

Comments Regarding Causal Associations Between Ecuador Oil Exploration and Health Claims

David J. Hewitt, M.D., M.P.H.
January 24, 2005

1.0 INTRODUCTION

I am an occupational medicine physician and have been requested to comment on the potential causal association of Ecuador oil exploration and various reported health effects. I currently serve as the Director of Occupational Health Services for the Center for Toxicology and Environmental Health (CTEH), L.L.C. in Little Rock, Arkansas. CTEH is an environmental consulting firm that has several specialties including toxicology, occupational medicine, emergency response to chemical releases, and risk assessment. CTEH works with clients throughout the U.S.

My educational background includes a Bachelor of Science degree in Chemistry in 1983, an M.D. in 1987, and a Masters of Public Health in Epidemiology in 1991. I have completed residencies in general preventive medicine/public health and occupational medicine and am board-certified in both of these specialties by the American Board of Medical Specialties. I am licensed to practice medicine in four states in the U.S. and am a member of the American College of Occupational and Environmental Medicine.

My medical training and subsequent work over the past 14 years has focused on environmental epidemiology, toxicology, and occupational medicine. I have worked with local, state, and national public health agencies in the U.S. in the areas of environmental epidemiology and toxicology. I served for two years as a medical officer with the U.S. Department of Health Services Agency for Toxic Substances and Disease Registry (ATSDR) in Atlanta, GA, where I conducted environmental epidemiology studies and provided consultation to both medical providers and the general public throughout the U.S. regarding chemical exposures. As an occupational medicine physician I have been involved directly in the treatment of various work-related injuries and illnesses regarding possible health effects from chemical exposures.

2.0 REVIEW OF HEALTH CLAIMS

I have reviewed several references which have examined various health effects in Ecuador residents living near oil exploration sites. These references have suggested that the reported health effects may be causally related to chemical exposures from oil exploration. The purpose of my review was to objectively determine whether these studies and other relevant information support such a causal relationship.

2.1 Criteria for Establishing Causation

When performing a scientific evaluation of a reported chemical exposure, two different types of causation analyses are often described: a *general* and a *specific* causation analysis. General causation refers to the determination as to whether or not the chemical in question is capable of causing a particular condition. Specific causation refers to the determination as to whether the exposure in question was the ultimate cause of illness in a particular individual. A number of different criteria have been proposed for establishing general causation (Doll, 1984; Hill, 1965). The original Hill criteria include 1) strength of the human association; 2) consistency of the human association; 3) specificity of the human association; 4) temporality; 5) biological gradient or dose-response; 6) biological plausibility; 7) coherence; 8) experimental evidence; and 9) analogy (structure activity relationships with other chemicals suggest the chemical should be capable of producing the toxic effect). An additional suggested criteria is 10) confounders or the elimination of alternative explanations that could explain the results.

These criteria are widely accepted among the scientific community. Scientific bodies that use most or all of these principles include the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), the United States Environmental Protection Agency (USEPA), and the American Conference of Governmental Industrial Hygienists (ACGIH). These criteria are also discussed in modern textbooks of epidemiology (Monson, 1990; Mausner and Kramer, 1985), occupational medicine (McLaughlin and Brookmeyer, 1994), and toxicology (Faustman and Omenn, 1996). Thus, the consensus opinion in the scientific community is that the “Hill” criteria as discussed above should be a cornerstone of the scientific method for establishing general causation.

In performing a case-specific causation analysis, clearly a general causation analysis should be completed to establish the toxicities that are known to occur with exposure to the chemical and the relevant conditions of exposure. Not all criteria used to establish general causation may be applicable to specific analyses. However, in examining individual issues of causation secondary to chemical exposures, these criteria can be summarized using several key questions: 1) Are the observed health effects consistent with the known toxicologic effects of the chemical? 2) Did exposure occur? 3) Is there a consistent dose-response relationship between exposure and effects? 4) Is there a consistent temporal relationship between the onset of effect and exposure? and 5) Are there any confounders or alternative explanations for the reported health effects which cannot be reliably excluded? In general, each of these questions must be answered affirmatively for each case in order to conclude a causal association exists between the alleged chemical exposure and health effect. This is essentially the same approach that has been proposed in the toxicology textbook *Hazardous Materials Toxicology: Clinical Principles of Environmental Health* by Sullivan and Krieger (1992).

To summarize, there is an established and accepted methodology by which scientists and physicians determine cause and effect relationships from chemical exposures. This methodology was applied in reviewing claims of health effects in residents living near oil

exploration areas. In this case, a causal relationship between residence near the oil fields and the reported health effects simply cannot be supported due to failure to satisfy one or more of these basic questions. Specific references and the rationale for these conclusions are discussed in detail below.

2.2 Cancer and Residence Near Oil Exploration Areas

Childhood leukemia

Hurtig and San Sebastian (2004) reported a possible relationship between childhood leukemia and living near oil exploration areas in the Ecuadorian Amazon. The authors examined cancer cases occurring in children 0-14 years of age which were reported to the National Cancer Registry in Quito during 1985-2000. Cases were defined as “exposed” if they lived in a county where oil exploration had been ongoing for at least 20 years at the time of the study. “Non-exposed” cases were defined as those who lived in counties without oil development activities.

The authors identified a total of 91 cancer cases in the study group of which 28 cases of leukemia and 27 cases of other cancers occurred in exposed counties. It was noted that the relative risk for leukemia showed significantly elevated levels in the exposed group for the youngest age group (0-4 years of age), and for females and both genders combined for all leukemia cases 0-14 years of age. There were no significant differences in relation to exposure status and other cancers. Of the leukemia cases, acute lymphoblastic leukemia (ALL) accounted for 20 (71%) of the leukemia cases. ALL was found to be significantly elevated in the exposed counties for females and for both genders combined. The authors suggested a possible exposure pathway was contaminated water. The petroleum hydrocarbons considered to be of toxicologic interest were volatile organic compounds (VOC’s) such as benzene, xylene, and toluene, and polynuclear aromatic hydrocarbons (PAH’s). It was noted that benzene is a “well-known cause of leukemia” although “no adequate data on the incidences of cancers after human exposures to the other volatile organic chemicals exist.”

As the authors acknowledge, there are a number of weaknesses in the study and “this ecologic study cannot lead to a causal inference.” The first of these weaknesses involves the validity of the rate calculations that were reported. As noted by the authors there were uncertainties regarding identification of all cases in both exposed and unexposed counties (i.e., incomplete case ascertainment) and potential errors in population estimates. Significant errors in either of these factors would result in calculated disease rates which are inaccurate and are not reliable. More specifically, baseline population for the study areas was determined using 1993 census data which were projections of the 1990 National Census. The authors have noted that it is possible that exposed counties have had a more rapidly increasing population compared to non-exposed counties. In terms of rate calculations, this would result in a comparative underestimate of the true population in the exposed counties after 1993 compared to the non-exposed counties. Such an error would result in an erroneously increased cancer rate in the exposed population due to the fact that the denominator data or baseline population used in the calculations was low. Additional uncertainty regarding the accuracy of case ascertainment was noted in that

cancer rates were based on the county of residence at the time of diagnosis without information on the current length of residence.

A primary weakness in the study is the lack of exposure assessment. A specific chemical of concern was not identified; a specific exposure pathway of concern was not identified; there was no environmental data presented for the exposed population; and there was no information presented to determine if “exposed” cases actually had different exposures. Without such data to confirm exposures in identified cases, a causal relationship cannot be supported. In addition, there was no review of medical records for cases to determine if other causes of illness had been ruled-out. Finally, there was no evidence presented that establishes a known association between chemical exposure and ALL.

ALL is the most common childhood cancer in the U.S. and other developed countries. The cause is unknown in almost all cases. Identified risk factors include exposure to ionizing radiation, Down’s syndrome, and certain other rare genetic diseases. A possible infectious etiology has often been considered but has not been established (Campana and Pui, 2004). Of potential relevance is the identification of malnutrition as a potential risk factor for ALL (Sahin et al., 2000).

Of the chemicals listed by the authors, only benzene has been established as a possible cause of leukemia. While benzene has been associated with a higher rate of leukemia in individuals who are occupationally exposed to high levels of benzene, the type of leukemia most often linked with benzene is acute myelogenous leukemia (AML) rather than ALL. AML associated with benzene exposure is rare even in individuals with high level exposures. Benzene exposure explains very few, if any, cases of leukemia in individuals without direct occupational exposure.

There is little evidence linking the occurrence of ALL in children to exposure to petroleum constituents. A recent study by Steffen et al. (2004) reported an association between childhood acute leukemia and living near auto-repair garages or petrol stations, which possibly expose children to benzene. However, the authors acknowledge that reporting bias or “over-declaration” by the cases’ mothers of possible risk factors could not be excluded. Actual exposures occurring in study participants were not confirmed with environmental data. In addition, the number of cases reporting such an association was relatively small (i.e., 17 of 249 cases reported living near a repair garage or petrol station versus 7 of 285 in the controls). As noted by Steffen et al., several other studies have attempted to link clusters of ALL to living near oil refineries or air pollution. Due to study weaknesses such as those described above, a causal association between benzene exposure and ALL has not been established. Steffen et al. note that “direct implication of exposure to benzene in childhood leukemia has never been reported.”

In summary, a causal association between living near an oil production area in Ecuador and childhood leukemia cannot be supported based on the following:

- A known association between ALL and exposure to various chemicals such as VOC’s has not been established in the scientific literature;
- A specific chemical of concern has not been identified;

- An exposure pathway of concern has not been established;
- Exposures in identified cases were not confirmed;
- The proximity of cases to actual oil exploration areas is unknown;
- Basic uncertainties regarding the baseline population and completeness of case ascertainment make reliable rate calculations impossible. It is not possible to determine whether the rates of leukemia in the identified populations are significantly different from background rates.
- Medical histories and potential other risk factors (i.e., Down's syndrome or others) for the identified cases were not reported.

Adult cancers

In a methodologically similar study, Hurtig and San Sebastian (2002) examined geographical differences in cancer incidence in Ecuador in relation to residence near oil fields. The authors examined cancer cases which were reported to the National Cancer Registry in Quito during 1985-1998. Cases were defined as "exposed" if they lived in one of four counties where oil exploration had been ongoing for at least 20 years at the time of the study. "Non-exposed" cases were identified as those who lived in one of 11 counties without oil development activities. The authors identified a total of 473 cancer cases in the exposed group and 512 in the non-exposed group. Several types of cancer were identified as being significantly higher in the exposed group and included stomach cancer, rectal cancer, melanoma, soft tissue cancer, and kidney cancer in men and cervical cancer and lymph node cancer in women. An increase in hematopoietic cancer was noted in individuals less than 10 years of age. The authors again suggested a possible exposure pathway was contaminated water. The petroleum hydrocarbons considered of toxicologic interest were volatile organic compounds (VOC's) such as benzene, xylene, and toluene, and PAH's.

As the authors acknowledge, there are a number of weaknesses in the study and "this ecologic study cannot lead to a causal inference." Specific weaknesses identified by the authors include uncertainties regarding identification of all cases in both exposed and unexposed counties (i.e., incomplete case ascertainment) and potential errors in population estimates. Of particular relevance is the possibility that the exposed counties have had more rapidly increasing population compared to non-exposed counties which would affect rates calculated based on 1992 census data. Thus, an underestimation of the baseline population in the exposed counties would result in spuriously increased cancer rates as explained previously. Significant errors in either case ascertainment or population estimates would result in calculated disease rates which are inaccurate and unreliable. It was also noted that cancer rates were based on the county of residence at the time of diagnosis without information on the current length of residence.

As in the leukemia study, a primary weakness in the study is the lack of exposure assessment. A specific chemical of concern was not identified; a specific exposure pathway of concern was not identified; there was no environmental data presented for the exposed population; and there was no information presented to determine if "exposed" cases actually had different exposures.

There was no discussion regarding the biological plausibility that the alleged exposures would result in elevations of widely different types of cancer or that significantly elevated risks for stomach cancer, kidney cancer, or soft tissue cancer were only seen in one sex. Except for stomach and cervix cancers, the number of cancer cases for other sites which were reported as significantly increased were all less than 10. Given the uncertainties regarding case ascertainment and population data, it is difficult to make any reliable conclusions regarding the significance of these rates based on so few cases.

In addition there was little or no discussion of other risk factors for the types of cancers that were elevated, particularly for cervical cancer and stomach cancer--the two most commonly identified types of cancer. The highest incidence rates for cervical cancer by far are seen in Central America, Africa, the Caribbean, and South America (Franco et al., 2001). The primary risk factor for cervical cancer is infection with the human papilloma virus (HPV) which is the cause of genital warts and has been estimated to account for more than 80% of all invasive cervical cancers (Russell et al., 2004). Franco et al. (2003) note that virtually all cervical carcinoma specimens contain HPV DNA suggesting that HPV infection is a necessary cause of this type of cancer. Other identified risk factors include early age at first intercourse, multiple sex partners, early childbearing, a history of sexually transmitted diseases, and cigarette smoking. Nutritional factors such as vitamin A or C deficiencies also have been identified as a potential risk factor (Stenchever, 2001). The study by Hurtig and San Sebastian has failed to address the influence of these risk factors in the population they studied. Finally, a plausible link between exposures from oil exploration and cervical cancer has not been identified in the scientific literature.

Stomach cancer is considered the second leading cause of cancer death worldwide with high rates in Japan, China, Central and South America. A large number of studies have indicated that dietary factors are a major risk factor. Reasons commonly cited for a decline of gastric cancer in developed countries include better refrigeration, reduced consumption of salted, smoked, and chemically preserved foods, and increased intake of food and vegetables (Plummer et al., 2004; Roder, 2002). Refrigeration is believed to result in lower levels of bacterial, fungal, and other contaminants of fresh food and decrease the bacterial formation of nitrites. Infection with *Helicobacter pylori* (*H. pylori*), often associated with peptic ulcer disease, has been considered a primary risk factor in the development of stomach cancer (Koh and Wang, 2002). Huang and Hunt (2000) have noted that gastric carcinogenesis is a multistep process which begins with *H. pylori* associated gastritis in most cases. Again, the influence of these recognized risk factors was not addressed by Hurtig and San Sebastian.

As the authors note in their discussion, the International Agency for Research on Cancer has concluded that there was inadequate evidence for the carcinogenicity of crude oil in humans, much less evidence for an association with a half-dozen or more different cancer types. Many of these weaknesses were identified in a review of the study published in the same journal issue (Siemiatycki, 2002).

The “Yana Curi” Report by San Sebastian and Cordoba (1999) similarly discussed the occurrence of 10 cancer cases in the community of San Carols from 1985-98 and attributed them to residence near oil exploration. Again, the types of cancers were widely divergent (i.e., 3 stomach cancers, one larynx cancer, one liver cancer, one melanoma, one bile duct cancer, one cervical cancer, one lymphoma, and one leukemia). Specific exposures in these individuals were not identified and there was no information provided on their medical histories.

In summary, a causal association between living near an oil production area in Ecuador and various cancers cannot be supported based on the following:

- A known association between exposure to various chemicals such as VOC’s and the reported types of cancer has not been established;
- A specific chemical of concern has not been identified;
- An exposure pathway of concern has not been established;
- Exposures in identified cases were not confirmed or quantified;
- The proximity of cases to actual oil exploration areas is unknown;
- Basic uncertainties regarding the baseline population and completeness of case ascertainment make reliable rate calculations impossible;
- Medical histories and potential other risk factors (i.e., dietary factors, nutritional status, infections, sexually transmitted disease, and others) for the identified cases were not reported or excluded.

2.3 Spontaneous Abortion and Residence Near Oil Exploration Areas

San Sebastian et al. (2002) examined pregnancy outcomes among “exposed” women living within 5 km of an oil field and compared them to “non-exposed” women who lived at least 30 km from an oil field. The target population was defined as women aged 17-45 who had lived in the study communities for at least three years. Participants were given a questionnaire which asked about reproductive history. Pregnancies were defined as a delayed period perception by the subject. Spontaneous abortion was defined as fetal loss at 28 weeks gestation or earlier. Only self-reported miscarriages were considered.

Total petroleum hydrocarbons (TPH) were measured in rivers near the study communities. It was noted that 18 of 20 streams near the exposed communities had TPH concentrations ranging from 0.02-2.883 ppm. Two of the streams in the exposed group showed no contamination and no TPH contamination was found in the two water samples taken from rivers close to non-exposed communities. Of note was the finding that only 7.3% of the exposed participants reported drinking from the river. Only 28-35.9% of the exposed participants reported either bathing or washing in the river.

Of the 610 identified exposed and 439 non-exposed women identified for participation in the study, questionnaire data was available for 365 (59.8%) and 283 (64.4%) of the exposed and non-exposed group, respectively. The percentage of pregnancies ending in spontaneous abortions was calculated as 9.8% for the exposed group versus 4.4% for the non-exposed. The authors concluded that the study “revealed a risk for spontaneous

abortion 2.34 times higher among women living in communities exposed to oil pollutants.” No association based on exposure status was seen for stillbirth.

As noted by the authors, there are a number of potential limitations in interpreting these results. In this case, spontaneous abortions were identified based on self-reported history with no confirmation through medical data or even confirmation of pregnancy prior to the reported spontaneous abortion. It is impossible to make any reliable conclusions regarding causation without more objective data to confirm that a) pregnancy actually occurred and b) a spontaneous abortion actually occurred. An additional problem with this type of design based exclusively on self-reported information is the potential for recall bias (i.e., the possibility that individuals who believe they have been exposed may be more likely to recall a spontaneous abortion than those who do not believe they were exposed).

A second major methodological weakness of the study is the relatively low participation rates (i.e., <60% in the exposed group). The reasons for the decreased participation rates were not identified. However, the possibility individuals in the study would be more likely to participate if they believed they had experienced an adverse pregnancy outcome than those who had not cannot be excluded. This is a form a response/non-response bias which may significantly affect calculated spontaneous abortion rates, particularly since there were relatively few reported cases. No data was presented to address whether self-reported spontaneous abortion rates in non-respondents were different.

A third major weakness of the study is that the spontaneous abortion rate calculated for the exposed group is actually well within normal background rates and is inconsistent with a significant environmental effect. It was noted by the authors that the baseline prevalence of spontaneous abortion for females living in the Orient is 10%. This is consistent with and actually lower than other estimates of spontaneous abortion rates in the general population of the U.S. and other countries. For example, Stenchever et al. (2001) has noted that 15-20% of all known human pregnancies terminate in clinically recognized abortion. Depending on the sensitivity of study methods for identifying pregnancy and participant risk factors such as increasing parity, increasing maternal age, or history of previous spontaneous abortions, much higher rates may be seen. San Sebastian et al. note that the rate of spontaneous abortion in the unexposed population was 4.4% which suggested a “true low risk or underreporting.” Regardless, the spontaneous abortion rate for the exposed population was still within normal or expected background rates. Thus, based on a calculated exposed population spontaneous abortion rate which was below commonly accepted background rates in the general population and a spontaneous abortion rate in the unexposed population which appears unrealistically low, it is difficult to conclude that an excess of spontaneous abortions was actually identified.

Finally, there is little information provided verifying exposure among the participants to TPH in water. Less than 10% of the exposed participants reported drinking water from the river. There was no correlation made between the amount of TPH identified in water and the spontaneous abortion rates. In fact, TPH was not even found in water from one

of the exposed communities. There was no discussion of the dose of TPH that would occur in the exposed individuals or whether such a dose has been shown to be associated with increased spontaneous abortion rates.

In summary, a causal association between TPH exposure from rivers in the area and spontaneous abortion cannot be supported based on the following:

- The validity of pregnancy reports or subsequent spontaneous abortion is unknown due to the lack of confirmatory medical data;
- Reliance on self-reported information for pregnancy and spontaneous abortion significantly limits interpretation of results due to the possibility of recall bias;
- A relatively low participation rate of <60% in the exposed population further limits interpretation of results due to the possibility of non-response bias;
- TPH exposure in the study population was not quantified;
- Questionnaire data indicates only 7% of exposed participants actually reported drinking water from the river;
- No data was presented indicating that exposure to TPH at the levels identified has been associated with increased risk of spontaneous abortion;
- Calculated spontaneous abortion rates in the exposed population were within normal background rates reported in the general population.
- Medical histories and potential other causes of spontaneous abortion for the study participants were unknown.

2.4 Other Medical Conditions and Residence Near Oil Exploration Areas

It is my understanding that a number of other medical conditions such as dermatologic or respiratory conditions have been attributed to various exposures related to oil exploration (San Sebastian and Cordoba, 1999). Specific studies of these conditions or documentation of increased rates in the area were not available for review. However, as described above, cases suspected of having a causal relationship to oil exploration-related exposure must be evaluated in a systematic way to determine the validity of such an association. The chemical of concern must be identified; the health effect must be consistent with known health effects of the chemical; an exposure pathway must be identified; the exposure must be quantified to determine if the health effect is consistent with known dose-response relationships; and the temporal relationship between exposure and the health effect must be consistent (i.e., the health effect must occur within the expected time-frame after exposure). Finally, alternative explanations or confounders for the health effect must be examined and ruled-out before attributing the health effect to a chemical exposure. Depending on the health effect in question, a number of relevant confounders may need to be examined including infectious disease, non-chemically related skin conditions, nutritional status; habits, past medical history, and others. In particular, the exclusion of infectious diseases which may be prevalent in Ecuador but relatively uncommon elsewhere may need to be examined in detail (Guzman et al., 1995).

As discussed in detail above, the influence of infections and nutritional factor in diseases such as cervical and gastric cancer is well-established and must be considered the

overwhelming etiologic factor in these types of cases rather than uncharacterized exposures attributed to oil field exploration.

3.0 CONCLUSION

Based on my training and experience in epidemiology, toxicology, and occupational and environmental medicine, it is my opinion that a causal relationship between living near areas of oil exploration in Ecuador and health conditions such as adverse pregnancy outcomes and cancer cannot be supported based on an inability to satisfy basic criteria for establishing causation. These deficiencies include:

- Health effects which are not consistent with known health effects of the reported chemicals;
- Incomplete exposure assessment;
- No objective verification of exposure or magnitude (dose-response) of exposure in study participants;
- Significant methodological problems in health studies which precludes any type of causal conclusion;
- Other potential causes for reported health effects were not reliably excluded. In the case of cancer, recognized risk factors such as infections or nutritional factors were not addressed.



David J. Hewitt, M.D., M.P.H.

4.0 REFERENCES

- Campana, D. and Pui, C. H. Childhood leukemia. Chapter 101 In: Abeloff, M. D., Editor. *Clinical Oncology*. 3rd ed. Philadelphia: Elsevier; 2004; pp. 2731-2764.
- Doll, R. Occupational cancer: problems in interpreting human evidence. *Ann Occup Hyg*. 1984; 28(3):291-305.
- Faustman, E. M. and Omenn, G. S. Risk assessment. In: Klaassen, D. C.; Amdur, M. O., and Doull, J., Editors. *Cassarett and Doull's Toxicology: The Basic Science of Poisons*. 5th ed. New York: McGraw-Hill; 1996; pp. 75-88.
- Franco, E. L.; Duarte-Franco, E., and Ferenczy, A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. *CMAJ*. 2001 Apr 3; 164(7):1017-25.
- Franco, E. L.; Schlecht, N. F., and Saslow, D. The epidemiology of cervical cancer. *Cancer J*. 2003 Sep-2003 Oct 31; 9(5):348-59.
- Guzman, J. R.; Jurado, H. M., and Kron, M. A. Infectious Disease in Ecuador. *J Travel Med*. 1995 Jun 1; 2(2):89-95.
- Hill, A. B. The environment and disease: association or causation? *Proc R Soc Med*. 1965 May; 58:295-300.
- Huang, J. Q. and Hunt, R. H. Review article: *Helicobacter pylori* and gastric cancer--the clinicians' point of view. *Aliment Pharmacol Ther*. 2000 Oct; 14 Suppl 3:48-54.
- Hurtig, A. K. and San Sebastian, M. Geographical differences in cancer incidence in the Amazon basin of Ecuador in relation to residence near oil fields. *Int J Epidemiol*. 2002 Oct; 31(5):1021-7.
- Hurtig, A. K. and San Sebastian, M. Incidence of childhood leukemia and oil exploitation in the Amazon basin of Ecuador. *Int J Occup Environ Health*. 2004 Jul-2004 Sep 30; 10(3):245-50.
- Koh, T. J. and Wang, T. C. Tumors of the stomach . Chapter 44 In: Feldman, M.; Friedman, L. S., and Sleisenger, M. H., Editors. *Sleisenger & Fordtran's gastrointestinal and liver disease : pathophysiology, diagnosis, management*. 7th ed. Elsevier; 2002.
- Mausner, J. S. and Kramer, S. The concept of causality and steps in the establishment of causal relationships. In: Mausner, J. S. and Kramer, S. *Mausner & Bahn Epidemiology--an introductory text*. 2nd ed. Philadelphia: W.B. Saunders Company; 1985; pp. 180-194.

- McLaughlin, J. K. and Brookmeyer, R. Epidemiology and biostatistics. In: McCunney, R. J., Editor. A practical approach to occupational and environmental medicine. 2nd ed. Boston: Little Brown; 1994; pp. 346-357.
- Monson, R. R. The interpretation of epidemiologic data. In: Monson, R. R. Occupational epidemiology. 2nd ed. Boca Raton: CRC Press; 1990; pp. 87-101.
- Plummer, M.; Franceschi, S., and Munoz, N. Epidemiology of gastric cancer. IARC Sci Publ. 2004; (157):311-26.
- Roder, D. M. The epidemiology of gastric cancer. Gastric Cancer. 2002; 5 Suppl 1:5-11.
- Russell, A. H.; Seiden, M. V.; Duska, L. R.; Goodman, A. K.; Lee, S. I.; Digumarthy, S. R., and Fuller, A. F. Jr. Cancers of the cervix, vagina, and vulva. Chapter 90 In: Abeloff, M. D. et al, Editors. Clinical oncology. 3rd ed. Elsevier; 2004.
- Sahin, G.; Ertem, U.; Duru, F.; Birgen, D., and Yuksek, N. High prevalence of chronic magnesium deficiency in T cell lymphoblastic leukemia and chronic zinc deficiency in children with acute lymphoblastic leukemia and malignant lymphoma. Leuk Lymphoma. 2000 Nov; 39(5-6):555-62.
- San Sebastian, M.; Armstrong, B., and Stephens, C. Outcomes of pregnancy among women living in the proximity of oil fields in the Amazon basin of Ecuador. Int J Occup Environ Health. 2002 Oct-2002 Dec 31; 8(4):312-9.
- San Sebastian, M. and Cordoba, J. A. "Yana Curi" Report. The impact of oil development on the health of the people of the Ecuadorian Amazon. Departamento de Pastoral Social del Vicariato Apostólico of Aguarico and London School of Hygiene and Tropical Medicine ; 1999 Jun.
- Siemiatycki, J. Commentary: Epidemiology on the side of the angels. Int J Epidemiol. 2002 Oct; 31(5):1027-9.
- Steffen, C.; Auclerc, M. F.; Auvrignon, A.; Baruchel, A.; Kebaili, K.; Lambilliotte, A.; Leverger, G.; Sommelet, D.; Vilmer, E.; Hemon, D., and Clavel, J. Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study. Occup Environ Med . 2004 Sep; 61(9):773-8.
- Stenchever, M. A. et al. Spontaneous and recurrent abortion: etiology, diagnosis and treatment. Chapter 16 In: Stenchever, M. A. et al. Comprehensive gynecology. 4th ed. St. Louis: Mosby; 2001; pp. 413-441.
- Stenchever, M. A. et al. Intraepithelial Neoplasia of the Cervix: Etiology, Screening, Diagnostic Techniques, Management. Chapter 28 In: Stenchever, M. A. et al. Comprehensive gynecology. 4th ed. St. Louis: Mosby; 2001; pp. 857-888.

Sullivan, J. B. Jr. and Krieger, G. R. Hazardous materials toxicology. Baltimore:
Williams & Wilkins; 1992.