	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 <sup>c</sup>	30.5 (30-31)	4	n/a	n/a	n/a	13 (4-22)	2	n/a	n/a	n/a
Unknown	19	1	n/a	n/a	n/a	22	1	n/a	n/a	n/a

\*Source for Expected Cases: Morbidity for malignant neoplasms, Jews, Males 1993; (Israel Cancer Registry, 1996)

<sup>a</sup>Trends in Cancer in Israel (Standardized rates per 100,000)

Cases include two women: 1 Leukemia, 1 Lymphoma; PYR follow-up: the mean average years in subgroup from initial exposure to end of follow-up (Dec 31, 2000). multiplied by the number of divers in each subgroup. Mean PYR followup for divers initially exposed before 1960 was 5716, and 11175 for divers initially exposed 1960 forward.

<sup>b</sup>Rates for malignant lymphoma are for Morbidity for malignant neoplasms, Jews, Males 1995 from Israel Cancer Registry, 1998 Trends in Cancer Morbidity and Mortality in Israel: 1970-1995. Data for 1993 malignant lymphoma rates were unavailable. (Standardized rates per 100,000)

<sup>c</sup>Other Tumors: Pre-1960 one case each of liver, pancreas, salivary, thymus. Post-1960 one case each of thyroid and thymus

דיעות אחרונות

ימים

1994  
יום שישי 25.3.1994

בפירוט לתום הסיפור,  
רוב ליכנסו דיל, ציל 25  
סנה מרדכי, גמרי לאיר  
סוחה מרדכי גמיל 44

תחקיר

עשרות מלוחמי הקומנדו הימי שצללו בטי הקישון, הנחל המזוהם ביותר בישראל, לקו בסרטן. רוחות רשמיים: המים מכילים ריכוז קטלני של חומרים מסרטנים. מומחים קובעים: יש קשר סיבתי בין הצלילות במקום להתפרצות המחלה. דובר צה"ל: הקשר לא הוכח

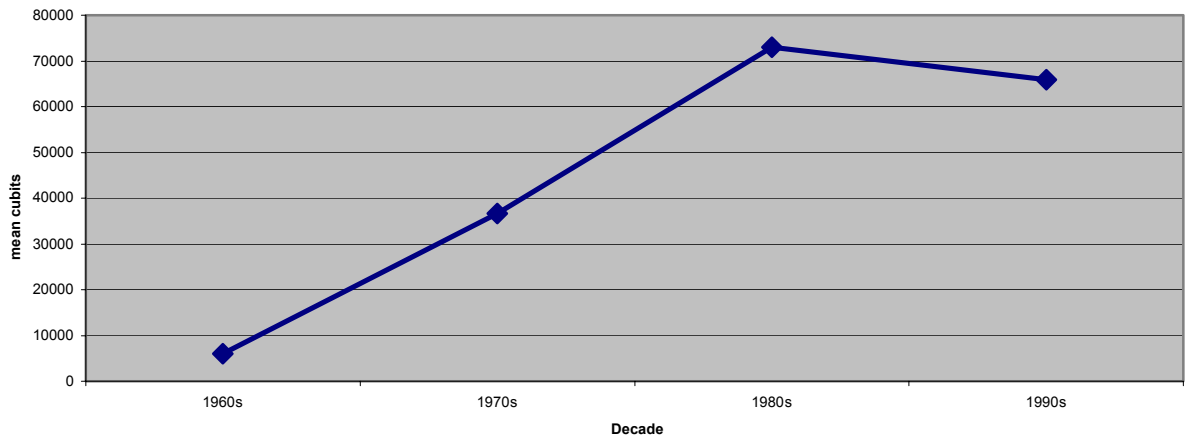
# סרטן בקומנדו הימי

ענת טר'שיר, צדוק יחזקאלי, עמ' 16





**Figure 3**  
**Total Reported Industrial Waste Released Daily into Kishon Water System and Haifa Bay**  
**Mean Daily Waste (cubits/day) by Decade 1960s-1990s**



Data source: Kishon Report p.48, 71, 81, 290-1  
 1960s: Data for 1962, waste from 7 companies, cumulative daily waste 6019.7 mean cubits/day; 1970s: Data for 1972, 1975, waste from 17 measurements (14 companies), cumulative daily waste 22115 (1972) and 51218 (1975); 1980s: Data for 1984, waste from 9 companies, cumulative daily waste 72990; 1990s: Data for 1993, 1996, 1997, 1998, 1999, waste for 36 measurements (10 companies), cumulative daily waste 99650 (1993), 55361 (1996), 57644 (1997), 76327 (1998) and 40373 (1999).

**Figure 4:**  
**Kishon Divers with Cancer: Induction Periods**

