OIL EXPOSURE AND CHRONIC HEALTH EFFECTS ON INDIGENOUS POPULATIONS IN SOUTH AMERICA

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Picture by Dematteis, from the book Crude reflections

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ABSTRACT

There is an ongoing discussion on whether the activity of oil companies and its environmental impacts are a threat for the health of the populations in affected areas. Some compounds present in crude oil (PAHs, VOCs, heavy metals and others) have been proven to cause health effects on humans. However, crude oil itself is still under discussion. The objective of this thesis is to review the epidemiological evidence available on this topic in the area of South-America to clarify the discussion. Occupational and population studies outside South-America were included in the analysis as well as supporting information. In general, the results seem to support that exposure to crude oil and some of its components can represent a threat at different levels (respiratory and reproductive health, some cancer types and acute effects). Nevertheless, the quality of some of these studies, both negative and positive ones, and its conclusions are sometimes dubious or questionable due to different factors (study designs, study populations and controls, exposure assessment, exposure miss-classification of the study population, etc). As a conclusion, further and efficient research is needed to finally prove causation.

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1. INTRODUCTION

1.1 History of petrol extraction activity in South America

Oil has been used since early human history. An early petroleum industry was established in the 8th century, when the streets of Bagdad were paved with tar, derived from petroleum[1]. Petroleum was already distilled in the 9th century to produce kerosene but it was not until the industrial revolution that petroleum was in great demand, increasing enormously until our days, especially after the 1st and 2nd world war[2, 3]. As a result several companies have acted in many countries along the world since 1960s; particularly in South-America the action of these companies has been quite extensive. Indigenous inhabitants of different regions within these countries have been exposed to crude oil due to[4-6]:

- Oil spillages (accidental or on purpose)
- Use of unlined open-air pits near the villages
- Spreading waste crude oil on roads to keep the dust down
- Construction of exploratory pools
- Production waters are dumped into the rivers instead of being re-injected back to the soils, where the environmental impact is less

Although these situations are not always reported and the exact amount of crude oil spread in the environment is not known there are several examples all over Latin American that are indicative of the problem:
Between 1995 and 1997 in the region of Loma de la Lata, **Argentina**, where Mapuches live, the Colorado River has been polluted with crude oil spills. In total, 630.000m^3 of soil was polluted with high levels of some constituents present in crude oil such as chromium (1.100μg/g dry soil), lead (1.550μg/g dry soil), arsenic (105μg/g dry soil), naphthalene (61,7μg/g dry soil), benzene (2.400μg/g dry soil), toluene (7.000μg/g dry soil) and ethylbenzene (1.400μg/g dry soil). Also, half of the studied waters were polluted with levels above the limits for heavy metals and PAHs[7].
In the Achuar's region, north **Peru**, several spills along the years have taken place as well[4]. High levels of some contaminants have been detected both in water and soil as well in blood of people; in some of the analyzed rivers levels of boron were twice the

WHO limit (0.5mg/L). Also for barium, which causes diarrhea, muscular weakness, kidney damage and heart problems, levels were more than twice the limits (levels=2mg/L, WHO limit=0.7mg/L). Levels of PAHs and benzo[a]pyrene were 222µg/L and 14µg/L, respectively, both exceeding the established limits. In blood samples, 43% of the children (n=59) had lead levels above the limits, with an average of 10µg/L. The same happened with 99% of the adults (n=199) and cadmium levels[8].

In **Ecuador** more than 18 billion gallons of oil has been spilled, generating more than 20.000 million gallons toxic water[9]. Recently, the affected area has been described by independent assessors as one of the world's most contaminated industrial sites[6]. In the most affected region of Ecuador, northern Amazonia, it has been suggested that health problems such as cancer and spontaneous miscarriages and birth defects could be linked to the contamination of waters, soils and air due to oil activity between 1964 and 1992; nowadays the rate of leukemia in children in northern Amazonia is four times higher than the national average[6]. Other consequences have been mentioned as well in a report sent to the courts, where psychological effects and social impacts were related to Texaco's activity in the affected area[10, 11].

In **Colombia**, the frequently sabotages in the oleo duct of Caño Limón-Coveñas have led to the sterilization of wide agricultural areas of the department of Arauca. In 2001 a terrorist attack caused a spillage in the Arauca River, polluting 80km of river and the water supply to Arauca city. Also, in the municipality of Tame the construction of exploratory pools 2km from the village contaminated soils and waters[4].

Figure 1. Map of South America

In 2000 between 29.000 and 40.000 barrels of oil were spilled in the Desaguadero River in **Bolivia** from the Ossa II Huayñacota Charaña Arica oleo duct, reaching 3 lakes 150 km away and affecting 127 communities of 18 municipalities who use those waters for their crops and cattle. The result was the death of thousands of animals and contamination of the tap water reserves. Thousands of Aymara families ended without water to drink, sterile lands and without pasture to feed their animals[12]. In the "Mbayeko Tekoronza" report published in 2008[12] levels of

total petroleum hydrocarbons (TPH), benzene, toluene, ethylbenzene and xylene (BTEX or VOCs), polycyclic aromatic hydrocarbons – Borneff (PAHb) and 22 heavy metals were measured in 46 water samples from different sources (river, tap water, streams and wells). Levels were compared to 5 legislations (WHO, EPA, Spanish, European and Bolivian ones). When combining the legislations and using the most restrictive one they saw that 76.7% (18 out of 21 communities) of the samples were contaminated by some of the compounds, being THP the most prevalent compound (76.2% of the communities), followed by heavy metals such as aluminum, arsenic, chromium, iron, nickel and manganese. Risk evaluation for health problems other than cancer was done for those heavy metals for which maximum established levels were available by comparing the exposition dose (drinking water) with the reference one for chronic exposure. For arsenic, chromium VI and molybdenum, seven, one and one communities were at risk, respectively.

Nowadays some companies have been brought to the courts, for instance Texaco, for its activities in Ecuador between 1964 and 1992[13]. In the meanwhile both companies and independent scientists have carried out studies with conflicting results, but the quality of most of these studies and its conclusions are sometimes questionable due to different factors (study design, study population, exposure assessment, exposure miss-classification of the study population, etc). Therefore, the aim of this thesis is to summarize and evaluate all the epidemiological evidence available on this topic, focusing on long-term exposure, since acute exposure and effects are better known and described [9, 12, 14-23]. Occupational and population studies outside South-America were included in the analysis as well as supporting information.

Figure 2. Child standing on a pipe[6]. Picture by Dematteis.

1.2 Crude oil compounds, toxicology and health effects

Crude oil is a mixture with a highly variable proportion of hydrocarbons and ranges from as much as 97% by weight in the lighter oils to as little as 50% in the heavier oils and bitumens[24]. The exact molecular composition varies widely from formation to formation but the proportion of chemical elements vary over fairly narrow limits as follows[25]:

Composition by weight

Element	**Percent range**
Carbon	83 to 87%
Hydrogen	10 to 14%
Nitrogen	0.1 to 2%
Oxygen	0.1 to 1.5%
Sulfur	0.5 to 6%
Metals	less than 1000 ppm

Figure 3. Crude oil composition by weight

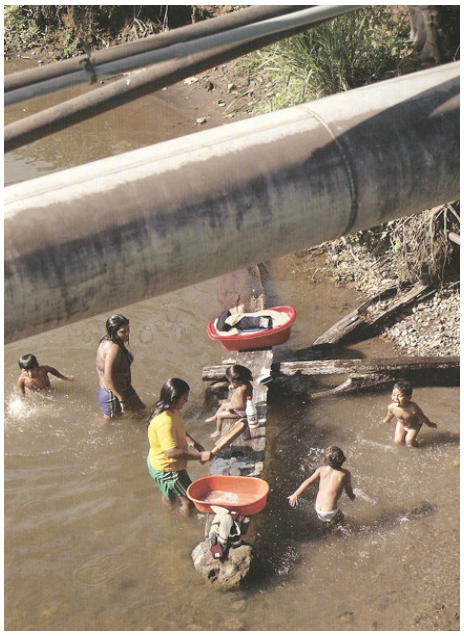
In addition, a variety of other toxic pollutants are typically used and generated during oil drilling and production operations, including drilling fluids, drilling cuts, and treatment chemicals that contain heavy metals, strong acids, and concentrated salts.

Crude oil contamination reaches different spots apart from the immediate area where the oil has been spilled. The heavier, less volatile constituents of crude oil, tend to sink into sediments from which they may repeatedly contaminate the water column or be consumed by benthic organisms, enter the food chain, and eventually come into contact with humans. Lighter compounds may evaporate in a matter of hours and be deposited far from the original source via air or rain[26].

Humans can be exposed to crude oil through three primary routes:

- Skin absorption: the fat solubility of most oil constituents allows them to be absorbed into and through the skin.
- Ingestion of food and drink: oil ingested in food and water is absorbed through the gut and distributed to other parts of the body.
- Inhalation of gases and oil on dust or soot particles.

Figure 4. People bathing in the river next to the pipes[6]. Picture by Dematteis.



Health's effects due to oil exposure are multiple and diverse depending on the type, duration and frequency of the exposition. A first classification is: carcinogenic effects and non-carcinogenic effects. Among the later there are the effects on psychological and emotional health (anxiety, depression, etc) and systemic effects (fever, headache, feeling tired, fatigue, kidney failure, etc). According to exposure type, occupational or residential, effects can be different as well[12]; while workers are exposed only via inhalation and in some cases via skin, populations can be exposed via ingestion of polluted water or food too. Skin contact can be an important route as well, but little is known about this in environmental exposure assessment.

Crude oil has been categorized by IARC as not classifiable as to its carcinogenicity to humans (Group 3) but in its monograph in 1989 it classified exposures to workers in petroleum refineries as probable human carcinogens (Group 2A) based on animal and epidemiologic evidence[27]. Despite this general classification, some compounds present in crude oil are classified as carcinogenic to humans (Group 1A)[28, 29]. Below a list of compounds present in crude oil, their health effects and IARC classification:

Polycyclic aromatic hydrocarbons (PAHs): PAHs is a group of about 100 chemicals that are formed during the incomplete burning of coal, oil, gas, garbage, tobacco and other organic substances. They are also present in crude oil, plastics and pesticides[17]. Out of these 100 compounds 17 were considered in the ATSDR report in 1995, being the selection criteria: toxicity, potential for human exposure, frequency of occurrence at National Priority List (U.S.) hazardous waste sites and the extent of information available. In this document it is reported that several PAHs have caused tumors in lab animals when they breathed these substances in the air but also when they ate them or had been in contact via skin for a long period. Mice exposed to benzo[a]pyrene had reproduction problems and so did their offspring. In another study birth defects were reported as well[17]. In humans a similar effects could be present; some studies suggest

that PAHs inhalation could be related to intrauterine growth retardation and others suggest an effect of these compounds on spermatogenesis[30]. Other studies of people who had been in contact for a long time with PAHs also show a correlation between PAHs exposure and incidence of cancer[17]. Non-cancer effects on the respiratory tract are not clear for humans. No toxicological studies on oral exposure in human have been reported so far. Via skin, some of these compounds have been described to cause skin cancer (benz[a]anthracene, benzo[b]fluoranthene). It is also suspected that some of these compounds have an influence on the immune system[17].

IARC classifies benzo[a]pyrene as carcinogenic to humans (Group 1A), dibenz[a,h]anthracene as probably carcinogenic to humans, benz[a]anthracene, benzo[b]fluoranthene, chrysene plus others as possibly carcinogenic to humans and others such as pyrene, fluoranthene or anthracene as not classifiable as to carcinogenic to humans[27].

Limit concentrations in drinking water for total PAHs is of 0.11µg/L within the European legislation[31]. EPA has no limits for total PAHs but does for benzo[a]pyrene, 0.2µg/L[32], while in Europe it is 0.01µg/L[31]. Air standards for benzo[a]pyrene are not yet established, but a report of the EU proposed limits between $0.01ng/m^3$ and $0.1ng/m^3$[33].

Volatile organic compounds (VOCs): the most common VOCs in crude oil are the ones know as BTEX: benzene, toluene, ethylbenzene and xylene. They are mainly found in household products (paints, paint strippers, solvents, aerosol sprays, cleansers, disinfectants). Health effects are diverse depending on the VOC[34]:
- *Benzene*: acute exposure to high levels of benzene produces central nervous system (CNS) effects and death. At lower levels, mild CNS effects appear to be concentration dependent and rapidly reversible. Other effects include immune system depression and bone marrow toxicity leading to deficiencies of phosphatases and transaminases levels, erythrocyte sedimentation rate and lymphocytes and blood counts among general population[34, 35] and refinery workers[36-38]. Some occupational studies reported genotoxic effects due to benzene exposure at work by showing a correlation between benzene exposure and presence of chromosome aberrations (CA), which are considered the most relevant biomarker for genotoxic exposure[39-41]. It has been shown that

benzene has the potential to cause CA in people exposed chronically to relatively low levels of benzene (≈ 1ppm)[34]. It is also related to acute myeloid leukaemia (AML) and possibly related to other leukaemia types and lymphoma[42, 43]. Effects on the male reproductive system has been described as well[44].
- *Ethylbenzene*: some of the symptoms reported after short-term exposures at levels above the established standards are drowsiness, fatigue, headache and mild eye and respiratory irritation. Chronic exposure causes damage to the liver, kidneys, central nervous system and eyes.
- *Xylene*: this compound can cause disturbances in the CNS, such as changes in cognitive abilities, balance, and coordination after acute exposures. Chronic exposure can cause damage to the CNS, liver and kidneys. Compared with benzene and toluene, much less is known of the human health hazards.
- *Toluene*: low oral toxicity to CNS may cause fatigue, nausea, weakness and confusion. Chronic exposure can cause spasms, tremors, imbalance; impairment of speech, hearing, vision, memory, coordination and liver and kidney damage.

The EPA has proposed a maximum concentration level for benzene in drinking water of 5µg/L, while in the EU it is 1µg/L[31]. For other compounds the EU has no guidelines. EPA recommends 0.7mg/L for ethylbenzene, 10mg/L for total xylene and 1mg/L for toluene[32]. For air no levels have been established by EPA[15], but the European Commission has adopted a proposal which sets the a limit value of 5µg/m^3 (≈1.54ppb) to be met by January 2010[45].

Hydrogen sulphide gas: some crude oils release high concentrations of hydrogen sulfide gas. Inhalation of this gas can affect the nervous system, causing headaches, dizziness, loss of consciousness, nasal tract irritation, respiratory arrest and death[14, 29].

Alkanes (paraffin) and cycloalkanes: at low concentrations are simple irritants and cause inflammation, redness, itching and swelling of the skin and respiratory tract. At high concentrations can cause eczema of the skin and pulmonary edema. It can also lead to unconsciousness and asphyxia[46]. They also cause anesthesia and narcosis in the CNS. As it is fatty soluble it can rapidly penetrate the fatty cells of the myelin sheath that surrounds nerve fibers, causing degradation of the axons and neural damage[46].

Metals and heavy metals: multiple metals can be present in crude oil. Some of them can be found naturally in the environment and some are necessary for humans in minute amounts (Co, Cu, Cr, Ni). Others are carcinogenic or toxic, affecting, among others, the CNS (Hg, Pb, As), the kidneys and liver (Hg, Pb, Cd, Cu) or skin, bones and teeth (Ni, Cd, Cu, Cr)[47]. Mercury (Hg) once released to the environment can be converted to methyl mercury. Chronic exposure to it can cause muscular incoordination and difficulties in speech. It is also a teratogenic substance, causing cerebral palsy and mental retardation on unborn children exposed to it. Chronic exposure to arsenic is related to skin lesions and cancer of skin, kidney and bladder[44]. Chrome VI is related to kidney damage, allergy, dermatitis and even perforation of cutaneous areas, lung cancer, liver failure and it can even cause death[12]. Cadmium consumption causes nausea, vomit, abdominal pain, diarrhea and kidney diseases. It has also been related to prostate[48] and lung cancer[49] and a reduction of life expectancy[50].

Maximum allowed levels in water are: mercury 0.002mg/L (EPA), arsenic 0.01mg/L (EU and EPA), cadmium 0.005mg/L (EU and EPA), total chrome 0.1-0.05mg/L (EPA-EU) and lead 0.015-0.01mg/L (EPA-EU).

Naturally occurring radon material (NORM): the presence of natural radioactivity in oil and gas fields has been recognized worldwide. This radioactivity can result from the occurrence, in both rocks and specific ores, of isotopes from the uranium and thorium decay series, both with alpha and gamma radiation activity[51, 52]. Activity concentrations in production water are higher than those in crude oil[53]. The mainly health effect related to chronic exposure to radiation is cancer, while short-term high levels of radiation cause more severe effects such as burns and radiation sickness (nausea, weakness, hair loss, skin burns or diminished organ function)[54].

EPA makes the conservative (cautious) assumption that any increase in radiation exposure is accompanied by an increased risk of stochastic effects. Some people who drink water containing alpha emitters in excess of the MCL (30µg/L for uranium and 15 pCi/L for adjusted gross alpha and not including radon or uranium) over many years may have an increased risk of getting cancer[55]. For non-stochastic effects, levels above 5-10 rem symptoms can be: changes in blood chemistry, nausea (50 rem), fatigue (55 rem), vomiting (70 rem) and others until death (>400 rem)[54].

1.3 Crude oil exposure and acute health effects

As mentioned before, acute health effects due to crude oil exposure are better known and described than chronic effects. The majority of the studies on this topic were done after oil spills and the study population was usually volunteers that helped in the cleaning tasks. Few studies are focused on acute health effects among petrochemical workers. Nevertheless, results were similar among both study populations. Some of the reported symptoms were: fever, headache, eyes pain, tiredness, weakness, nauseas[19-21, 23, 56], as well as other symptoms on skin[57], respiratory, digestive and nervous systems[18, 58-60]. In two studies acute exposure to crude oil was related also to depression and anxiety[18, 22].

In Latin America two reports showed similar symptoms among population exposed to crude oil. "Mbayeko Tekoronza" (Medicus Mundi)[12] is the report of a study done in the Bolivian Chaco. The objective of this cross-sectional study was to determine levels of crude oil compounds present in water in the studied communities and relate the exposure with people's health. Levels of the different compounds detected have already been mentioned in the introduction. Regarding health effects, people classified as exposed reported significantly more difficulties to breath, throat pain, nauseas and joint pain in the last 2 weeks. For the last 12 months exposed people reported significantly more fever, headache, eyes and ear ache, tiredness, frequent urine, sickness, weakness, cough, chest pain, throat ache, nauseas, vomit, diarrhea, stomach ache, appetite loss, skin fungi, skin eruption, join pain, body pain, cramps, a more nervous feeling and humor changes. San Sebastián *et al.*[61] investigated health effects other than cancer among women living in the polluted areas of the northern Ecuador. The symptoms they found significantly higher among the exposed women (weakness, headache, tiredness, nausea, eye and nasal irritation) were also in accordance with the studies done on acute health effects after oil spills or among petrochemical workers.

2. EPIDEMIOLOGICAL STUDIES ON CHRONIC HEALTH EFFECTS

2.1 Occupational studies on crude oil

Table 1.1 Summary of cohort occupational studies on crude oil.

Cohort Years	Outcome	Results	Funding source	Year	Author
19000 w. Refinery 1947-1977	Mortality SMR	- SMR greater than 100 for: pancreas cancer, brain cancer, leukemia, Hodgkin's disease, other lymphatic cancer, and benign neoplasms. None statistically significant.	Industry	1985	Divine, BJ., *et al*[62].**
11000 w. Production & pipeline location 1947-1980	Mortality SMR	- No associations, only an excess of thyroid cancer, but based on 4 cases only.	Industry	1987	Divine, BJ., *et al*[63].**
1200 w. Refinery 5 years of follow-up	Mortality SMR	- Brain cancer in men who died within 20 years of first exposure. - A thorough investigation of the several exposures of the brain cancer cases could not relate what seems to be a "cluster" to any hazard encountered at the workplace	Institution, university or research centre	1987	Theriault, G., *et al* [64]**
1595 w. Refinery 1949-1982	Mortality SMR	- Kidney cancer among maintenance workers (small number). - Lung cancer plus all kind of cancers higher for moving department. -Leukemia related to exposure levels within the production department.	Institution, university or research centre	1989	Bertazzi, PA., *et al* [65]**
9500 w. Refinery 1940-1984	Mortality SMR	- Lymphocytic leukemia among those starting to work before 1940 or in later (other thing than benzene). - Myelocytic leukemia among workers starting to work in or later 1940 (benzene).	Institution, university or research centre	1989	Wongsricha-nalai, C., *et al* [66]**
6800 w. Refinery Chemical plant 1948-1972	Mortality SMR	- Lymphoma among both work places. - Leukemia, SNC and liver cancer among refinery workers.	Industry	1991	Marsh, GM., *et al* [67]**
7850 w. Petrochem. 1941-1983	Mortality SMR	- Liver cancer among production workers.	Industry	1991	Teta, MJ., *et al*[68]**
25300 w. Refinery Ch. plant 1970-1982	Mortality SMR	- Kidney cancer only in a specific department. - Significant increase in hematopoietic and lymphatic cancer in workers employed between 1940&1949.	Industry	1992	Shallenberger, LG., *et al* [69]
14100 w. Two refineries 1950-1986	Mortality SMR	- Possible occupational relation with lymphoma and leukemia among Richmond refinery workers starting before 1949.	Industry	1992	Dagg, TG., *et al* [70]
1973-1989 Two refineries	Mortality SMR	- Non-significant increases of some cancers. No associations.	Industry	1993	Tsai, SP., *et al* [71]**

Continuation of Table 1.1

Cohort Years	Outcome	Results	Funding source	Year	Author
1950-1989 8 refineries & 750 dist. centers	Mortality SMR	- Leukemia within 1 refinery and in distribution centers. - Kidney cancer in distribution centers.	Institution, university or research centre	1993	Rushton, L.[72]**
17800 w. Refinery 1937-1987	Mortality SMR	- Bone, leukemia and benign cancer, not related to occupational exposure. - No exposure-effect time relationship.	Industry	1996	Satin, KP., *et al* [73]**
4900 w. Refinery 1946-1987	Mortality SMR	- Prostatic and non-Hodgkin's cancer not related to work.	Industry	1996	Collingwood, KW., *et al* [74]**
3800 w. 1973-1994 Refinery & petrochem.	Mortality SMR	- Non-significant increase of brain cancer. - Lower rate of leukemia than expected.	Industry	1997	Tsai *et al*.[75] **
92300 w. Refinery & chemical production	Mortality SMR	- Brain cancer. - Leukemia.	Institution, university or research centre	1997	Cooper, SP. *et al*[76]**
21000 w. 1947-1977 & 28000 w. Until 1993 Refineries, Petroche., & research lab	Mortality SMR	- Favorable mortality experience for Texaco's workers. - Increase of lymphatic tissue cancer in subgroups (fluid catalytic cracking & crude stills) and brain cancer (lab stuff & motor oil). - No relationship with the time working at the company.	Industry	1999	Divine, BJ. *et al*[77].
8950 w. Petrochem. 1970-1992	Cancer incidence SIR	- Small increase in incidence of overall lymphohaematopoietic (LH) malignancies in workers before 1950.	Industry	2000	Huebner, WW. *et al*[78].
34600 w. Diverse departments 1964-1994	Mortality SMR	- Increased deaths from mesothelioma in refinery and petrochemical workers (related to asbestos exposure). - Deaths from multiple myeloma among marketing and distribution workers. remained increased in the update period 1984–94 (no clear pattern by duration of employment or latency). Aortic aneurysms remained increased too for the same workers.	Industry	2000	Lewis, RJ. *et al*[79].
7500 w. Petrochem. 1945-1996	Mortality SMR	- Non-significant acute myeloid leukemia for workers hired before 1950, being increased in workers with maintenance tasks. - No time working correlation.	Industry	2001	Wong, O. *et al.*[80]
18500 w. 1950-1995 Two refineries	Mortality SMR	- Mortality excess for multiple myeloma was marginally significant (workers before 1949). - Non-significant increase of leukemia (1 refinery).	Industry	2002	Satin, KP. *et al.*[81]
25300 w. Petrochem. 1964-1994	Mortality SMR & Cancer incidence SIR	- Exposure-response trend for cumulative H_2S exposure and transportation accidents. - Lung cancer risk was increased among workers in the highest cumulative exposure category for petroleum coke/spent catalyst.	Industry	2003	Lewis, RJ. *et al.*[82]

Continuation of Table 1.1

Cohort Years	Outcome	Results	Funding source	Year	Author
4600 w. 1983-1999 From two petrochem.facilities	Cancer incidence SIR	- Non-significant increased incidence of cancer for women (SIR=1.24). - Non-significant increased risk of breast cancer for women (they attribute it to other reasons. 70% of the cases were office workers). - Increased incidence of bone and joint cancer in 1 plant. Only 3 cases, with different histologies and locations.	Industry	2004	Tsai, SP. *et al.*[83]
17100 w. Petroleum industry 1981-1996	Mortality SMR & Cancer incidence SIR	- Significant increase of the incidence of melanoma, bladder and prostate cancer. - Marginally significant excess of pleural mesothelioma (related to exposure to asbestos), leukemia and multiple myeloma.	Industry	2004	Gun, RT. *et al.*[84]
17100 w. Petroleum industry 1981-2001	Mortality SMR & Cancer incidence SIR	- Significant increased incidence of mesothelioma (related to exposure to asbestos), melanoma and prostate cancer. - Tanker drivers had a significantly elevated incidence of kidney cancer, possibly related to exposure to hydrocarbons. - Acute non-lymphocytic leukemia (ANLL) cases were clustered in the middle to high hydrocarbon exposure categories.	Industry	2006	Gun, RT. *et al.*[85]
16500 w. 1951-2003 Refinery and petroleum distribution	Mortality SMR & SRR	- Significantly elevated SMRs in oil refinery workers for mesothelioma and melanoma, nothing for petroleum distribution workers. - Significantly elevated standardized registration ratios (SRRs) were only shown in oil refinery workers for mesothelioma, melanoma and other skin cancer.	Industry	2007	Sorahan, T.[58]

* Note: The retrospective studies use the **Standard mortality ratio (SMR)** or instead, the **Standard incidence ratio (SIR)** using the population of the region or country of study as reference to determine if there is a risk for the oil industry workers. ** Only abstracts available.

Table 1.2 Summary of case-control occupational studies on crude oil.

Information	Outcome	Results	Funding source	Year	Author
102 cases, 4 controls per case within 5 companies	Risk of kidney cancer	- No associations.	Industry	1993	Poole, C., *et al*[86].
37 cases from Shalleberger study[69].	Risk of kidney cancer	- No associations, but numbers were too small, with a wide CI.	Industry	1996	Gamble JF., *et al*[87].
91 cases, 4 controls per case.	Risk of leukemia	- Myeloid leukemia related to low levels of benzene and workers working for more than 10 years in the company. - No associations for lymphoma.	Industry	1997	Rushton, L., *et al*[88].

The majority of the studies are cohort studies (Table 1.1). Only 3 case-control studies were found (Table 1.2). Also, only one study investigated effects on reproduction among working women (Xu *et al.*[89], not included in the tables). For some of the articles only the abstract was available; as it was not possible to read the whole article the quality or weak points could not be assessed or discussed properly. In 1991 Clapp and colleagues[90] published a review where more than 50 studies done in Europe and the USA were analyzed. In this review they concluded that there was evidence of an association between exposure to petroleum refinery emissions and increased death rates from leukemia and from cancers of the stomach, kidney, pancreas, brain, skin, and lung. The evidence was strongest for leukemia. Later in 1999 a new review was carried out by the same author to include the new studies until that year[91]. In this review they focused on leukemia and other lymphopoietic cancers. The conclusion was that there was an association between exposure to oil refinery emissions and the risk of developing these types of cancers. Contrary, in 2000 Wong and Raabe[92] published a meta-analysis focusing on nonlymphohematopoietic cancers. They combined data-bases from US, UK, Canada, Finland, Australia and Italy, with more than 350000 workers included. Their conclusion was that there was no increased mortality from digestive cancers (stomach, large intestine, liver, or pancreas) and lung, bladder, kidney, or brain cancers. Only some UK refinery workers and upstream operation workers in Canada showed more risk of melanoma. Three new studies also reported a significant increase for melanoma[58, 84, 85]. In all cases authors argued that it could be related to exposure to sun during work (information to affirm this conclusion was not available) or that it was not possible to link it to crude oil exposure. Wong and Raabe also found an elevated mortality for prostate cancer among short-term workers in some companies of the US, but the absence of an upward trend by length of employment in these workers argued against an association between exposure to petroleum products and prostate cancer. Nevertheless, in this review they only used cohort studies that used SMR, which has some limitations that will be discussed later on.

Studies done from 1999 until now also suggest that lymphohematopoietic malignancies (leukemia and lymphomas) are related to this occupational field. As said before, this was already concluded in the review done by Clapp *et al.* in 1999[91] and by Landrigan in his editorial about benzene[93], although certain types of lymphoma and leukemia related to exposure to benzene are still under debate[94]. In the review of Clapp *et al.* it is also mentioned that the increased mortality for leukemia was higher for those workers

employed before 1950. Within the analyzed studies in this thesis the SMR for some cancers are higher for worker populations who were hired before 1949-1950. This is because at that time new exposure controls to benzene were implemented[74]. Some studies suggest that there could be a relationship between exposure and kidney, prostate and brain cancer as well[85]. Harrington mentioned this possible health effect in a review of 120 articles in 1987[95]. Later in 1999, Clapp's review supported this hypothesis[91].

Some of the studies included in Tables 1.1 and 1.2 have received different criticisms. Some of them, like Divine *et al.*[77] or Tsai *et al.*[75], claimed to have a deficit for "all causes mortality" and for "all cancers mortality" among the oil company workers compared to the general USA population. The use of national or regional populations as reference can lead to biased results due to the healthy worker effect, since the working population tends to be in a better health status than the general population. This is supported by the differences between SMR and SIR found by Gun *et al*[84]. A lot of these studies also claimed no relationship between exposure (to different crude oil compounds these workers might be exposed to) and cancers since for some of them the SMRs or SIRs were not over 100. Nevertheless, a time trend of the SMRs and SIRs should be checked, to see if the ratios tended to increase or decrease along the years, since most of these cohorts had a follow-up time of 20-30 years. On the other hand, in the updates of some studies (Tsai *et al.*[96]) high SMR previously reported became diluted with time. This can be due to the fact that a high percentage of new workers was hired after 1950 and 1970 and added to the cohort[91]. Also, the possibility that in some studies workers are misclassified according to their exposure to certain compounds could lead to results with diluted effects, since exposure levels were always estimated according to the job titles, departments or area where workers worked. Only one study investigated the effect of petrochemical exposure and its effects on spontaneous abortions among 2853 women, 57% of them working in a petrochemical plant (Xu *et al.*[89]). In this study they concluded that the risk of spontaneous abortion among women working with petrochemical products was higher compared to those working in the same plant but without this exposure and also with women not working in the petrochemical complex. The increased risk was found with exposure to most chemicals, but it was only significant for benzene, gasoline and hydrogen sulfide. Nevertheless, levels of these compounds are highly correlated so it seems hard to tell which compounds were playing a role and which were not.

2.2 Population studies on crude oil

2.2.1 Studies outside Latin America

Table 2.1 Population studies outside Latin America. E (exposed) and NE (non-exposed).

Study design	Study population	Methodology & Exposure	Results	Year & place	Author
Respiratory outcomes					
Cross-sectional	- 436 E/488 NE - 30-64 years old	- Questionnaire - Significant differences in $S0_2$, NO_2 and PM_{10} levels.	- E and NE had similar respiratory health. - E had more acute irritative symptoms (eye and throat irritation, nausea). Chemical odour perception was significantly much higher in the exposed area.	1997 Taiwan	Yang *et al.*[97]
Cross-sectional	417 E/ 611 NE - Children (6-12)	- Questionnaire - Significant differences in $S0_2$, NO_2 and PM_{10} and acid aerosols.	- More upper respiratory symptoms and asthma among exposed, not wheeze, cough or bronchitis.	1998 Taiwan	Yang *et al.*[98]
Cross-sectional	- Children from 6 to 12 years old. 282 exposed to petrochemical air pollution, 270 exposed to traffic pollution, 639 controls	- Questionnaire - 181 children also did lung function test - PM_{10} and VOC, significantly higher than the control areas (semi-rural and residential).	- Children living near the plants had higher risk of developing asthma and exacerbations, wheeze, dyspnea, nocturne cough, rhinitis and a lower lung function. - Distance from the petrochemical company was a risk factor.	2008 Argentina	Whichmann *et al.*[99]
Case-crossover study	- Children from 2 to 4 years old	- Short-term measurements of SO_2 - Distance from 0.5 to 7.5km from refinery - Interquartile range	- The risks of asthma visits and hospitalizations were more pronounced for same-day SO_2 peak levels than for mean levels on the same day. The OR were significantly more than 1 over the interquartile range.	2009 Canada	Smargiassi *et al.*[100]
Reproductive outcomes					
Ecologic	- Born children	- Two cities near a petrochemical company were used to compare sex ratios with national ratio.	- Sex ratio of these two cities did not differ from the national ratio or along time.	2000 Taiwan	Yang *et al.*[101]
Ecologic	- Born children	- 16 cities were classified as exposed and compared to the rest of Taiwan. - PM_{10} and SO_2 where significantly higher in exposed cities.	- Mean sex ratios at birth for the combined period 1987-1996 in exposed cities were significantly high compared to national live birth sex ratios	2000 Taiwan	Yang *et al.*[102]
Cohort	- 50388 first-parity singleton live births in NE area and 7095 in E area	- Exposed areas were so if they were within a 3km ratio from 3 petrochemicals companies	- Preterm delivery was highly significant among exposed women.	2004 Taiwan	Yang *et al.*[103]

Continuation of Table 2.1

Study design	Study population	Methodology & Exposure	Results	Year & place	Author
Cancer incidence and mortality					
Ecologic	- White population	- Petrochemical exposure estimates (SO_2, HC and NO_x), 4 different regions. - Cancer incidence rates and major-cause mortality rates (1969 -1977)	- Significant increased incidence of buccal and pharynx cancer. Both sexes. - Strong positive association between degree of residential exposure and death rates from cardiovascular disease and cancer, less strong positive association between exposure and death rates from cerebrovascular disease. Both sexes. - In males cancers of the stomach, lung, prostate and kidney and urinary organs were also associated with petroleum and chemical plant air emission exposures.	1984 USA	Kaldor et al.[104]
Ecologic	- Population from the area of study	- Cancer mortality (1981-1991) and cancer incidence (1974-1991)	- 8% excess of cancer incidence within 7.5km but not mortality. Possibly due to cancer registration in Wales. - Nothing for leukaemia.	1995 UK	Sans *et al.*[105]
Ecologic	- Population of 7 areas with oil refineries around	- 7 sites within 7.5km from the refineries - Cancer incidence (1974-1991)	- No evidence of association between residence near oil refineries and leukaemia, or NHL. - Weak positive association between risk of HL and proximity to major petrochemical industry. - Negative association with multiple myeloma.	1999 UK	Wilkinson *et al.*[106]
Ecologic	- Female living in two cities near a petrochemical company.	- SMR of two cities near a petrochemical company compared to the national mortality.	- SMR for lung cancer rose gradually about 30-37 years after the company started working in the area.	2000 Taiwan	Yang *et al.*[101]
Ecologic	- Population from the area of study	- SMR calculations. - Distance from a petrochemical company	- No relationship with living in the area and brain cancer	2003 USA	Neuberger *et al.*[107]
Ecologic	- Population from the area of study	- Benzene exposure (air) measured and estimated. Although other routes are plausible as well.	- Cluster of Hodgkin lymphoma within 1 mile from the refinery, prevalence 7 times higher compared to the USA population	2008 USA	Dhalgren *et al.*[108]
Matched case-control study	- Children younger than 19 years old	- Deaths from 1995 to 2005 - Children classified according to employed population of the municipality in petrochemical companies as an indicator of exposure.	- Higher risk of leukaemia among children exposed to higher levels of polluted air due to petrochemical activity.	2008 Taiwan	Weng *et al.*[109]

The studies in the table above (Table 2.1) are organized according to the following criteria: outcome of study (respiratory outcomes, reproductive outcomes and cancer mortality and incidence), study design and year of publication. They are all studies done outside Latin America, except Wichmann *et al.*[99] study, which was done in Argentina; the reason to include this study in this table is because the population in the area of study (Buenos Aires) is mainly not indigenous. Also, environmental and social problems due to petrochemical activity in this area are different from the ones described previously in the Mapuches area (Loma de la Lata) in Argentina and other South American countries. Finally, all these studies, including the Argentinean one, focused on air pollution and inhalation, none of them studied other routes of exposure like drinking water or food consumption (soil and water pollution), probably because that was not the main issue in the areas of study.

From the four studies done on respiratory problems it looks like emissions from petrochemical companies compromise health of the citizens around. Nevertheless, all the studies had a cross-sectional design, except for one. This design has the limitation that one needs to be cautious when making causal inference. Still, it gives an idea of the situation. Also, the two cross-sectional studies with children obtained similar results, while for adults no chronic effects were detected, only acute irritative symptoms. The author argued it could be due to the fact that adults might be less sensitive to air pollution than children. Smargiassi *et al.*[100] (case-crossover study) gave positive results on peak exposure to SO_2 and asthma episodes and hospitalizations among children, but this study had also several limitations: children are not always at home and they spend most of their time indoors, errors on exposure estimate could be present as well. Another limitation of all these studies is that the contribution of each pollutant can not be distinguished; air has a mix of contaminants and, on the other hand, levels of these contaminants are often correlated[99].

Regarding sex ratio[1] at time of birth, Yang gave two different results depending on the study population. In the first study[101] they only used two exposed cities, while in the second one[102] more cities were included (N=16), which might result into more power. It is in the latter where a possible relationship between exposure to

[1] Sex ratio: is the ratio of males to females in a population.

petrochemical pollutants and sex ratio difference was suggested. Nevertheless, they mention that the difference between exposed and national sex ratio was significant, but numbers for the latter are not given in the article and actually the average national sex ratio for Taiwan at the moment of birth is 1.09[110], which is similar to the numbers given by Yang *et al*. for the exposed areas. On the other hand, both studies are ecologic, therefore the ecologic fallacy[2][111] can not be ruled out. Actually, later in 2002 (only abstract available) Yang *et al*.[112] compared the sex ratio of 16 exposed cities and 16 non-exposed cities in Taiwan; no significant differences in sex ratios were found. In another study done in Iran (only postscript available) a higher significant sex ratio was found as well when comparing the ratio of the contaminated areas with the ratio of the rest of the region[113]. On the other hand, there is one study that put in doubt the use of sex ratio as a tool to detect health hazards from industrial air pollution[114]. With respect to preterm deliveries Yang *et al*.[103] reported a significant positive OR among women living in the polluted areas in 2004. In this study they classified exposed as so if they were living with a 3km ratio from 3 petrochemical companies. There are two other studies (only the abstract available) that also showed an association between exposure to petrochemicals and preterm delivery[115, 116]. Leem *et al*.[117] studied the relationship between air pollution and preterm deliveries. With a birth cohort of more than 52000 singleton births they found significant positive relationships between levels of CO, SO_2, NO_2 and PM_{10} and preterm deliveries. The relationship was dose dependent with CO, SO_2, NO_2. Leem, though, mentioned that the possibility of exposure misclassification is present, since they used spatially and temporally explicit exposure models. Tabacova *et al*.[118] found that women living near petrochemical and with complication of pregnancy had higher levels of styrene metabolites in their urine than those women living in the area but with no pregnancy complications. Also, spontaneous abortion, toxaemia and anaemia were associated with higher levels of lead exposure compared to non-complicated pregnancies.

Most of the studies on cancer mortality and incidence are also ecologic, except for the study by Weng *et al*.[109]. Again the ecological fallacy problem is present making results harder to interpret. While Sans *et al*.[105] did not find any association between

[2] The major limitation of ecologic analysis for testing etiologic hypotheses is the potential for substantial bias in effect estimation. The central problem, known as the "ecological fallacy", results from making a causal inference about individual phenomena on the basis of observations of groups.

exposure and leukaemia Weng *et al*. (case-control study) did find an association between higher levels of polluted air and risk of leukemia among children younger than 19. Exposure estimates, though, are debatable since they used as indicator the number of workers in the petrochemical company for each city to classify children as exposed or not. On the other hand, exposure does not need to be equal for everybody in each municipality either. Weng *et al*. also described an association between leukemia among children and petrol station density (PSD), but that was a study on general air pollution and not specifically on pollution due to petrochemical industrial activity[119]. Dahlgren *et al*.[108] described a 7 times higher prevalence of Hodgkin's lymphoma in an affected area compare to the national prevalence (USA). Wilkinson *et al*.[106] did not find significant results for leukemia or non-Hodgkin's lymphoma but they did find a correlation between distance from the oil companies and Hodgkin's lymphoma. One weak point reported in Sans *et al*'s study is that cancer registries in UK were not equally complete in the whole territory at the time of the study. This is an advantage of the Taiwanese studies, since the island has a complete registry of deaths, births, cancer cases, etc. Other reasons could be differences on exposure levels between these countries, genetic differences or the study designs (case-control are considered more appropriate to establish causation). Finally, despite Sans *et al*. did not find associations for leukemia they detected an 8% excess of cancer incidence within 7.5km from the oil companies. Other cancers like lung cancer showed a correlation with time exposure[101] while brain cancer did not seem to be related with exposure[107]. Nevertheless, in this other study done by the same author (only abstract available) 16 counties with petrochemical activity were matched with 16 counties with non-petrochemical but with other industrial activities. They found that there was an excess rate for liver cancer among male, but not for any other type of cancer[120], which puts in doubt the before mentioned results for lung cancer among females that Yang *et al*. obtained[101]. In 1984 Kaldor *et al*.[104] related air pollution from petrochemical activity with several types of cancers: buccal, larynx, stomach, lung, prostate, kidney and urinary organs. This was also an ecologic study and they could not control for a lot of potential confounders such as socioeconomic status, smoking or alcohol consumption.

2.2.2 Studies within Latin America

A) Ecuador

Table 2.2 shows the results of studies carried out in Ecuador, some of which are compiled in the report called "Yana Curi" (Medicus Mundi[121]). Studies are presented according to: health outcome under study, study design and year.

Table 2.2 Population studies within Latin America. E (exposed) and NE (non-exposed).

Study design	Study population	Methodology & Exposure	Results	Year & place	Author
Cancer incidence and mortality					
Ecologic	- 1000 citizens of affected village, Quito population as control	- Observed vs expected cancer incidence and cancer mortality (1989-1998). - Total petroleum hydrocarbons (TPH) were over the EU limit in all the rivers sampled (4).	- Not significant excess for all cancers incidence among males. - Significant death excess for all cancers, stomach and melanoma cancers among males.	2001 Ecuador	San Sebastian *et al.*[122]
Ecologic	- Population of 4 exposed counties and 11 non-exposed	- Cancer incidence data from the National Cancer Registry in Quito (1985-1998). - E counties were considered as so if oil exploitation had been going on for at least 20 years. NE counties were considered as so if there was no oil exploitation.	- Significantly elevated RR in both men and women in exposed counties for all cancers combined. - Significantly elevated RR were observed for cancers of the stomach, rectum, skin melanoma, soft tissue and kidney in men and for cancers of the cervix and lymph nodes in women. - Increase in hematopoietic cancers was also observed in the population under 10 years in the exposed counties in both males and females.	2002 Ecuador	Hurtig *et al.*[123]
Ecologic	- Children from 0 to 14 years of 4 exposed counties and 11 non-exposed	- Cancer incidence data from the National Cancer Registry in Quito (1985-2000). - E counties were considered as so if oil exploitation had been going on for at least 20 years. NE counties were considered as so if there was no oil exploitation.	- Significant higher risk for all leukaemias among 0-4 years old children E (both genders combined). - Significant higher risk for E females and both genders combined when taking all ages (0-14) together. - No differences for other cancers.	2004 Ecuador	Hurtig *et al.*[124]
Ecologic	- Population from 5 low-non exposed, 4 mid exposed and 5 high exposed cantons	- Cancer data from the National Cancer Registry in Quito (1990-2005) - Exposure estimation according to number of wells, spud, surface of the county. - RR comparing E and NE and comparing Amazon counties vs Pinchica (Quito county).	- Among Amazon cantons: no evidence of increased rates of death from all causes or from overall cancer. RR estimates were also lower for most individual site-specific cancer deaths. - Amazon vs Pinchica: mortality rates in the Amazon provinces overall were significantly lower than those observed in Pichincha for all causes and overall cancer.	2008 Ecuador (Chevron)	Kelsh [125]

Continuation Table 2.2

Study design	Study population	Methodology & Exposure	Results	Year & place	Author
Reproductive outcomes					
Cross-sectional	- 428 E and 347 NE women between 17-45 years old who lived at least 3 years in the area.	-Questionnaire on reproductive problems and calculation of the prevalence rate and OR were done. - TPHs were over the EU limit in 18 of the 20 rivers sampled.	- Significant higher OR for spontaneous abortion among exposed women. - No associations for stillbirth.	2002 Ecuador	San Sebastian *et al.*[126]

In the study where San Sebastián *et al.*[126] studied the effects of exposure to crude oil on reproduction health no association with stillbirth was found, but due to its low frequency it is not considered to be a good indicator of developmental toxicity when exposed to oil pollutants[127]. They did find a significant higher risk of spontaneous abortion (OR=2.47) among exposed women. This is in accordance with other studies done, and previously discussed, among women living near an oil company or working in it[89, 118], although the percentage of reported miscarriages in the non-exposed area was too low compared to other developing countries where women self-reported miscarriages[128]. Some limitations of the study need to be taken in account; recall bias, since exposed people might think they have more chances of having spontaneous abortions. To avoid that problem the study was presented as a general health study and, on the other hand, women did not know about the relationship between exposure to crude oil and reproductive problems. Another limitation is that medical records were not available to validate the reported spontaneous abortions, but in studies done in developed countries the correlation between self-reported miscarriages and medical records was pretty high[129, 130]. Finally, exposure misclassification is plausible.

Studies on cancer incidence and mortality are conflicting. First of all it needs to be mentioned that all studies done were ecologic, therefore the limitations linked to this kind of study design must be taken in account along the discussion and conclusions of the studies[111]. In the first study published by San Sebastián *et al.*[122] levels of total petroleum hydrocarbons (TPH) exceed the limits established by the EU in all the rivers sampled, being from 10 to 288 times higher. They reported a significant higher risk of cancer mortality among males living in the affected area of San Carlos for all cancers and for stomach and melanoma cancers. All cases had lived in the area for a long time, which is consistent with a possible environmental carcinogen. The authors, though,

mention different disadvantages of the study that need to be taken in account. For instance, the number of cases was very small, which makes it difficult to reject chance. Some confounders were not taken in account, like the alcohol consumption of the cases, which is related with stomach cancer. Only one case was known to be smoker. Also, the health services or the socioeconomic differences between Quito (control) and San Carlos populations might be different and could play a role. In 2007 Arana *et al.*[131] wrote a letter saying that the calculations done by San Sebastián *et al.* were wrong since they assumed that the population of San Carlos was 1000 and steady along time (from 1989 to 1998), while in the first official registry available in 2001 the number of citizens was 1471 (50% more). San Sebastián *et al.* estimated the population to be approximately 1000 (555 men and 445 women) in 1998 since no registration data was available. Using the 2001 census the excess on cancer mortality reported by San Sebastián *et al.* became diluted and not significant anymore. Although the census of 2001 is the official one, still the census from previous years are unknown, so for the period 1989-1998 it is hard to give reliable results.

The study of Hurtig *et al.*[123] in 2002 showed geographical differences in the incidence of several cancers, which was correlated with the distribution of oil exploitation sites. As it is an ecologic study some important factors like migration patterns could not be taken into account. Also, it could be that results are related to occupational exposure and not to environmental one, but they did not have data on that. Another possible confounder which could explain part of the cancers cases is that in 2 of the exposed areas palm oil, where pesticides are used, is cultivated[132]. Some of these remarks were made as well by Siemiatycki[133] in his commentary, where he questioned the strength of evidence (no good cancer registry and social class, geographic sub-region and other differences not present in the study) and the replication of the study (individual exposures are different than the group ones). Finally, in Hurtig's article they mentioned that racial and lifestyle differences could be a bias factor as well. This was actually described later on by San Sebastián *et al.*[134] in another study to describe differences in cancer incidences between indigenous and non-indigenous people in the same areas that Hurtig *et al.* studied. In this study they found that the risk to develop cancer of stomach, skin, prostate, lymph nodes and leukemia was lower for indigenous men than for non-indigenous. Also, indigenous women had lower risk for cancer of stomach, skin, breast, cervix uteri and lymph nodes. The reason could be a better diet and lifestyles of the indigenous people (stomach cancer) or the fact that

indigenous have more melanin (skin cancer), including genetic differences. They also mention that the cancer patterns described for the non-indigenous are similar to the ones in Quito (capital), which makes sense, since less indigenous people live in the capital. On the other hand, the non-indigenous in the study areas were more affected by oil pollution, which could also explain part of the excess found in the study. In 2008 Kelsh *et al.*[125] published a paper with results contradicting the ones found by Hurtig *et al.* in 2002. They did not find increased rates of deaths for all causes, or from overall cancer. Indeed, they found lower risk among exposed populations and Amazonian populations. When comparing the Amazon areas with Pichincha area (capital), which has less indigenous citizens, they found significant lower mortality rates in the Amazonia counties all together for all causes and for overall cancer as well. In this study the risk of dying of cancer was lower among indigenous than among non-indigenous, probably due to their lifestyles. This is in accordance with the results obtained by San Sebastián *et al.* study[134], previously mentioned. On the other hand, the cancer registry was more complete in the region of Pichincha than in the Amazonia; therefore a dilution of the real cancers cases in this last area is plausible and should be taken in account. Also, Hurtig *et al.* used cancer incidence while Kelsh *et al.* used mortality as a measure of developing disease[135]. The first is a better approximation, although according to Kelsh the cancer incidence and mortality might not differ a lot in the study areas due to poorer health services. Nevertheless, if exposed people had a better health system than non-exposed (socioeconomic differences) then those people might have had more chances to recover from cancer than the non-exposed, which could have lead to an underestimation of the real risk. Diagnosis and causes of death would be also better reported in those areas with proper labs and health services. Also, immigration in the exposed areas is higher. In some studies it has been shown that migrants have a better health status, therefore the influence of this factor must be taken in account [136-139]. In a second paper of Hurtig *et al.*[124] higher risk of developing leukemia among children was reported, especially among those aged from 0 to 4. When considering all ages together (0-14 years) and gender separately, exposed females had a significant higher risk while men did not. A possible explanation could be that females are more exposed to polluted water due to daily activity, but these differences in behavior are not likely to occur until children become 6-7 years old, age in which female children might start doing some home tasks. The same possible confounders mentioned during the

discussion of the first paper of Hurtig *et al.* would apply for this one: parental occupation and palm oil activity in the area.
As general remarks, in all these Ecuadorian studies only palm oil industry (only in some areas) was present, so the pollution came all from the petrochemical activity. The total petroleum hydrocarbon levels (TPH) found in the studies were the ones present at the moment of study. Contamination levels started in the early 70's, period for which there are not measured levels. Nevertheless, there is a study in 1994 that reported levels over the limits in the studied areas[26], indicating long-term contamination in these areas.

B) Bolivia:

As mentioned in the introduction and in the section of acute health effects, "Mbayeko Tekoronza"[12] (Medicus Mundi) is the report of a study done in the Bolivian Chaco (only in Spanish). The objective of this cross-sectional study was to determine levels of crude oil compounds present in water in the studied communities and relate the exposure with people's health. A non-exposed person was considered as so if that person used water with contaminant compounds levels under the Bolivian legislation. For reproductive health 247 women participated in the study (133 exposed and 114 non-exposed). The percentage of women smoking and drinking alcohol was higher among the control population. No differences were found between the two groups for stillbirths or abortions. These results contrasts with the ones that did find positive associations in other populations in Bulgaria and Ecuador[118, 126]. Nevertheless, the occurrence of these outcomes is low, therefore more participants should have been included in the study to detect enough cases and therefore increase the statistical power. Another limitation of the study is the possible misclassification of exposure, since they only used reported water use as an exposure indicator, together with the levels detected for some of the compounds.

3. DISCUSSION

The aim of this thesis was to do an overview of the effect of long-term exposure to crude oil and its chronic effects on indigenous populations' health. For that, a review of occupational studies and populations studies has been done. During the analysis and reading of the articles the author realized that the effects should not only be focused on indigenous people specifically, since the reality is that populations in the developing countries where studies took place are a mix of indigenous and mestizos; therefore the analysis should focus on these populations that have in common certain social and environmental impacts due to oil extraction activity. First there is a specific discussion by health outcome, later on comes the general discussion.

3.1 Specific discussion

a) Respiratory health:

Only population studies were found for respiratory health, none of them done in Ecuador or Bolivia. Nevertheless, the South-American[12, 61] studies did find an association between crude oil exposure and respiratory complains, such as cough, chest pain, respiratory difficulties or throat ache when asking for acute symptoms. This is in accordance with the results obtained by Yang *et al.*[97] in a study also done with an adult population. Studies on children indicate a correlation between air contamination levels or distance from a petrochemical site and respiratory effects such as asthma or wheeze. A lower lung function was also found. Although there are only 4 articles relating petrochemical activity and respiratory health results obtained in other studies on general air pollution support these results[140-142].

b) Reproductive health:

There are few studies on reproductive effects due to exposure to crude oil. One occupational and one population study reported higher risk of spontaneous abortion among exposed women. The first one[89] pointed to benzene, gasoline and hydrogen sulphide as the responsible compounds, although the high correlation between these compounds makes it hard to tell which one really plays a role and which not. The population study also found a higher risk of preterm delivery among exposed women[103]. Another study detected higher levels of mandelic acid (biomarker of

exposure to styrene) in patients that had to be hospitalized for threatened abortion[118]. Two other studies (only abstract available[115, 116]) supported these results as well as another one on general air pollution exposure[117]. Studies done on sex ratio are not conclusive and contradictive results are obtained[101, 102, 112, 113]. It has even been questioned if it is a good tool to detect health hazards from industrial air pollution[114]. Finally, in Ecuador indigenous complain that children are born with birth defects due to oil exposure[6]. The only problem is that birth defects are not that prevalent and therefore big numbers of participants are needed [143-145].

c) Cancer incidence and mortality:

Cancer incidence and mortality has been the most difficult topic to analyze in this thesis. First of all, most of the occupational studies used the SMR or SIR to carry out the analysis. As discussed above SMR can be a good tool to have an idea of the situation but it can lead to wrong conclusions, especially for those cancers which have a good prognostic, since they are not represented in the final numbers, therefore SIR would be a better indicator. Second, for the calculation of SMR and SIR the reference population used is the general one from an area or country, in this way the risk of having biased the results due to the healthy worker effect is high, which leads to an underestimation of the real risk. Third, almost all the population studies had an ecologic design, which has the limitation of the ecologic fallacy; causation is hard to infer, having the risk of wrongly correlate an outcome with an exposure, principally because confounders can not be taken into account in the analysis. Fourth, and as mentioned above, in Ecuador the census and cancer registries are poor, if available; therefore results should be carefully interpreted. Regarding results, the occupational studies show a relationship between hematopoietic cancers, except for NHL, and exposure to crude oil. Benzene seems to be the principal cause, since the risk to develop cancer was higher among those workers employed before 1950, when exposure controls to benzene were absent. The number of studies on general population outside Latin America is limited and results are contradictive; nevertheless it looks like for children the risk of developing leukemia is clearer than among adults. Other cancers in developed countries are still in doubt and further studies should be carried out to clarify whether stomach, kidney, pancreas, lung or skin cancers could be also caused by oil exposure. San Sebastián and Hurtig[122-124] reported higher risk of certain cancers (mainly leukemia, digestive and skin cancers) among Amazonian populations. Although their studies had

certain limitations which have been already discussed previously, the selection of the study population and the design of the studies were better done than Kelsh[125], who found lower risk of cancer mortality comparing Amazonian populations among them and compared to the citizens of the capital. First, San Sebastián and Hurtig used cancer mortality but also cancer incidence, which is a better approach. And second, although they also used Quito population as control, they tried to use control populations with similar socio-economic and demographic distributions as the ones under study.
Finally, one thing that can not be denied is that in the area of San Carlos levels of total petroleum hydrocarbons (TPH) exceeded 10 to 288 times the EU established limits. As mentioned, studies on humans showed that exposure to crude oil, including these TPH, increases the number of chromosomal aberrations (CA), showing the biological mechanism that could explain the epidemiological findings.

3.2 General discussion

Apart from the remarks done already in the specific discussion there are other issues that need to be taken into account. First of all, although occupational studies are a good guide of possible adverse effects on humans the exposure routes are different from the general population. Indeed, within general population the exposure routes vary as well depending on the country and the situation. Therefore, workers and general population from developed countries will be exposed mainly via inhalation, unless oil spills take place in the area, for instance. In contrast, the populations in the study areas of Ecuador and Bolivia and other developing countries are more predisposed to be exposed through other routes such as water and food intake (fish), skin (cleaning or bathing), or due to soil contamination (see cover picture). In this sense the affected organs might be different as well. On the other hand, levels of contamination are probably also different, since spills and other problems take place more often in developing countries, where environmental laws and controls are less restrictive and where the conditions and maintenance of infrastructures are poorer. As mentioned in the introduction, crude oil is a complex mixture of different compounds and the percentage of these components can vary from region to region, also the waste thrown away by the companies. Therefore compounds to what populations are exposed to can vary a lot from place to another. A final difference between occupational and population studies is that individuals participating in the first ones are only male adults (except for one study on reproductive

effects), in this sense they can not be used to explain certain disease, like reproductive problems, or effects on children, who are more predisposed to develop certain cancers like leukemia.

In some studies they compared population of regions with different socio-economic levels (i.e. Quito vs Amazonian Ecuador) but, as shown in the Bolivian study, socio-economic differences play an important role on people's health. This is an important factor to take in account when interpreting the results, since these factors could be potential confounders: life style (smoking, alcohol intake or diet), life conditions at home, health services, education, rate of immigration, etc.

Most of the studies focus on the relationship between crude oil exposure, its compounds and cancer. Showing a clear correlation between crude oil and cancer is very hard, especially in developing countries, where cancer detection, diagnosis and registries are poor and other factors play an important role on people's health. Because of this, future studies should try with better study designs to take in account as much confounders as possible and be able to infer causation. The best design for that would be a cohort study. The only problem is that for cancer it takes time before conclusions can be drawn or enough cases accumulate. In case there is really a threat this waiting time can be too much for indigenous populations complaining about the impact of oil companies' activities. Another alternative would be to carry out (matched) case-control studies, which also allows scientists to draw more reliable conclusions. Also, the need for money and time for this study design is less than for cohorts.

Finally, one weak point of some of the studies was exposure miss-classification of subjects. Therefore future studies should improve exposure assessment to avoid this problem.

4. CONCLUSION

As it has been described during the analysis of several occupational and population studies exposure to crude oil and some of its components can represent a threat at different levels (respiratory and reproductive health, some cancer types and acute effects). Nevertheless, the quality of some of these studies, both negative and positive ones, and its conclusions are sometimes dubious or questionable due to different factors (study designs, study populations and controls, exposure assessment and miss-classification, etc). Nowadays there is a big discussion on whether the activity of the oil companies and its environmental impacts are a threat for the health of the populations in the affected areas (see case of Texaco in Ecuador). Companies defend themselves by saying that the studies done by independent scientists are not accurate or well done, especially studies on cancer. In this sense, the best study design to demonstrate causation (cohort study) should be carried out, together with an appropriate exposure assessment. Finally, there are specific factors that can not be denied and that can explain the correlation between exposure and health effects detected; human exposition is possible to happen since high levels of crude oil or some of its compounds have been detected in the affected areas. On the other hand, there are biomarkers (i.e. chromosomal aberrations) that strengthen the epidemiological findings on exposure to crude oil and cancer.

As a conclusion, further and efficient research is needed to finally prove causation.

5. PERSONAL NOTE

From the personal point of view I would like to add two points in this report. The first one is to show the current discussion between companies and independent scientists. In a topic like this, industrial interests are present and strong; therefore some information should be carefully interpreted. The second one is a personal and general view of the situation.

In 2005 Texaco (Chevron) published a report made by Lowell[146] where the studies done by San Sebastián and Hurtig were severely criticized, sometimes doing assumptions or accusations with few fundaments: "leaders of the communities were asked to identify the women who met the age and residence time requirements. The selection of the final study sample does not appear to have been random; the participants were identified by a community leader who may have been aware of health problems, suggesting the possibility of selection bias". He continuously denied oil exposure as the cause of the increase of certain cancers and other diseases among populations in the Amazon basin exposed to crude oil, saying that other reasons might play a more important role (deforestation, labor mobility, agro-industry and colonization processes). Actually, in an information pamphlet presented by Texaco[147] they cited Lowell's and other consultant's critics to support the idea that oil exposure is not the cause of health problems among exposed people. They attribute all gastrointestinal and skin problems to bacteria infections, since, according to them, these are present in 90% of the waters analyzed (no methodology or samples sites are mentioned). Although it is true that other factors might be related to a poorer health status in that area that does not mean that crude oil exposure is not an important factor in the case of the Amazonian basin. Indeed, Lowell says that workers moving in these areas live in poorer conditions (less infrastructures and poorer sanitation), having more chances to become sick. It is actually not true, since all the studies reported a better socioeconomic status for people living in the exposed areas, with also better health services. He also mentions migration as the cause for a higher prevalence of leukemia cancers among children: "the population mixing hypothesis is perhaps most closely associated with Kinlen[148] who postulated that childhood leukemia is an uncommon response to an infectious agent following influxes of people into isolated areas. This was the situation in the oil producing areas, where migrations of people from both the

coastal and mountainous regions of Ecuador occurred". Although he mentions that other studies support this theory (it will not be discussed here), it can not be denied that several studies reported relationships between exposure to crude oil or some of its compounds, such as benzene, and leukemia among children and adults. As said in a letter[149] signed by 61 scientists to reply to Texaco's affirmations, it is true that the studies done by San Sebastián and Hurtig have certain limitations, but that is something inherent to epidemiological studies. Especial limitations are present in the ecologic study design, and in a less extend in cross-sectional studies. All these limitations are discussed and mentioned by San Sebastián and Hurtig in their papers. Actually, the same limitations apply for the ecologic study done by Kelsh *et al.*[125]. So, from this point of view, the results obtained by the Chevron's consultant could receive sever critics as well. As Breilh[149] says, it looks like "Texaco's consultants went to great pains to find flaws in the studies". As an example, he mentions that even the validity of self-reported health effects, which is a widely used and accepted practice, is also questioned by the consultants. In response to this letter Chevron[150] wrote that "the scientific data and findings that Chevron's technical experts have presented to the Court are consistent with the view that the health concerns of the region are not associated with the oilfield operations, but rather, are more likely to be associated with other, non-oil-related concerns that have been well established". This "attacking" attitude of the company was mentioned again in 2008 by Dr. Carlos Martín Beristain[11], who had made a report on the psychosocial impacts of Texaco's activity in Ecuador[10].

Studies that tried to correlated oil exposure and cancer are various and more than for other health effects, obtaining sometimes different results as it has been discussed. Although it is important to find out whether this correlation exists or not, it is necessary to keep in mind that health effects of crude oil are various and different and, despite cancer is a serious and tough disease to go through, what counts at the end is the quality of life of the people. I think it is sensible to say that crude oil represents a threat on populations exposed to it; it has been already shown that populations in developed countries are affected by this exposition, mainly at a respiratory level. In developing countries, and due to socio-economic differences and also to a different and higher exposure, the effects on the populations are wider and probably more sever; therefore special attention should be paid to this problem.

To conclude this report I would like to remark that apart from South-America other populations in the developing countries are affected by oil extraction activity as well, especially in Africa[151]. On the other hand, although in this thesis I focused on health effects, the environmental impacts of this activity are really a problem and have been proved to happen, as well as the social changes and psychological impacts that the introduction of the oil company causes when entering the territory of these indigenous tribes[4]. As scientists and human beings we should not forget that taking care of the environment is also taking care of our own health and quality of life.

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