

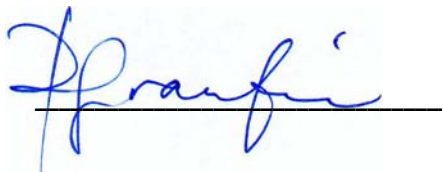
**The Matter of An Arbitration Under the Rules of the United
Nations on International Trade law
Chevron Corporation and Texaco Petroleum Company v. The
Republic of Ecuador
PCA Case 2009-23**

Opinion of Philippe Grandjean, MD

November 22, 2013

**Prepared for
Winston & Strawn, LLP
1700 K Street N.W.
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Prepared by



**Philippe Grandjean, MD, DMSc
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I. Summary of credentials

I am Professor and Chair of Environmental Medicine at the University of Southern Denmark, Odense, Denmark. I am also Adjunct Professor of Environmental Health at Harvard School of Public Health, where part of my research is based.

My academic degrees (MD and DMSc) are both from the University of Copenhagen, Denmark. Following postgraduate university fellowships and a Fulbright senior research scholarship at Mount Sinai School of Medicine in New York City, I became the founding Director of the Department of Occupational Medicine at the Danish National Institute of Occupational Health in 1980. I moved on to become a full university professor in 1982, and the following year I was recruited as the Consultant in Toxicology at the Danish National Board of Health. I continue to serve in both positions. In 1994, I became Adjunct Professor of Environmental Health and Neurology at Boston University Schools of Medicine and Public Health until I moved to Harvard in 2003.

I have served on or chaired committees under the auspices of the World Health Organization, the International Agency for Research on Cancer, the International Union of Pure and Applied Chemistry, and European Union agencies, and current memberships include the Scientific Committee of the EU's European Environment Agency. I serve on editorial boards of several scientific journals and, since 2002, am co-founding editor-in-chief of Environmental Health. I have published over 500 scientific articles and book chapters focused on adverse human health effects associated with exposures to toxic chemicals. Among books that I have written or edited is a textbook on risk assessment. A detailed CV is available as Appendix B.

II. Scope of retention/underlying basis of opinion

In connection with the arbitration between Chevron and the Republic of Ecuador, I have been retained to evaluate the likelihood of adverse health effects in Ecuadorean populations exposed to environmental hazards from oil exploration, production, and transport in the El Oriente region of Ecuador.

My opinions in this expert report are given to a reasonable degree of scientific probability. They are based on my education, professional experience, information and data available in the scientific literature, and information and data about this lawsuit made available to me at the time these opinions were formulated. If additional information becomes available, I reserve the right to supplement my opinion to reflect such information.

III. Summary of opinions

TexPet operated in El Oriente, an Ecuadorean region that has limited access to health care, and where medical records are incomplete. Extensive data summarized by Dr. Strauss in her opinions show that TexPet's exploration, extraction, and transportation of crude oil led to releases of toxic chemicals into the environment, and that the toxicants remain a serious hazard many years after the operations were halted. Some dissemination still

occurs via the air, but most current exposures are via water, soil, and food. The multi-pathway exposures encountered by the residents are likely to have resulted in uptakes of toxic compounds that equal or exceed those known to occur in occupations related to oil extraction, production, or clean-up.

Because of the remoteness of the exposed areas from Quito and other major cities, access to health care and the completeness of record-keeping are less than optimal. Nonetheless, initial community-based studies recorded links between oil-related exposures and acute or short-term effects, such as skin rashes and skin or eye irritation, and less well defined problems, such as headaches, nausea, anxiety and ill-health.

Due to the known carcinogenicity of crude oil constituents, several subsequent studies focused on the cancer occurrence in areas involved in oil extraction. These studies began with case series and were then extended to the four cantons where the oil industry had been most active near residential areas for the longest time. Despite the known difficulties in obtaining accurate data on cancer cases, the most reliable studies have shown clear excesses in cancer rates. These results are remarkable, as the cases mainly occurred in middle-aged adults while allowing only for fairly short latency times that were mostly less than two decades after first exposure to oil chemicals. An increased rate of childhood leukemia was also found, and other reports show increased rates of spontaneous miscarriage, malformations and child mortality.

These links between the exposures in the affected areas and cancer are supported by the finding of DNA damage in blood cells from inhabitants in the Sachas canton, i.e. one of the areas with long-term oil production.

On the other hand, two studies funded by Chevron considered several additional cantons as “exposed”, either based on “visual inspection” of a map showing oil production activities or based on the presence of oil production. These two studies found no clear evidence of excess cancer rates in the larger groups of cantons. Although the follow-up was longer than in the initial studies, the residence at the time of death results in an increasing degree of exposure misclassification due to movement in and out of exposed cantons. Given the method of canton selection, the likely dilution of the average exposure of the residents considered exposed, and misclassification based on residence at the time of death, the non-informative findings are not surprising.

Overall, the balance of evidence clearly favors the presence of a serious environmental hazard that is already impacting human health. The short follow-up, the general weaknesses of the study designs, and the incomplete nature of the available information suggest that the risk of adverse human health effects may have been seriously underestimated, as has been shown in numerous similar cases in the past, where early information was uncertain and erroneously interpreted as “negative.”

Given the uncertainties involved, solid scientific proof and statistical significance are not to be expected from this setting. Instead, the prudent assessment of the health risks in El Oriente must consider the following question: *How large a problem may have been overlooked?* The total and accumulated exposures to chemical mixtures from the different sources of environmental releases have not been characterized in detail. Accordingly, the risks are far from known or understood at this point. Nonetheless, available evidence suggests that carcinogenic PAHs and benzene, and other toxicants are and have been important contributors to the exposures in El Oriente.

In regard to health outcomes, none of the studies carried out so far was capable of determining a direct link between exposures at an individual level and the subject's disease or symptoms. The evidence is instead at a so-called ecologic level, where residents are considered as exposed based only on their address (e.g., at the time of death) in a canton with a history of oil production. Residential history was not available, and no information on exposure potentials was obtained. Thus, by assuming that everybody with a particular residence has been exposed will result in a dilution, as some residents will have had only a short-term or low, if any, exposure. The degree of misclassification will increase with time, as people move in and out of the cantons, and this problem will dilute any association with adverse outcomes. In my opinion, the extent of the pollution-related health effects is therefore most likely underestimated.

Further, an even greater underestimation is likely in regard to cancer in adults, because the disease develops after a latency period that can be much longer than 20 years. The available cancer data from El Oriente confirm a peak age for cancer of 50 years and above. Thus, the mortality data may provide information of little usefulness if exposed subjects by the end of follow-up had not yet reached mid-adult age or not yet accumulated at least 20 years since first exposure. Too few cancer deaths may have occurred to generate statistically significant results. While the exposed subjects may have an increased cancer risk, this risk will only become apparent during subsequent years. However, by that time, exposed subjects may have moved away from the canton, where they were originally exposed. Unfortunately, the limited results available do not allow analysis by age at first exposure, time since first exposure, and duration of exposure, issues of key importance in cancer epidemiology. By considering only the overall number of cases, no matter when they occurred and the age at diagnosis, the evidence is not sufficiently informative.

All of these factors support the notion that a serious health hazard is present from the oil production activities in El Oriente, and that information available so far most likely substantially underestimates the magnitude of adverse health consequences.

IV. Basis of opinions

Oil exploration began in the 1960s in El Oriente, a rainforest region with a population of about a half million indigenous peoples and mestizos. Population counts are somewhat uncertain, as some groups live in isolated areas. During the subsequent 20 years or so, oil exploration activities as well as extraction, production and transportation are known to have resulted in releases of a variety of chemicals, including polyaromatic hydrocarbons (PAHs) and volatile organic compounds, such as benzene.¹ Many of these compounds are known carcinogens. According to the Louis Berger report, a number of additional toxicants and possible carcinogens were released from the drilling wastes that were initially deposited in waste pits or separation ponds. Thus, pipelines, tanks, and storage drums

¹ Expert Opinion of Kenneth J. Goldstein, M.A., CGWP and Jeffrey W. Short, Ph.D. Regarding the Environmental Contamination From Texpet's E&P Activities in the Former Napo Concession Area Oriente Region, Ecuador, February 2013 ("Louis Berger report").

leaked large volumes of crude oil, and toxic brines released from production wells added further complexity to these releases.

For this report, I have relied on published literature (see Appendix A), as well as the expert opinions by Dr. Harlee Strauss from February and December, 2013, the Louis Berger report, and the report by Dr. Suresh Moolgavkar from May, 2013. In addition, I have previously visited El Oriente and I have conducted epidemiological studies in Ecuador. I am thus familiar with the Ecuadorean health care system and the opportunities for epidemiologic projects.²

Given the extent of documentation available and the uncertainties involved in evaluating the actual risks of adverse health effects, this opinion will consider the evidence in light of what is currently known in regard to such hazards and the likelihood that adverse health effects exist or will become apparent later on. In this regard, I am also considering what could be known in regard to past and current adverse effects, given the availability of exposure assessments, actual studies, and health data.

Exposure assessment

As described in the two reports by Dr. Strauss and in the Louis Berger report,³ multiple sources document the extent of environmental contamination from TexPet's operations in El Oriente. Thus, extensive records show that TexPet's exploration, extraction, and transportation of crude oil led to releases of toxic chemicals into the environment, and that the toxicants remain a serious hazard many years after the operations were halted.⁴ Residents were exposed to crude oil and its residues, produced water, drilling mud, hydrogen sulfide, diesel emissions, and flares. Exposures of particular relevance include polyaromatic hydrocarbons and benzene, because they are known to be human carcinogens. Other volatile hydrocarbons from crude oil and chemicals used in oil production are known to cause mucous membrane irritation and neurotoxicity.

Some exposure is continuing at locations where Texpet-released contamination remains in the environment.⁵ Exposure pathways for residents include domestic use of water contaminated with oil, whether visibly or not, washing in streams with oil contaminated sediments, and consumption of fish contaminated by oil residues. While some dissemination may still occur via the air, most current exposures are via water, soil, and food. It is likely that the multi-pathway exposures encountered by the residents has resulted in uptakes of toxic compounds that equal or exceed those known to occur in occupations related to oil extraction, production, or clean-up.

² Grandjean P, Harari R, Barr DB, Debes F. Pesticide exposure and stunting as independent predictors of neurobehavioral deficits in Ecuadorian school children. *Pediatrics* 2006; 117: 546-56. Harari R, Julvez J, Murata K, Barr D, Bellinger DC, Debes F, Grandjean P. Neurobehavioral deficits and increased blood pressure in school-age children prenatally exposed to pesticides. *Environ Health Perspect* 2010; 118: 890-6.

³ Louis Berger report, op. cit. Expert Opinion of Harlee S. Strauss, PhD Regarding human health-related aspects of the environmental contamination from Texpet's E&P activities in the former Napo concession area Oriente region, Ecuador. February 18, 2013. Rejoinder Opinion of Harlee Strauss, Ph.D. Regarding Human Health Risks, Health Impacts, and Drinking Water Contamination Caused by Crude Oil Contamination in the Former Petroecuador-Exxon Concession, Oriente Region, Ecuador. December, 2013.

⁴ Louis Berger report, op. cit.

⁵ Harlee Strauss report, February, 2013, op.cit.

As described in Dr. Strauss' reports, the available information regards occurrence of carcinogenic or otherwise highly toxic chemicals in the El Oriente environment. Detailed exposure profiles and their time-dependence for individuals or groups of residents would be of great value for clinical and epidemiology studies, but such data are not realistic to obtain.

Background knowledge on risks involved

A detailed risk assessment would require documentation on dose-dependent associations for major exposure components and their adverse effects. As such data are unavailable from the EL Oriente setting, one must rely on documentation from other sources. While information is available in regard to occupational exposures at oil refineries, circumstances in El Oriente are very different due to the multiple pathways of exposure among the residents. Perhaps the closest exposure situations occurred in connection with major marine oil spills that resulted in exposures to clean-up workers and residents. A recent review of adverse effects from oil spills concluded that the health consequences remained incompletely known, as the few studies available were typically cross-sectional and suffered from several deficiencies.⁶ Only seven of a total of 38 oil spills have resulted in published reports on adverse health effects. These reports emphasized skin and mucous membrane irritation along with some neurobehavioral symptoms, but detailed information on long-term effects is missing.

This incomplete evidence from other, comparable exposure settings makes it almost impossible to judge the possible and likely health consequences for the El Oriente population exposed to toxic chemicals from decades of oil production.

Such lack of generic toxicology information is not unique, however. The vast majority of industrial chemicals remains unstudied. I have recently shown that even current research on environmental chemicals primarily focuses on well-known problems, not on the potential hazards about which new information is particularly needed.⁷ This inertia and the continued focus on well-known substances relates in part to a traditional science paradigm, where solid conclusions depend on replication and verification. However, repeated replication attempts can also result in inertia. When extracting information on publications in scientific journals, we found a continued and narrow research focus on well-studied hazards, such as lead, cadmium and mercury, much beyond the mere need for replication.

The incompleteness of the science base is particularly unfortunate in a situation where the responsible parties have not produced the relevant toxicology evidence or carried out targeted studies when the pollution problems emerged. Thus, the available scientific documentation cannot contribute the necessary generic data that might, at least in part, compensate for the lack of information on the specific health risks encountered in the exposed population.

As a further complication, the contaminated El Oriente region has limited access to health care, medical records are incomplete, even population records are imperfect. Thus,

⁶ Aguilera F, Méndez J, Pásaro E, Laffon B. Review on the effects of exposure to spilled oils on human health. *J Appl Toxicol* 2010; 30: 291-301.

⁷ Grandjean P, Eriksen ML, Ellegaard O, Wallin JA. The Matthew effect in environmental science publication: A bibliometric analysis of chemical substances in journal articles. *Environ Health* 2011; 10: 96.

documentation of limited quality can be extracted for evaluating the health risks associated with the exposures that the local population is and has been facing. Nonetheless, existing documentation must be carefully analyzed to determine any evidence of adverse health effects among El Oriente residents exposed to toxic hazards.

Available evidence on adverse health effects

The human health studies carried out include questionnaire surveys, cross-sectional examinations, and ecological epidemiology studies. All of these study types have general weaknesses that are well known. Briefly, the findings are affected by uncertainties in regard to the true level of exposure of individual residents and the true occurrence of the outcome studied, such as cancer. El Oriente is far from Quito and other large cities, and access to health care and the completeness of record-keeping are less than optimal. Even carrying out studies in the affected communities is a logistic challenge. Nonetheless, initial community-based studies recorded links between oil-related exposures and acute or short-term effects, such as skin rashes and skin or eye irritation, and less well defined problems, such as headaches, nausea, anxiety and ill-health.⁸ These findings are highly plausible and not likely to be due to chance or bias.

Due to the known carcinogenicity of crude oil constituents, several studies focused on the cancer occurrence in areas involved in oil extraction. One study examined subjects with well documented exposures in the Sachas canton and documented DNA damage in blood cells.⁹ Such genotoxicity effects are known to be associated with later development of cancer.

The first cancer epidemiology studies in El Oriente began with case series and were then extended to the four cantons (Sucumbios, Orellana, Napo and Pastaza) where the oil industry had been most active for the longest time.¹⁰ Despite the known difficulties in obtaining accurate data on cancer cases in a remote area like El Oriente, these early studies showed clear excesses in some cancer rates. In adults, the cancer cases occurring up to 1998 mainly involved middle-aged adults with short latency times only of about two decades or less after first exposure to oil chemicals.¹¹ As many cancer types primarily appear in older adults and after longer latency periods, this finding suggests the presence of an important cancer risk.

In addition, an increased rate of childhood leukemia was found in the same cantons.¹² This disease usually occurs at shorter latency times than most adult cancers, and, given the exposures, this finding is therefore meaningful and plausible. An additional study reported

⁸ Center for Economic and Social Rights. Rights Violations in The Ecuadorian Amazon, The Human Consequences of Oil Development. CESR, 1994.

⁹ Paz-y-Miño C, López-Cortés A, Arévalo M, Sánchez ME. Monitoring of DNA damage in individuals exposed to petroleum hydrocarbons in Ecuador. *Ann N Y Acad Sci* 2008; 1140: 121-8.

¹⁰ San Sebastián M, Armstrong B, Córdoba JA, Stephens C. Exposures and cancer incidence near oil fields in the Amazon basin of Ecuador. *Occup Environ Med.* 2001; 58:517-22. Hurtig AK, San Sebastián M. Geographical differences in cancer incidence in the Amazon basin of Ecuador in relation to residence near oil fields. *Int J Epidemiol* 2002; 31: 1021-7.

¹¹ Hurtig et al. 2002, op.cit.

¹² Hurtig AK, San Sebastián M. Incidence of childhood leukemia and oil exploitation in the Amazon basin of Ecuador. *Int J Occup Environ Health* 2004; 10: 245-50.

increased rates of spontaneous miscarriage, malformations and child mortality.¹³ Again, these outcomes are plausible and likely relate to recent or accumulated exposures.

On the other hand, in a study funded by Chevron, Dr. Kelsh and colleagues used a different collection of cantons and found no clear evidence of excess cancer rates up to 2005. The cantons in this study were selected by “visual inspection” of a map showing oil production activities.¹⁴ The authors then chose to include the Cascales, Cuyabeno and Putumayo cantons in addition to the cantons considered exposed by Drs. Hurtig and San Sebastián. Dr. Strauss in her reports from February and December, 2013 has already commented on differences between the cantons in regard to exposures; the inclusion of three cantons with less exposure potential must have resulted in a dilution of the overall exposures within the population considered exposed in Dr. Kelsh’s study. Interestingly, the authors did not provide comparison data between the two sets of cantons in regard to the outcomes. Given the subjective – and in my opinion inappropriate – method of canton selection used in Dr. Kelsh’s study and the likely dilution of the exposure, the non-informative findings are not surprising and do not add any important information on the health risks encountered by exposed El Oriente residents. Incidentally, the confidence intervals reported in Dr. Kelsh’s study show that the findings are not in conflict with those obtained by Drs. Hurtig and San Sebastián.

In his opinion, Dr. Moolgavkar summarizes a recent study that he has carried out to update the cancer mortality data from El Oriente. Apparently, a manuscript has been submitted to a scientific journal, but his study has not been published so far. In his brief summary, Dr. Moolgavkar indicates that he has included cancer deaths from 1990 to 2010 (five years more than Kelsh). Although leaving out the years 1985-1989 that were included by Drs. Hurtig and Sebastián, the extended follow-up represents an advance, as this time period better reflects the usual latency period of many cancer types, which may not appear until 20, 30, or more years after first exposure to the carcinogenic chemicals. However, Dr. Moolgavkar bases his primary analysis on seven cantons with some level of oil exploration and production, and he compares the cancer mortality there with the one in 13 cantons with “little or no such activity”. Thus, similar to Dr. Kelsh’s study, the exposed group of cantons is diluted with cantons with less intensive exposures, and the comparison group is not free of exposure. When examining single cantons as well as the same group of cantons used by Drs. Hurtig and San Sebastián, Dr. Moolgavkar found “no statistically significant excess of overall or site-specific cancer mortality”. No results are presented, and it is therefore difficult to evaluate this conclusion. The lack of significance may simply be due to numbers of cases observed being too small in the individual cantons to obtain the necessary statistical power. The same applies to Dr. Moolgavkar’s conclusions on other causes of death, such as aplastic anemia. As a further observation, mortality from infectious diseases showed a significant deficit, thus suggesting that diagnostic misclassification, incomplete case assessment, or exaggerated population counts may have biased the findings. Dr. Moolgavkar recognizes the problems associated with “lack of individual-level

¹³ San Sebastián M, Armstrong B, 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; 8: 312-9.

¹⁴ Kelsh MA, Morimoto L, Lau E. Cancer mortality and oil production in the Amazon Region of Ecuador, 1990-2005. *Int Arch Occup Environ Health* 2009; 82: 381-95.

data on exposures and potential confounders, (...) duration of residence, and probable incompleteness and inaccuracy in data on cause of death". I concur, and for this reason, Dr. Moolgavkar's conclusion of "no scientifically reliable evidence that residential proximity to oil exploration and production activities increases mortality..." and "no support for a causal relationship between environmental exposure to petroleum, its compounds, and related wastes and any form of cancer" are not convincing. In fact, this study, at least from the summary provided in Dr. Moolgavkar's report adds little additional information on the presence of health risks in the exposed population.

Critical assessment of the evidence

When considering the overall evidence in regard to the possible presence of health risks associated with the pollution in El Oriente, the incomplete data on exposure levels in El Oriente's cantons and the resulting imprecision of the exposure assessment constitute a major source of uncertainty. As a further complication, when recorded at the time of death, the residence will be a highly imprecise measure of a subject's past exposures. Thus, during a period of three or four decades, especially mestizo population is likely to move, e.g., through gravitating toward the cities. If mestizos are also the most highly exposed subjects, any cancer death occurring later on will not be reflected by El Oriente mortality.

Such imprecision (and the associated selection bias) is a key weakness, as standard statistical methods assume that no imprecision is present in the exposure assessment, an assumption that is usually not true – and certainly not in the present case. Although this problem is often ignored, such types of uncertainty can be potentially used to manipulate research findings, and any obvious uncertainty may be erroneously claimed to cause exaggeration of the risks. In reality, the greater degree of the imprecision of the exposure estimate, the larger the average bias will be toward the null, i.e., the likelihood of finding no effect.¹⁵

In my judgment, the studies by Dr. Kelsh and co-authors and by Dr. Moolgavkar are seriously affected by imprecision and the resulting likelihood of finding no association. In fact, as the follow-up was extended to 2010 by Dr. Moolgavkar, his use of the deceased subject's most recent residence as criterion for exposure classification is bound to be even more imprecise than in Dr. Kelsh and coworkers' five year shorter follow-up, as additional exposed subjects may have moved away from their original residence.

The studies by Drs Hurtig and San Sebastián are by no means free of imprecision and possible selection bias. However, based on their intimate knowledge of the exposure conditions in El Oriente, they used a narrower definition of exposed cantons, thereby limiting the extent of dilution by unexposed subjects in the group considered exposed. Also, as their follow-up was through 1998 only, their results were less impacted by recent movement of residents away from the exposed areas.

Among the uncertainties are also the completeness of case identification, i.e., the likelihood that death certificates will be recorded by the registry in Quito and that the cause of death indicated on the death certificate will be accurate and reflect the outcomes

¹⁵ Grandjean P. Seven deadly sins of environmental epidemiology and the virtues of precaution. *Epidemiology* 2008; 19: 158-62.

of interest in regard to the oil pollution. These problems will lead to underestimation of the cancer risk in all of the studies carried out in El Oriente.

Given these concerns, careful assessment of the evidence is needed beyond a simple calculation whether the observed data are “statistically significant” or whether they can be attributed to chance. The probability that the results are significant is usually expressed as p values, or probability values. Originally proposed by the UK statistician Ronald Fisher, the p was evaluated using a limit of 5%. This method allows the researcher to identify findings that deviated significantly – unlikely due to random variation – so that the hypothesis that no difference was present would be rejected. When the p was above 5% researchers concluded that their findings did not reliably reject the “null” hypothesis of no difference or no association. This 5% limit is now widely applied and has become almost sacrosanct. A few studies and many anecdotes suggest that scientists place greater emphasis on results that have a p value of, say, 4.9% than on results with a p value of 5.1%.¹⁶ Statistically, there is of course no meaningful difference between outcomes with such similar p values. So-called statistical significance should therefore not be used as the only parameter of interest when evaluating epidemiological results.

When a study addresses an environmental hazard using study parameters that are unreliable or perhaps not representative, the results will usually not reach statistical significance. Sometimes, such results may be misinterpreted as evidence against the hazard causing any risk at all. Accordingly, studies showing no statistically significant effect are claimed to be “negative”. A more correct term would be non-informative (or non-positive). Misleading conclusions that refer to “negative” studies are sometimes referred to as a Type III error.¹⁷

Oil company experts have criticized the epidemiological studies by Drs. Hurtig and San Sebastián for being “weak and biased”.¹⁸ To some extent, the evidence is indeed weak, as only limited data of suboptimal quality are available from this resource-poor setting. As discussed above, the results may well be biased for this reason. Although the likely direction of the bias is misinterpreted by Dr. Moolgavkar in his opinion, ample evidence is available that studies on average are biased toward the null, thus leading to an underestimation of the risk.¹⁹

An alleged bias put forward by oil industry representatives refers to the fact that the Ecuadorean researchers worked closely with the affected communities. I don’t think that this assertion is fair; it rests on subjective opinion only, without substantiation. On the contrary, the researchers’ intimate knowledge of the environmental setting and

¹⁶ Holman CD, Arnold-Reed DE, de Klerk N, McComb C, English DR. 2001. A psychometric experiment in causal inference to estimate evidential weights used by epidemiologists. *Epidemiology* 12: 246-55.

¹⁷ Schwartz S, Carpenter KM. The right answer for the wrong question: consequences of type III error for public health research. *Am J Public Health* 1999; 89: 1175-80.

¹⁸ Hurtig AK, San Sebastián M. Epidemiology vs epidemiology: the case of oil exploitation in the Amazon basin of Ecuador. *Int J Epidemiol* 2005; 34: 1170-2.

¹⁹ Grandjean P, Budtz-Jørgensen E. An ignored risk factor in toxicology: The total imprecision of exposure assessment. *Pure Appl Chem* 2010; 82: 383-91.

understanding of the health issues allowed them to carry out a study of the highest possible quality and relevance. I concur with this view, as expressed by San Sebastián and Hurtig.²⁰

As another alleged source of bias, the presence of oil activities may also be linked to other health risks, such as tobacco smoking. However, this explanation seems to be unrealistic. The El Oriente culture, widespread poverty, and the cancer pattern, do not suggest tobacco smoking, or alcohol drinking for that matter, as underlying confounders.

Overall, the balance of evidence favors the presence of a serious environmental hazard that is already impacting human health in the El Oriente population. The weaknesses and the incomplete nature of the available information suggest that the risk of adverse human health effects may in fact have most likely been seriously underestimated.

The focus on *p* values is therefore inappropriate. As a useful complement, the 95% confidence limits are highly useful. They are usually calculated in epidemiological studies, as they represent the range that would be in statistical accordance with the empirical results obtained, i.e., without the deviation reaching statistical significance. Thus, studies that show a risk that is not significantly increased will have a lower 95% limit is below 1.

We need to focus also on the upper confidence limit, which reflects the highest extent of excess risk that would be in accordance with the findings (i.e., without showing a significant difference). When reviewing the results obtained in the cancer studies from El Oriente, we see that a presence of highly elevated cancer risks is in full accordance with the results. For example, the results reported by Hurtig and San Sebastián show a confidence interval for melanoma of 2.19-46.97. In other words, a melanoma risk 47-fold greater than expected cannot be excluded. Several other cancer sites show confidence intervals that are in accordance with a 10-fold increased risk, or more.

Prudent interpretation

In reaching a decision whether a conclusion is amply supported by the evidence, we traditionally favor acquisition of ample verification to obtain robust documentation that will resist critiques about possible sources of error or bias. But this ideal may not be feasible, as the study conditions may not allow replication or the application of the highest-quality parameters as in the case of El Oriente. Exaggerated critique and skepticism may be inappropriate in regard to emerging insights on complex environmental situations in a resource-poor setting.

In the past, special interest groups have praised what they call “sound science”, which supports conclusions that are considered attractive (for other reasons). An exaggerated skepticism toward unwelcome research, in combination with unrealistic (or manufactured) doubt has been used time and again, e.g., by plaintiffs in tobacco litigations.²¹ A call for guidelines on “Good Epidemiological Practice” was embraced at first by independent researchers as a useful tool to stimulate high quality (and sound) science. However, strict interpretation of epidemiological quality criteria can be – and were – also applied to disregard epidemiological findings that for other reasons were regarded as unwelcome.

²⁰ San Sebastián M, Hurtig AK. Oil development and health in the Amazon basin of Ecuador: the popular epidemiology process. *Soc Sci Med* 2005; 60: 799-807.

²¹ Michaels D. 2005. Doubt is their product. *Sci Am* 292(6): 96-101.

This tactic was employed by industry groups to disqualify unwelcome “junk science”.²² Thus, these groups turned on its head the scientific rigor that had been considered a prerequisite in the traditional science paradigm, creating instead an unrealistic requirement for repetitive, controlled studies as a precondition for acceptable conclusions. This concept allowed for unwanted results to be criticized as “junk” and for uncertainties to be erroneously interpreted as an indication that no hazard was present.²³

Another common strategy is to apply “criteria” for causality in a very strict sense to counter unwanted conclusions. Although biostatistician (Sir) Austin Bradford Hill is often cited as a source for so-called criteria for causal relations, these aspects (not “criteria”), as Hill called them, should not be overinterpreted. In Hill’s own words, “All scientific work is incomplete... All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us the freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at the given time.”²⁴

Thus, the epidemiological studies carried out in El Oriente should not be considered “junk science”, and causal “criteria” are not violated when drawing cautious conclusions. While the evidence available must be critically considered, the limitations of science must also be recognized. A balance needs to be achieved, where both the knowns and the unknowns are taken into account. The key in prudent interpretation is that, when a study fails to document with statistical certainty that a hazard is present, the results should not be misinterpreted as proof that a hazard is not present. Or, in short, absence of evidence is not evidence of absence.

Research is always affected by uncertainties, and many of them can easily blur a real association between an environmental hazard and its adverse effects. Thus, “noisy” studies, e.g., with imprecise estimates of the causative exposure, insensitive and nonspecific outcome measures, and incomplete or too short follow-up, are likely to detect only the most serious risks. The fact that the null hypothesis could not be rejected with confidence (or statistical significance) may be irrelevant. Thus, rather than simply relying only on studies that show statistical significance, we need to judge the overall plausibility and the possible impact of the uncertainties that may involve underestimation of adverse effects. We also need to consider the long-term consequences, the effects of mixed exposures and the impacts on vulnerable subpopulations, such as children and pregnant women – none of which have been studied to a sufficient extent so far.

In the past, skepticism has often prevailed, and “manufactured doubt” sometimes made the evidence look less convincing than it really was. While asbestos is a well-known example, a recent monograph from the European Environment Agency outlines many other illustrative cases, such as lead, mercury, and DDT.²⁵ In each of these cases, the risk was found to be greater as more and better evidence was obtained. Thus, the initial and early documentation underestimated the adverse health effects. The costs to society caused by

²² Ong EK, Glantz SA. Constructing “sound science” and “good epidemiology”: Tobacco, lawyers, and public relations firms. *Am J Public Health* 2001; 91: 1749-1757.

²³ Grandjean P. 2008. *op cit*.

²⁴ Hill AB. The Environment and disease: association or causation? *Proc. R. Soc. Med.* 1965; 58: 295-300.

²⁵ Gee D, Grandjean P, Hansen SF, van den Hove S, MacGarvin M, Martin J, Nielsen G, Quist D, Stanners D. Late Lessons from Early Warnings, volume II (EEA Report No 1/2013). Copenhagen: European Environment Agency, 2013.

disregarding these risks were enormous. Thus, false negatives (i.e., ignoring true hazards) can be costly to the individual victims as well as to society.

On the other hand, many other cases illustrate the advantages of reacting on early, plausible, although yet uncertain evidence. Among the best known US examples are the actions to control scrapie (thereby avoiding BSE and human disease risk), the bans of thalidomide and diethylstilbestrol (both toxic to the fetus), and the control of fluorocarbon uses (that destroy the ozone layer). All of these actions were precautionary and were later found to have saved society from enormous losses. Of note, few of these prudent actions would have withstood modern-day skepticism promoted by vested interests.

Given this experience, we need to avoid underestimation of early and uncertain information that may be erroneously interpreted as “negative”. Accordingly, the question on possible causality need to be rephrased: “Are we sufficiently confident that this exposure to a potential hazard leads to doses of a magnitude that can result in adverse effects that are serious enough to initiate transparent and democratic procedures to decide on appropriate intervention?”²⁶ Decisions based on a positive response to this question are often referred to as precautionary in the EU, although the EU, on balance, is not more precautionary than the US.

This is not to say that the possibility of false positives, i.e., alleged hazards that turn out to be innocuous, can be ignored.²⁷ But environmental hazards constitute a totally different situation, as the majority of industrial chemicals has been poorly studied, if at all. For example, after the EU promulgated chemicals regulations in 1981, of new chemicals marketed in the EU and tested by standardized procedures, about 70% are considered hazardous one way or another. The same is true for only a few percent of the “old” chemicals (including oil chemicals), most of which have not yet undergone similar toxicity testing. As new substances would seem unlikely to be particularly toxic as compared to those previously marketed, any belief in the safety of unstudied or understudied chemicals would appear naïve.

Actual occurrence of false positives in regard to environmental chemicals and preventive interventions would justify a view that “chemophobia” is affecting our assessment of chemical hazards. As also discussed in the European Environment Agency’s monograph, the study considered a total of 88 alleged false positives (i.e., chemicals or exposures that were erroneously claimed to be dangerous). This error was actually found to be true only in four cases, one of which being the swine flu scare, where vaccines, later found to be unnecessary, were stockpiled.²⁸ Thus, the evidence suggests that the prevalent tradition to withhold scientific conclusions pending solid proof most likely results in serious underestimations of environmental hazards.

²⁶ Grandjean P. Science for precautionary decision-making. In: Gee D, Grandjean P, Hansen SF, van den Hove S, MacGarvin M, Martin J, Nielsen G, Quist D, Stanners D. Late Lessons from Early Warnings, volume II (EEA Report No 1/2013). Copenhagen, European Environment Agency, 2013, pp. 517-35.

²⁷ The conclusions of many often-cited publications in major medical journals were later found to be wrong, probably in part because major medical journals prefer to publish attention-attracting results (Ioannidis JP. 2008. Why most discovered true associations are inflated. *Epidemiology* 19: 640-8).

²⁸ Hansen SF, Kreyer von Krauss MP, Tickner JA. Categorizing mistaken false positives in regulation of human and environmental health. *Risk Anal* 2007; 27: 255-69.

Of additional importance, risks are often considered within a narrow frame, and formal risk assessments often ignore impacts of exposures that happen during early development, delayed or long-term adverse effects, cumulated and aggregated (via different pathways) exposures, and the consequences of mixed exposures. These concerns were recently highlighted by an expert committee of the National Research Council.²⁹

All of these considerations provide a general framework on which to build a prudent and considerate opinion on the health risks associated with the El Oriente pollution.

Conclusions

Existing evidence is insufficient to reach firm conclusions on the presence and magnitude of health risks associated with chemical hazards from the oil production in El Oriente. However, current knowledge on the hazards known to be present allows plausible conclusions that are also supported by existing epidemiology results. Although far from ideal, the human studies carried out support the existence of adverse health effects, some of which will likely develop further in the coming years. Several known uncertainties suggest that the studies available substantially underestimate the true extent of adverse effects, especially in regard to cancer. From a critical review of the evidence and from the perspective of experiences in various settings with other environmental hazards, the vast majority of which have been underestimated, I conclude that a serious health hazard is present from the oil production activities in El Oriente.

²⁹ National Research Council. Science and decisions: advancing risk assessment. Washington, D.C.: National Academy Press; 2009.

Appendix A

References

Expert opinions

Expert Opinion of Kenneth J. Goldstein, M.A., CGWP and Jeffrey W. Short, Ph.D. Regarding the Environmental Contamination From Texpet's E&P Activities in the Former Napo Concession Area Oriente Region, Ecuador, February 2013.

Expert Opinion of Suresh H. Moolgavkar, M.D., Ph.D. May 31, 2013.

Expert Opinion of Harlee S. Strauss, PhD Regarding human health-related aspects of the environmental contamination from Texpet's E&P activities in the former Napo concession area Oriente region, Ecuador. February 18, 2013.

Rejoinder Opinion of Harlee Strauss, Ph.D. Regarding Human Health Risks, Health Impacts, and Drinking Water Contamination Caused by Crude Oil Contamination in the Former Petroecuador-Exxon Concession, Oriente Region, Ecuador. December, 2013.

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Hansen SF, Krayner von Krauss MP, Tickner JA. Categorizing mistaken false positives in regulation of human and environmental health. *Risk Anal* 2007; 27: 255-69.

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Michaels D. 2005. Doubt is their product. *Sci Am* 292(6): 96-101.

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Paz-y-Miño C, López-Cortés A, Arévalo M, Sánchez ME. Monitoring of DNA damage in individuals exposed to petroleum hydrocarbons in Ecuador. *Ann N Y Acad Sci* 2008; 1140: 121-8.

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Schwartz S, Carpenter KM. The right answer for the wrong question: consequences of type III error for public health research. *Am J Public Health* 1999; 89: 1175-80.

Appendix B - CV

Date: 11/20/2013

NAME: PHILIPPE GRANDJEAN, M.D., D.M.Sc.

ADDRESS:

Naboløs 4, DK-1206 Copenhagen, Denmark
10 Dana Street, Apt 315, Cambridge, MA 02138, USA

DATE & PLACE OF BIRTH:

March 1, 1950. Copenhagen, Denmark.

EDUCATION:

1974, M.D., University of Copenhagen
1975, Diploma in basic medical research, University of Copenhagen
1979, D.M.Sc. (dr.med.), University of Copenhagen

POSTDOCTORAL TRAINING (Research Fellowships):

1974-1975 Postgraduate training fellowship, University of Copenhagen
1975-1978 Research fellow, Institute of Hygiene, Univ. Copenhagen
1978-1980 Senior research scholar, Fulbright Foundation
Visiting fellow, Department of Community Medicine,
Mount Sinai School of Medicine, New York

ACADEMIC APPOINTMENTS:

2003- Adjunct Professor of Environmental Health, Harvard School of Public Health,
Boston
1994-2002 Adjunct Professor of Public Health (Environmental Health), Boston University
School of Public Health, Boston
Adjunct Professor of Neurology, Boston University School of Medicine, Boston
1983- Consultant in Toxicology, National Board of Health, Danish Ministry of Health
1982- Professor and Chair of Environmental Medicine, Odense University / University of
Southern Denmark, Odense, Denmark
1980-1982 Director, Department of Occupational Medicine, Danish National Institute of
Occupational Health, Copenhagen, Denmark

HONORS AND DISTINCTIONS:

Prize essay in medicine, University of Copenhagen (1972)
Fulbright senior research scholarship (1978)
Keynote speaker, Odense University anniversary (1983)
Gitlitz Memorial Lecture, Association of Clinical Scientists, USA (1985)
Fellow, Collegium Ramazzini (1987)
Knight of the Dannebrog, awarded by the Queen of Denmark (1990)
The Dannin prize for medical research (1991)
Fellow, American Association for the Advancement of Science (1994)

Irish Congress Lecturer, Royal College of Physicians of Ireland and Irish Society of Toxicology (1996)

Knight of the Dannebrog, First Degree, awarded by the Queen of Denmark (2003)

'Mercury madness award' for excellence in science in the public interest from eight US environmental organizations (2004)

Emeritus Fellow, International Union of Pure and Applied Chemistry, IUPAC (2009)

Honorary Research Award, International Order of Odd Fellows (2010)

Science Communication Award, University of Southern Denmark (2012)

MAJOR PROFESSIONAL SERVICE:

United States:

Agency for Toxic Substances and Disease Registry:

Workshop Rapporteur, Neurobehavioral Test Batteries for Use in Environmental Health Field Studies (1992);

Member, Expert Panel of Mercury (1998)

Boston Environmental Hazards Center: Consultant (1994-1999)

National Institutes of Health: Member of Special emphasis panel (2009-)

Society of Occupational and Environmental Health: Member, Governing Council (1990-1993)

U.S. Environmental Protection Agency:

Member, SAB/SAP Endocrine Disruptor Screening Program Subcommittee (1998-1999);

Member, Food Quality Protection Act (FQPA) Science Review Board (SRB)(1999-

2003); White House Office of Science and Technology Policy: Team leader and presenter, Workshop on Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury (1998)

U.S.FDA, Food Advisory Committee, Methylmercury: Invited expert (2002)

White House Office of Science and Technology Policy: Team leader and presenter, Workshop on Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury (1998)

Denmark:

Danish Medical Research Council:

Consultant on environmental medicine (1985-1990);

Member, Joint Research Council Committee on Environmental Research (1986-1991);

Member of DMRC (1992-1998);

Danish Society of Community Medicine:

Secretary (1977-1978)

Danish Society of Industrial Medicine:

Board Member (1974-1983)

Ministry of Education:

Member, Committee on Toxicology (1984-1986);

Member, Committee on Environmental Education (1986-1987)

Ministry of the Environment:

Member, Council on Environmental Chemicals (1983-1989);

Member, Environmental Appeal Board (1986-2010);

Member, Environmental Research Council (1990-1992);

Member, Advisory Committee on Pesticide Research (1995-2004);

Member, Advisory Committee on Arctic Research (1996-2004)

Ministry of Health: numerous committee appointments;
Chair, Committee on Risk Perception (2000-2001)

Ministry of Labour:
Consultant on Occupational Health, Council on Occupational Safety and Health (1983-1993);
Member, Occupational Health Council Research Committee (on behalf of the Danish Medical Research Council) (1984-1990 and 1999-2003)

Ministry of Research:
Chair, Committee on Research at the Faroe Islands (1995-1996);
Member, Committee on Scientific Dishonesty (2004-2006);
Chair, Program Committee on Non-Ionizing Radiation (2004-2009)

Odense University (from 2000 University of Southern Denmark), elected offices:
Chairman, Institute of Community Health (1982-1985; 1996-1999);
Member of Executive Committee, Institute of Community Health (From 2000 Institute of Public Health) (1986-1995; 2000-2005);
Member, Faculty Research Committee (1983-1985);
Member, Curriculum Committee (1984-1986);
Member, Faculty Council (1985-1993);
Vice-Dean (1991-1993)

International:

Academy of Finland:
Member of panel evaluating the National Institute of Public Health (1995), site visit of center of excellence (2001)

Association of Schools of Public Health in the European Region:
Treasurer (1975-1977)

BioMedCentral: Member, Editors Advisory Group (2011-2013)

Collegium Ramazzini:
President, International Conference, The precautionary principle: Implications for research and prevention in environmental and occupational health (2002);
Member, Executive Council (2005-2013)

Commission of the European Communities:
National Expert, Working Party on Environmental and Lifestyle-Related Diseases (1988-1990); Member, Scientific Committee on Emerging and Newly Identified Health Risks; - Working group on Dental Amalgam (Human Health) (2012-2013)
Ad hoc Scientific Advisor on Risk Assessment (2009-)

European Environment Agency: Member of the Scientific Committee (2012-2015)

European Food Safety Authority:
Member, Panel on Contaminants in the Food Chain (2003-2009)
Member of Working Groups on mercury, polychlorinated biphenyls, cadmium, lead, and benchmark dose (2004-2010)

International Agency for Research on Cancer:
Member of Task Group, Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 47 (1988), 49 (1989), as chairman, 58 (1993), and as subgroup chair 100C (2009)

International Commission on Occupational Health:

Danish Delegation Secretary (1982-90);

Member, Scientific Committee on the Toxicology of Metals (1987-present);

Member of the Board (1990-1996)

International Programme on Chemical Safety:

Member of Task Group, Environmental Health Criteria, Vol. 36 (1984) and 72 (1986)

International Society for Environmental Epidemiology:

Councillor (1991-1994)

International Union of Pure and Applied Chemistry:

Member, Subcommittee on the Toxicology of Nickel (1979-1989);

Titular Member (1985-1991) and Chairman (1987-1991), Commission on Toxicology;

Chairman, Subcommittee on Risk Assessment (1985-1989)

Karolinska Institute (Stockholm, Sweden):

Member of international evaluation panel on environmental medicine (1993)

Ministry for Scientific Policy (Belgium):

Consultant on national research program on health hazards (1990 and 1994)

NATO Priority Area Panel on Environmental Security:

Member (1996-1997)

Norwegian Research Council:

Ad hoc reviewer (2001-2008)

Chairman, Environment and Health Review Group (2009-2010)

Member of steering committee (2011-present)

Spain: INMA (Infancia y Medio Ambiente) Project Steering Committee: Member (2010-present)

Swedish Council for Work Life Research:

Member, Priority Committee on Chemical Health Risks (1997-1998)

U.N. Environment Programme:

Member, Global Mercury Assessment Working Group (2002)

World Health Organization:

Temporary Adviser or Consultant on numerous occasions, five times elected Rapporteur

PROFESSIONAL SOCIETIES:

American Association for the Advancement of Science (Fellow, 1994)

American Public Health Association

Collegium Ramazzini (Fellow, 1987; Member of the Executive Council, 2005-2013)

Danish Medical Association: Member, Prevention Council (2011-2014); Danish Societies of Clinical Chemistry, Epidemiology, Occupational Medicine and Community Medicine

Faroese Society of Science and Letters

International Commission on Occupational Health

International Epidemiological Association

International Society for Environmental Epidemiology

Society of Occupational and Environmental Health

EDITORIAL BOARDS:

American Journal of Industrial Medicine (1987-)

Applied Organometal Chemistry (1985-1991)

Arbejdsmiljø (Occupational Environment, in Danish, 1983-1990)

Archives of Environmental Health (*European Editor*, 1986-1992)
Archives of Toxicology (1987-present)
Biomarkers (1996-2001)
Critical Reviews in Toxicology (1985-2012)
Danish Medical Bulletin (1994-2003)
Environmental Health (*Editor-in-Chief*, 2002- present)
Environmental Health Perspectives (2003- present)
Environmental Research (1981-1994, *Associate Editor*, 1995- present)
Industrial Health (2000-2005)
International Journal of Hygiene and Environmental Health (2001- present)
International Journal of Occupational and Environmental Health (1994- present)
International Journal of Occupational Medicine & Environmental Health (1991- present)
Journal of Clean Technology, Environmental Toxicology, and Occupational Medicine (1992-1998)
Journal of Environmental Medicine (1998-1999)
Naturens Verden (Natural Science, in Danish) (1987-1991)
Ugeskrift for Laeger (Danish Medical Journal, in Danish) (1991-2007)

MAJOR RESEARCH INTERESTS:

Dr. Grandjean's environmental epidemiology research focuses especially on delayed effects of developmental exposure to environmental chemicals. Studies on marine contaminants were initiated with Dr. Pal Weihe in the Faroe Islands in the mid-1980s; prospective cohort studies on almost 3,000 Faroese children have focused on neurotoxicity, but the most recent projects have also examined general development and immunotoxicity. The results have inspired downward revisions of methylmercury exposure limits internationally. Other recent studies have targeted age-related functional deficits and degenerative diseases, such as Parkinson's disease, cardiovascular disease, and diabetes in regard to life-time exposure to methylmercury and persistent lipophilic contaminants. Other efforts relate to endocrine disruption caused by organochlorine substances; carcinogenicity of exposure to zeolite and other mineral fibers; percutaneous absorption of chemicals, and carcinogenicity and neurotoxicity of fluoride exposure. Dr. Grandjean has also published on research ethics, genetic susceptibility, the setting of exposure limits, and the impact of the precautionary principle on prevention and research.

RESEARCH SUPPORT:

2000-2006 NIEHS	PI: Philippe Grandjean
Mercury associated neurobehavioral deficit in children	
2001-2003 Nordic Arctic Research Programme (NARP)	PI: Philippe Grandjean
Changing patterns of biomagnified pollutants in the northern marine environment	
2001-2004 Danish Medical Research Council	PI: Philippe Grandjean
Exposure assessment for endocrine disruptors	
2002-2004 Danish Medical Research Council	PI: Philippe Grandjean
Environmental epidemiology research	
2003-2004 European Commission	PI: Philippe Grandjean
Assessment of Neurobehavioral Endpoints and Markers of Neurotoxicant Exposures (ANEMONE)	
2003-2005 Danish Medical Research Council	PI: Philippe Grandjean

Research in hormone related substances
 2003-2006 NIEHS ES 11687 PI: Philippe Grandjean
 Effects of perinatal disruptors in children
 2003-2007 EPA STAR RD-83075801-0 PI: Philippe Grandjean
 Children's vulnerability to environmental immunotoxicant
 2004-2007 NOAA NA04OAR4600207 PI: David Senn
 Coastal eutrophication and hypoxia: implications for mercury methylation, mercury
 biomagnification, and human health
 2004-2011 NIEHS ES12199 PI: Philippe Grandjean
 Epidemiology of immunotoxicant exposure in children
 2006-2011 NIEHS ES13692 PI: Philippe Grandjean
 Health effects of lifetime exposure to food contaminants
 2006-2011 European Commission (Coordinator, Staffan Skerfving, Sweden)
 Public health impact of metals exposure PI: Philippe Grandjean
 2006-2012 NIEHS ES14460 PI: Philippe Grandjean
 Three-generation human study of reproductive effects of marine food contaminants
 2007-2012 NIEHS ES14433 PI: Dariush Mozaffarian
 Mercury, selenium, and risk of cardiovascular disease in women and men
 2008-2012 Danish Council for Strategic Research PI: Philippe Grandjean
 Environmental pollutant impact on antibody production against current and new childhood vaccines

Major Current Funding:

2007-2013 NIEHS ES009797 PI: Philippe Grandjean
 Mercury associated neurobehavioral deficit in children
 2011-2016 NIEHS ES012199 PI: Philippe Grandjean
 Epidemiology of immunotoxicant exposure in children
 2012-2017 NIEHS ES021993 and NSF OCE-1321612 PI: Philippe Grandjean
 Immunotoxicity in Humans with Lifetime Exposure to Ocean Pollutants
 2013-2018 NIEHS ES021477 PI: Philippe Grandjean
 Glucose Metabolism in Adults Prenatally Exposed to Diabetogenic Pollutants
 2013-2017 NIEHS ES023376 PI: Philippe Grandjean
 Gut Microbiome in Adults with Early Life Exposures to Environmental Chemicals

TEACHING EXPERIENCE

1982- Professor of Environmental Medicine, Odense University / University of Southern
 Denmark
 1994-2002 Adjunct Professor of Public Health (Environmental Health) and Neurology, Boston
 University School of Medicine, Boston
 2003- Adjunct Professor of Environmental Health, Harvard School of Public Health, Boston

Numerous teaching assignments abroad, including guest lectures at many universities and related tasks, e.g. as external examiner, National University of Singapore (1995). Regular teacher at the École des hautes études en santé publique (French school of public health).

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21. Grandjean P. Occupational fluorosis through 50 years: clinical and epidemiological experiences. *Am J Ind Med* 1982; 3: 227-36. PMID: 7137176
22. Nielsen OV, Grandjean P, Bennike P. Chemical analyses of archaeological bone samples: Evidence for high lead exposure on the Faroe Islands. *J Dan Archaeol* 1982; 2: 145-8. (also published in Faroese: Blyggj i foroyingum, *Mondul* 1983; 9: 27-31)
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24. Grandjean P, Wulf HC, Niebuhr E. Sister chromatid exchange in response to variations in occupational lead exposure. *Environ Res* 1983; 32: 199-204. PMID:6617612
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31. Grandjean P. Reference intervals for toxic metals: Problems and prospects. *Ann Clin Lab Sci* 1986; 16: 67-74. PMID:3511837
32. Grandjean P, Bach E. Indirect exposures: The significance of bystanders at work and at home. *Am Ind Hyg Assoc J* 1986; 47: 819-24. PMID:3799485
33. Grandjean P, Lyngbye T, Hansen ON. Lead concentration in deciduous teeth: Variation related to tooth type and analytical technique. *J Toxicol Environ Health* 1986; 19: 437-45. PMID:3772989
34. Grandjean P. After Chernobyl (Editorial). *Arch Environ Health* 1986; 41: 277.
35. Andersen O, Grandjean P. Effects of inorganic and organic lead compounds on chromosomal length in human lymphocytes. *Appl Organomet Chem* 1987; 1: 15-19.
36. Grandjean P, Andersen O, Nielsen GD. Carcinogenicity of occupational nickel exposures: An evaluation of the epidemiological evidence. *Am J Ind Med* 1988; 13: 193-209. PMID:3281454
37. Christoffersen J, Christoffersen MR, Larsen R, Rostrup E, Tingsgaard P, Andersen O, Grandjean P. Interaction of cadmium ions with calcium hydroxyapatite crystals: A possible mechanism contributing to the pathogenesis of cadmium-induced diseases. *Calcif Tissue Int* 1988; 42: 331-9. PMID:2840183
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