British Journal of Medicine & Medical Research
10(6): 1-14, 2015, Article no.BJMMR.19491
ISSN: 2231-0614

SCIENCEDOMAIN *international*
www.sciencedomain.org

Chronic Metal Exposure, Air Pollution and Cancer in Haifa, Israel

E. Blaurock-Busch[1*], Y. Busch[1] and N. Buium[2]

[1]Micro Trace Minerals, Germany/Trace Minerals International, USA.
[2]Nava Health and Wellness Ltd., Israel.

Authors' contributions

This work was carried out in collaboration between all authors. Author EBB designed the study, wrote the protocol, including laboratory analysis and statistics and wrote all drafts of the manuscript. Author YB organized study details and managed literature searches. Author NB was in charge of sample collection and patient management. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/19491
Editor(s):
(1) Toru Watanabe, Department of Pediatrics, Niigata City General Hospital, Japan.
Reviewers:
(1) Anonymous, University of Genoa, Italy.
(2) Taratisio Ndwiga, Moi University, Kenya.
(3) Giovanni Ghirga, San Paolo General Hospital, Rome, Italy.
Complete Peer review History: http://sciencedomain.org/review-history/10658

Original Research Article

Received 12th June 2015
Accepted 30th July 2015
Published 23rd August 2015

ABSTRACT

Air pollution is a worldwide problem to millions of people exposed to concentrations of air pollutants above safety standards, including fine particulate matter ($PM_{2.5}$). In Haifa, Israel, the apparent link between pollution and cancer development is a topic of concern. The study focused on evaluating the metal exposure of children and adults residing in the Haifa area. A high toxic burden to combustion metals such as nickel and potential carcinogens such as mercury was determined.
Samples of hair were collected from people living in and around Haifa between 2007 and 2015. Selected patients were separated into three groups, adult males and females, and children with a median age of 6.6 years. Multiple metal exposure was determined in all groups, with the greatest burden found in children.

Keywords: Hair mineral analysis; environmental exposure; fine particle matter; cancer.

**Corresponding author: Email: ebb@microtrace.de;*

1. INTRODUCTION

Air pollution is a serious health problem in mega cities around the world (Calderon 2014). Haifa, Israel with a population of 267300 is comparatively small; however Haifa Bay is the center of heavy industry. Petroleum refining and chemical processing are considered the main source of pollution. Recent reports from Israeli Health Ministry officials acknowledged a causal link between air pollution and cancer in the Haifa Bay region. According to Health Ministry data, the number of people diagnosed with cancer in Haifa Bay over the last decade is 22 percent higher than the national average for men and 23 percent higher for women. In 2005, there were 377 cancer cases per 100,000 residents in the Haifa Bay area compared to 355 per 100,000 in Tel Aviv, 348 in Be'er Sheva and 326 in Acre [1]. Two types of cancer showed a causative connection: lung cancer, of which the number of patients in Haifa was 29% more than in the rest of the country, and bladder cancer, which Haifa residents were 26% more likely to get [2].

Israeli newspapers published varying opinion regarding this issue. On May 17, 2015 Joshua Davidovich stated in the *Times of Israel:* "The firestorm over the bay city's pollution and increased rates of cancer found there from a number of factories spewing toxic fumes makes headlines across all three major dailies. Monday morning though the papers find little to agree on over the research behind the numbers and what the city is and should be doing to combat it [3].

Longtime exposures to high concentrations of particulate matter (PM) with significant amounts of metals related to combustion are a recognized problem among urban dwellers, particularly those living in industrial regions finding of increased concentrations of combustion-associated metals i.e. nickel, raises questions about the induced inflammatory responses [4].

Due to the proximity of Haifa's port, oil refineries, chemical and pharmaceutical plants are operating in the Haifa Bay area. Among the hazardous materials undergoing governmental scrutiny are bromine, chlorine and liquefied petroleum gas (LPG). In the chlorine production, the mercury process is least energy-efficient of the three main technologies (mercury, diaphragm and membrane), but its main drawback is the associated emission via air (exhaust) and waste. Haifa's coal fired power plant is one of the most polluting industries. Other industrial plants located in Haifa are processing raw materials for fertilizers, petroleum and metal products, including inorganic chemicals, all sources of potential metal pollution.

Governmental actions to reduce pollution included threats to remove business licenses of several factories, and continuous monitoring of the most relevant pollutants. As a result, the presence of inhalant particles decreased by over 80% in the years between 2000 and 2014, but according to Haifa Mayor Yona Yahav, strict measures are needed to further improve the health of Haifa residents and to reduce the high cancer rate [5].

Human scalp hair is used for biological monitoring in environmental medicine. According to the German Environmental Agency (UBA) hair is a readily accessible specimen reflecting exposure to contaminants over a relatively long period of time. Hence, hair metal analysis is used in epidemiological and case studies to assess the internal exposure to metals and metalloids [6]. For this research, samples were collected from 2007 to 2014. Thus, results indicate the metal burden accumulated over a significant period.

Certain environmental pollutants, organic and inorganic, are carcinogenic. Among the metals nickel, arsenic and chromium are recognized as widespread environmental pollutants. Chronic exposure has been linked to increased risks of numerous cancers including non-carcinogenic health outcomes such as cardiovascular disease, neurologic deficits, neurodevelopmental deficits in childhood, and hypertension [7].

It was the aim of this study to evaluate the metal exposure of Israeli residents, because our previous Indian studies on cancer [8] and childhood diseases [9] located a high metal exposure in cancer patients, suggesting that excessive metal exposure is a factor in the pathogenesis of cancer. In the Indian studies, the elements most prevalent in the biological samples evaluated were aluminum (Al), barium (Ba), nickel (Ni), lead (Pb) and strontium. Biomonitoring of samples from Arab children living in Egypt and Saudi Arabia showed similar results [10] and once again, it was these metals we found in high concentrations in the hair of the Haifa population.

Resident adults and children from the Haifa region showed a considerable metal burden,

indicating that this long term, chronic metal exposure may very well be a contributory cause for a variety of cancers as has been suggested by international research [11,12]. In this study, children showed the greatest burden of carcinogenic metals.

2. MATERIALS AND METHODS

Hair was the material tested. Toenails are particularly useful for the assessment of arsenic, but sample collection is difficult. Both, nails and hair are body tissue. Hair metal analysis can be utilized to evaluate chronic metal exposure. Rashad and Hossam from the Chemistry Department, South Valley University Aswan, Egypt proved that 'human scalp hair and fingernails could be used successfully as a biological indicator for the assessment of heavy metal pollution' [13]. Hair is the metabolic end product that incorporates metals into its structure during the growth process (Ashraf et al., 1994; Pereira et al., 2004). Hair is a suitable test for heavy metal exposure and its advantage over the conventional blood metal analysis is that hair reflects exposure and uptake of previous months, even years. Thus, representing a longer time of heavy metal exposure [14]. The uptake of lead, for example, suggests a three compartmental tool for the lead metabolism, namely circulation in blood, accumulation in soft tissue with keratin and collagen being the target proteins [15]. Hair has advantages over other biological materials [16], namely:

- Sample collection is without injury to the donor.
- Samples can be stored for a long time, before and after analysis without any changes.
- Higher concentrations of toxic metals are found in hair samples when compared to blood or urine.
- Samples reflect past exposure and accumulation of metals over a long period of time.

2.1 Participants and Criteria for Sample Selection

A total of 1159 hair tests was received from an Israeli clinic between 2007 and 2015. Randomly selected and evaluated were 337 female patients, 289 male patients and 90 children. All test persons lived in the Haifa Bay area. The criteria for selection was as follows:

1. No interfering hair treatment such as colouring, perming, bleaching was used
2. Patient age and sex was given
3. Sample size was sufficient (100 mg +/- 10%). Mean weight was 102.51 mg.
4. The object was to cut hair close to the scalp. Total length approximately 10 cm.

The mean age of the female group of 337 patients was 48 years, for the 289 male patients it was 42 years, for the 90 children the mean age was 7 years.

2.2 Analysis of Hair Samples

Hair samples were collected at the Nava Health and Wellness Ltd. of Israel and shipped for testing to the laboratory Micro Trace Minerals/Labor Friedle in Germany. In the laboratory, sample preparation included repeated washing with a metal-free detergent, a three-time rinse with ultrapure water and drying in a special oven. After sample weighing, certified metal-free acids were used for the digestion process, which took place in a closed-vessel microwave digestion system. For the final sample dilution, ultrapure water was used. The elemental analysis was performed via inductively coupled plasma mass spectrometry (ICP-MS) utilizing collision/reaction cell methods coupled with ion-molecule chemistry, a reliable new method for interference reduction. Of the 50+ elements tested, the elements Aluminium (Al), Barium (Ba), Chromium (Cr), Nickel (Ni), Lead (Pb), Mercury (Hg), Tin (Sn) and Strontium (Sr) showed unusually high results. For Sr, the naturally occurring isotope ^{88}Sr was measured. It is considered non-radioactive and non-toxic.

2.3 Reference Range Values Used for Comparison with the Hair Sample Data from Israel

Certified hair standards and in-house standards were used as part of the laboratory quality control and validation of results. Reference range values were developed from apparently healthy people. For the most common metals in blood and urine, governmental agencies provide guidelines. For hair, no guidelines are given, thus institutions have to set up their own reference ranges based on the particular populations they serve. Reference intervals serve as the basis of laboratory testing and aid the physician in differentiating between the healthy and diseased patient. Standard methods for determining the

reference interval are to define and obtain a healthy population of at least 120 individuals and use nonparametric estimates of the 95% reference interval [17]. The hair reference ranges used in the present study are statistical evaluations of 1984 by Micro Trace Minerals (MTM), Germany and Trace Minerals International (TMI), USA. Ranges are based on a healthy, mostly Western population (Europe and US). The 2006 re-evaluation was based on 674 people, the last re-evaluation (N=525) was made in 2010. The reference ranges used in this study are largely in agreement with those of other US and German laboratories. For Reference Ranges (RR) and Limits of Quantitation (LOQ) see Table 1.

Table 1. Hair LOQ (Limit of Quantification) and Reference Ranges (RR) as of 2014

Element	LOQ	95%ile RR f. adults	95%ile RR f. children
	mg/kg=µg/g	mg/kg=µg/g	mg/kg=µg/g
Ag	0.010	<1	<1
Al	0.250	<8	<8
As	0.010	<0.2	<0.2
Au	Not available	Not available	Not available
B	0.250	<0.84	<0.84
Ba	0.010	<4.64	<2.65
Be	0.010	<0.10	<0.03
Bi	0.010	<0.20	<0.18
Ca	10.000	220-1600	200--850
Cd	0.001	<0.20	<0.20
Ce	0.000	<0.05	<0.05
Co	0.005	0.01-0.30	<0.15
Cr	0.020	0.02-0.21	0.02--0.15
Cs	0.005	<0.01	<0.01
Cu	0.100	10--41	6.70--37
Dy	0.001	<0.01	<0.01
Er	0.001	<0.01	<0.01
Eu	0.001	<0.01	<0.01
Fe	1.000	4.6-17.70	7.7--15
Ga	0.001	<0.07	<0.07
Gd	0.001	<0.01	<0.01
Ge	0.003	<1.65	<0.50
Hg	0.020	<0.60	<0.30
Hf	0.050	Not available	Not available
I	0.002	0.05--5.00	0.15--3.50
Ir	0.005	<0.01	<0.01
La	0.001	<0.03	<0.02
Li	0.001	<0.30	<0.20
Lu	0.001	<0.01	<0.01
Mg	5.000	20--130	20--115
Mn	0.050	0.05--0.92	0.07--0.50
Mo	0.001	0.03--1.10	0.02--1.00
Nb	0.005	Not available	Not available
Nd	0.005	Not available	Not available
Ni	0.010	<1.00	<0.85
Pb	0.010	<3.00	<3.00
Pd	0.050	<0.10	<0.10
Pr	0.005	<0.10	<0.10
Pt	0.005	<0.01	<0.07
Rb	0.001	Not available	Not available
Re	0.005	<0.01	<0.01
Rh	0.005	<0.01	<0.01
Ru	0.001	<0.10	<0.32

Element	LOQ	95%ile RR f. adults	95%ile RR f. children
	mg/kg=µg/g	mg/kg=µg/g	mg/kg=µg/g
Sb	0.001	<0.30	<0.20
Se	0.010	0.40--1.70	0.40--1.70
Sm	0.001	<0.01	<0.01
Sn	0.001	<0.70	<0.93
Sr	0.001	0.65--6.90	0.11—4.28
Ta	0.001	<0.01	<0.01
Te	0.010	<0.01	<0.01
Th	0.010	<0.01	<0.01
Ti	0.010	<1.50	<0.65
Tl	0.001	<0.01	<0.01
Tm	0.001	Not available	Not available
U	0.001	<0.10	<0.10
V	0.001	0.01--0.20	0.01-0.15
W	0.001	<0.02	<0.02
Yb	0.001	<0.01	<0.01
Zn	5.000	150--272	110-227
Zr	0.050	<0.50	<1.47

To validate its hair analysis measurements, Micro Trace Minerals, Germany, participates in the Quebec Multi-elemental External Quality Assessment Scheme (QMEQAS), and has passed all tests.

2.4 Statistical Analysis

The 95percentile of each patient group was calculated and compared with the 95 Percentile Reference Ranges as developed by MTM/TMI. In Table 2, the highest 95Percentile range of each element in each group is highlighted, provided the 95%ile exceeded the standard reference range.

Values exceeding reference ranges are considered pathological. Table 3 lists the percent of pathological tests for each element and group. Percentages exceeding the standard reference range by 20% or more are in highlights.

Table 2. Comparing 95%ile ranges of Israeli adults and children to 95%ile reference ranges of normal population

	95%ile RR MTM adults	95%ile range Israeli females N=337	95%ile range Israeli males N=289	95%ile RR MTM children	95%ile range Israeli children N=90
Element	**mg/kg=µg/g**	µg/g	µg/g	µg/g	µg/g
Ag	<1	**6.37**	1.81	<1	3.48
Al	<8	23.1	22.85	<8	**32.23**
As	<0.2	**0.08**	**0.08**	<0.2	0.06
Au	Not available	Not tested	Not tested	Not available	Not tested
B	<0.84	1.05	1.39	<0.84	**1.40**
Ba	<4.64	**6.61**	4.68	<2.65	4.70
Be	<0.10	0.00	0.00	<0.03	0.00
Bi	<0.20	**0.34**	0.11	<0.18	0.29
Ca	220-1600	4473	**4718**	200--850	3733
Cd	<0.20	0.24	0.17	<0.20	**0.35**
Ce	<0.05	0.03	0.03	<0.05	**0.07**
Co	0.01-0.30	0.30	0.19	<0.15	**0.35**
Cr	0.02-0.21	0.34	0.29	0.02--0.15	**0.55**
Cs	<0.01	0.00	0.00	<0.01	0.00

	95%ile RR MTM adults	95%ile range Israeli females N=337	95%ile range Israeli males N=289	95%ile RR MTM children	95%ile range Israeli children N=90
Cu	10--41	96.43	99.47	6.70--37	**175.16**
Dy	<0.01	0.00	0.00	<0.01	0.01
Er	<0.01	0.00	0.00	<0.01	0.00
Eu	<0.01	0.00	0.00	<0.01	0.00
Fe	4.6-17.70	20.77	18.83	7.7--15	**30.17**
Ga	<0.07	**0.21**	0.13	<0.07	0.18
Gd	<0.01	0.00	0.00	<0.01	0.01
Ge	<1.65	0.02	0.02	<0.50	0.02
Hg	<0.60	1.26	**1.57**	<0.30	0.56
Hf	Not available	0.05	0.05	Not available	0.03
I	0.05--5.00	17.26	9.90	0.15--3.50	**27.65**
Ir	<0.01	0.00	0.00	<0.01	0.00
La	<0.03	0.02	0.03	<0.02	**0.06**
Li	<0.30	0.02	0.01	<0.20	0.02
Lu	<0.01	0.00	0.00	<0.01	0.00
Mg	20--130	**515**	418	20--115	472
Mn	0.05--0.92	**1.13**	0.81	0.07--0.50	0.98
Mo	0.03--1.10	0.08	0.07	0.02--1.00	0.08
Nb	Not available	0.00	0.00	Not available	0.00
Nd	Not available	0.00	0.01	Not available	0.04
Ni	<1.00	2.02	1.62	<0.85	**2.47**
Pb	<3.00	**6.60**	5.58	<3.00	5.17
Pd	<0.10	0.04	0.03	<0.10	0.02
Pr	<0.10	0.00	0.00	<0.10	0.01
Pt	<0.01	0.00	0.00	Not available	0.00
Rb	Not available	0.02	0.02	Not available	0.02
Re	<0.01	0.00	0.00	<0.01	0.00
Rh	<0.01	0.00	0.00	<0.01	0.00
Ru	<0.10	0.00	0.00	<0.32	0.01
Sb	<0.30	0.14	0.09	<0.20	0.22
Se	0.40--1.70	1.17	1.30	0.40--1.70	1.15
Sm	<0.01	0.00	0.00	<0.01	0.01
Sn	<0.70	**2.46**	0.78	<0.93	2.33
Sr	0.65--6.90	**18.23**	12.49	0.11—4.28	14.11
Ta	<0.01	0.01	0.00	<0.01	0.00
Te	<0.01	0.00	0.00	<0.01	0.01
Th	<0.01	0.00	0.00	<0.01	0.00
Ti	<1.50	1.49	0.89	<0.65	1.50
Tl	<0.01	0.00	0.00	<0.01	0.00
Tm	Not available	0.00	0.00	Not available	0.00
U	<0.10	0.08	0.09	<0.10	0.10
V	0.01--0.20	0.25	0.19	0.01-0.15	**0.44**
W	<0.02	0.02	0.01	<0.02	0.01
Yb	<0.01	0.00	0.00	<0.01	0.00
Zn	150--272	**786**	620	110-227	620
Zr	<0.50	2.31	**2.75**	<1.47	1.53

Table 3. Percent pathological values in Haifa females, males and children

	Israeli females N=337	Israeli males N=289	Israeli children N=90
Element	% pathological	% pathological	% pathological
Ag	**21.96**	8.3	**22.2**
Al	**34.12**	**25**	**64.4**
As*	0	0.3	1.1
Au	Not tested	Not tested	Not tested
B	11.59	15.2	1.1
Ba	13.35	5.2	**22.2**
Be*	0	0	0
Bi	8.01	3.5	7.8
Ca	**61.72**	**28.61**	**68.91**
Cd*	6.82	3.5	13.3
Ce	0	0	12.2
Co**	5.04	2.1	15.6
Cr*	11.28	8.3	**46.7**
Cs	0	0	0
Cu	**28.19**	**22.6**	**44.4**
Dy	0	0	1.1
Er	0	0	0
Eu	0	0	0
Fe	8.31	5.9	**38.9**
Ga	**0**	0	**36.7**
Gd	0	0	0
Ge	0	0	0
Hg	16.02	**24.3**	**32.2**
Hf	Not tested	Not tested	Not tested
I	15.18	10.8	**42.2**
Ir	0	0	0
La	0	0	**0**
Li	0	0	0
Lu	0	0	0
Mg	**62.91**	**29.9**	**56.7**
Mn	6.82	3.5	**32.2**
Mo	0	0	0
Nb	0	0	0
Nd	0	0	0
Ni*	18.69	10.1	**33.3**
Pb**	17.51	13.2	**27.8**
Pd	0	0	0
Pr	0	0	0
Pt	1.78	1.4	0
Re	0	0	0
Rh	0	0	0
Ru	0	0	0
Sb	2.08	2.1	6.7
Se**	2.37	3.5	2.2
Sm	0	0	2.2
Sn	**20.47**	6.6	**21.1**
Sr	**42.43**	17	**47.8**
Ta	0	0	1.1
Te	0	0	1.1
Th*	0	0	0
Ti	5.04	2.4	**35.6**
Tl	0	0	0

	Israeli females N=337	Israeli males N=289	Israeli children N=90
Tm	0	0	0
U	3.26	2.4	5.6
V	9.20	3.8	**48.9**
W	8.01	4.2	0
Yb	0	0	0
Zn	**31.16**	**27.8**	**44.4**
Zr	**20.18**	**20.5**	6.7

*Note: *Elements marked with * have been classified as carcinogens. Source: ATSDR*
***Elements marked with ** are reasonably anticipated to be human carcinogens. Source: ATSDR*

3. RESULTS

The statistical evaluation of the 95percentile of hair metals from female and male residents as well as children younger than 12 years of age (mean age 6.6.years) exceeded the standard reference range for a number of elements (Table 3).

Of the known carcinogens chromium (Cr) exposure was most significant, with children showing the greatest burden, Cr 46.7% compared to 11.28% in female adults and 8.3% in male adults. For nickel, an element considered carcinogenic and allergenic, the children group showed the highest percentage (33.3%) of pathological values, followed by the female adult group with 18.69% and the adult male group with 10.1%.

Cadmium, a highly toxic and carcinogenic element was also highest in children, 13.3% of them showed pathological levels, followed by the female group (6.82%) and the male group (3.5%).

Children were also showing the highest lead burden, 27.8% showed levels exceeding the reference range for children, once again followed by the female adult group (17.51%) and the male group (13.2%). Lead is a well-researched neurotoxin and potential carcinogen. Lead like many other toxic metals has the ability to inactivate enzymes, thus affecting red blood cell production, amino acid function and a number of biochemical systems in the body. In the USA, the threat of childhood lead poisoning was recognized in the 1970s when screening programs were initiated. The obvious link to air pollution sparked the movement to remove lead from gasoline, which improved the standard of air quality. As a result, blood lead levels dropped in the entire American population [18].

Like lead, ATDSR considers cobalt a reasonably anticipated carcinogen. We noted 15.6% of pathological values in the children group, which amounts to a three-fold higher burden over the adult female group (5.04%) and an 8-foldhigher burden over the male adult group (2.1%).

Arsenic (As) is a known carcinogen. Along with cadmium, lead, and mercury, As is considered a potential health risks to children who are exposed through inhalation or ingestion.[19] However, our data could not identify that arsenic exposure is a risk to the Haifa population. Similarly, all test groups showed zero exposure to the carcinogenic metals beryllium and thorium.

Overall, the children of Haifa show multiple and considerable exposure to carcinogenic metals. In addition, these children are more burdened with metals such as barium, manganese and mercury (Table 3). Of the adults, female show a greater metal burden than males.

4. DISCUSSION

In the industrialized world, childhood cancer is listed as the 4th most common cause of death in children less than 15 years of age [20]. According to WHO data, published in 2011, the death rate for childhood leukaemia (6.3 per 100000) is among the highest in the world. Israel ranks 8th in the world. Israel also ranks high with CNS (Central Nervous System) cancers in children. Metals such as lead, manganese and mercury are known neurotoxins, affecting central nervous function, but there is no proof at this time that they cause brain cancer. However, Anderson stated that environmental exposure can occur during the perinatal/postnatal period, potentially increasing the risk of cancer [21]. When discussing risk factors such as environmental exposure, the evidence of causality may be stronger or weaker between a risk factor and a disease, depending on the cause-effect link. If more risk factors such as genetic, ethnic and environmental exposure coincide, disease development is more likely to

progress [22]. Linet noted that 'factors associated with cancer may occur many years before the disease is apparent', hence attention to environmental factors as one risk factor and early assessment becomes important.

Metal intake can be via air, water and food [23]. Air pollution exposure includes inhalation or ingestion of ultrafine particulate matter, also called nanoparticles. Particle size is between 1 and 100 nanometers, allowing for ease of passing the body's natural barriers such as the blood brain barrier. Epidemiological studies have consistently found an association between small increases in urban particulates and health effects, including increased morbidity and mortality in people with respiratory and cardiac disease. Ultrafine manganese oxide particles translocate to the central nervous system and observed effects are associated with the fine rather than the coarse particles in the atmosphere [24]. Utell and Frampton observed a strong and consistent association between adjusted mortality rates and ambient particle concentration [25]. EPA research linked ultrafine particles of $PM_{2.5}$ (and less) to oxidative stress and inflammation [26]. Calderón's study of Mexico City Metropolitan Area (MCMA), demonstrated that children with high exposure show an early brain imbalance in key genes for oxidative stress, inflammation, innate and adaptive responses and accumulation of misfolded proteins as observed in Alzheimer and Parkinson's diseases [27]. In addition, there is a clear demonstration that inhalation exposure to pollution degrades and alters BBB permeability and is associated with neuro-inflammation [28].

Hair is body tissue reflecting long-term, chronic exposure [29]. Geographical variations of hair trace element concentrations depend on nutritional factors and geochemical conditions [30]. People living in polluted environments are more prone to chronic metal overexposure. Studies by Ionescu demonstrate that malignant breast tissue have higher metal concentrations than healthy breast tissue [31].

All metals in excess can cause disease. Long-term exposure is a cause of increased metal accumulation in a variety of body tissue. Some metals are more toxic then others.

4.1 The Carcinogenicity and Toxicity of Metals in Human Health

In the human body, metals are inter-reactive. High strontium concentrations were found in 42.43% of females and 47.8% of the children. The male group showed 17% pathological values. Several studies indicate that strontium may have a metabolic pathway similar to that of calcium and indeed, strontium closely parallels calcium as an index of skeletal function [32]. When the calcium metabolism is disturbed, strontium has a tendency to replace calcium on the cellular level. Strontium affects the musculoskeletal system, possibly affecting growing children more than adults. High exposure to radioactive strontium may cause cancer. (Note: isotope ^{88}Sr was tested, the naturally occurring strontium.) ATSDR states that blood, hair, faeces and urine are useful tests to for strontium [33].

The carcinogenic metal chromium (Cr) is found in all phases of the environment including air, water, and soil, and its many chemical forms are pollutants with serious implication to the environment and human health. Shanker states that there are still gaps in the basic knowledge of the toxic effects of chromium on human health, but the most common apart from lung cancer are skin rashes, upset stomachs, ulcers, respiratory problems, immune system weakness, kidney and liver damage and alteration of genetic material [34]. The ATSDR states that "It is likely that health effects seen in children exposed to high amounts of chromium will be similar to the effects seen in adults." Chromium can be measured in hair, urine, and blood [35].

For chromium, Haifa males showed 8.3% pathological values, followed by females (11.28%). Children with a medium age of 6.6 years exceeded the RR for children <12 years of age by 46.7%.

The most common forms of chromium that occur in the environment are trivalent chromium (Cr3), and hexavalent chromium (Cr6). Chromium-3 is an essential human dietary element and occurs naturally in many vegetables, fruits, meats, grains and yeast. Chromium-6 occurs in the environment from the erosion of natural chromium deposits, but is also a product of industrial processes. Only Cr6 is classified carcinogenic and there are demonstrated instances of Cr6 being released into the environment by leakage, poor storage, or inadequate industrial waste disposal practices [36]. Our analytical process did not differentiate between Cr3 and Cr6.

Manganese is used in steel production to improve hardness, stiffness, and strength. It may

be used as an additive in gasoline to improve the octane rating of the gas. Exposure to high levels of manganese in air can cause lung irritation and reproductive effects. The ATDSR states that "Exposure to excess levels of manganese may occur from breathing air, particularly where manganese is used in manufacturing, and from drinking water and eating food. At high levels, Mn can cause damage to the brain" [37].

Exposure to manganese affects CNS function and can cause Pseudo Parkinson (and as such is treatable and reversible). Willis at all reported a link to metal emission and urban incident Parkinson disease [38]. For Mn, the children group showed 32.2% of pathological values, compared to 6.82% for the female and 3.5% for the male group.

The children group also displayed the highest values for copper (44.4%), followed by the female group (28.18%). The male group showed 22.6% pathological values. A similar trend was noted for lead. Children: 27.8%, females 17.51% and males 13.2%. Lead (Pb) has been widely researched, especially in connection with neurological ailments and learning impairments. The use of lead as an additive to gasoline was banned in the United States in 1996. In 2003, leaded gasoline was still available in Israel.

Blood is recommended for the diagnosis of a manganese, copper and lead, but other tests such as urine, hair or feces are also used to determine exposure [39]. Blood lead concentration correlates with all cancer and lung cancer mortality [40]. The US Center for Disease Control recommends blood screening in young children because blood lead concentrations below 10 µg/dl have been linked to intellectual impairment [41]. Gerhardsson et al. [42] demonstrated as early as 1986 that workers exposed to lead showed higher mortality rates, and were more afflicted with malignant neoplasms, lung and stomach cancer, ischaemic heart disease and cerebrovascular diseases then the general population.

Nickel (Ni) has been researched extensively. Nickel sensitivities are the most common harmful health effect in humans. Approximately 10 to 20% of the population is sensitive to nickel, and skin rashes at the site of contact are most common. People working in nickel refineries or nickel-processing plants are more affected with chronic bronchitis, asthma and reduced lung function then the general population. Workers who drank water containing high amounts of nickel suffered stomach aches and adverse effects to blood and kidneys. The EPA (Environmental Protection Agency) has determined that nickel refinery dust and nickel sub-sulfide are human carcinogens. Calderón reported that nickel was significantly higher in cerebral spinal fluid samples of Mexico City children vs controls ($p=0.03$)[8].

According to the ATSDR, tests are available to measure nickel in your blood, feces, and urine. Higher nickel concentrations were found in the urine of workers exposed to water-soluble nickel compounds than in the urine of workers exposed to hard-to-dissolve nickel compounds. This indicates that it is easier to tell exposure to soluble nickel compounds [43].

A higher nickel burden was found in the hair of children (33.3%), compared to 18.69% in the hair of female and 10.1% in the male group.

For mercury, the children group showed 32.2% of pathological values, the male group 24.3% and the female group 16.02%. In Germany, mercury exposure is mostly due to dental amalgam fillings, but since children with a median age of 6.6 years are unlikely to have many amalgams, other causes such as eating Hg-laden seafood should be considered. The US Food and Drug Administration has set a limit of 1ppm for methylmercury in seafood. Mercury is also used to produce chlorine gas and caustic soda. Exposure to breathing air from spills, incinerators and industries burning mercury-containing fuels can be another source.

Mercury, at high levels, may damage the brain, kidneys, and the developing fetus. ATSDR states that "Mercury combines with other elements, such as chlorine, sulfur, or oxygen, to form inorganic mercury compounds. Of the organic compounds, methylmercury (MM) is highly toxic. MM is produced by microscopic organisms found in water and soil. More mercury in the environment can increase the amount of methylmercury produced by these organisms.

The nervous system is sensitive to all forms of mercury. MM and metallic mercury vapors are more harmful than other forms, because mercury in these forms easily reaches the brain. Exposure to high levels of metallic, inorganic, or organic mercury can permanently damage brain, kidneys, and the developing fetus. Effects on brain functioning may result in irritability,

shyness, tremors, changes in vision or hearing, and memory problems.

Short-term exposure to high levels of metallic mercury vapors may cause lung damage, nausea, vomiting, diarrhea, increases in blood pressure or heart rate, skin rashes, and eye irritation [44].

Mercury is a possible carcinogen. Young children are more sensitive to mercury than adults. The harmful effects of mercury include its ability to pass from the mother to the fetus, potentially causing a number of metal-related neurological ailments including brain damage and mental retardation. According to ATSDR, blood, urine or hair samples can be used to test for exposure to metallic mercury and to inorganic forms of mercury.

5. SUMMARY

Knowledge about the accumulative effect of potentially toxic metals is sparse, but it seems logical that an accumulation of more than one poison in body tissue leads to greater health problems than overexposure to a single metal. In his evaluation of neurotoxins and their effect on brain development and function, Grandjean stated, “A serious difficulty that complicates many epidemiological studies of neurodevelopmental toxicity in children is the problem of mixed exposures. Most populations are exposed to more than one neurotoxicant at a time, and yet most studies have only a finite amount of power and precision in exposure assessment to discern the possible effects of even single neurotoxicants” [45]. In this study, a high burden of several neurotoxins was determined in all patient groups, with children showing the highest metal exposure. Most concerning, the children showed the greatest accumulation of carcinogenic or potentially carcinogenic metals.

Childhood cancers and other childhood diseases have been linked to environmental pollution exposure. The US Cancer for Disease Control (CDC) reviewed seven studies involving over 8000 children living near busy roads in urban areas, and found a greater risk of childhood leukemia among them [46]. Similar results have been documented internationally [47,48]. A US multidisciplinary research team found excessive chromium exposure in leukemia patients living near a waste disposal site [49]. It is suggested that medical evaluation of children and adults living in polluted regions include metal testing and early detoxification treatments. Blumer and Cranton demonstrated as early as 1989 that EDTA chelation treatment reduced mortality in adult cancer patients [50]. While EDTA chelation is not a suitable treatment for children, other detoxification therapies are available for safe use in exposed children.

It is recognized that cancer is multifactorial. It should be more recognized that the removal of only one cause can positively affect cancer development.

It should also be recognized that people living in environmentally polluted areas are not equally affected and that socioeconomics and genetic variations can change an individual’s susceptibility to carcinogens and other toxins [51]. Of the various detoxification enzymes, the Glutathion-S-Transferases(GST) is involved in the detoxification of environmental toxins. Individuals with a missing GSTM1 are at greater risk to develop carcinomas. GSTP1 is missing completely in about 50% of today’s Caucasian race. Karban et al. [52] noted a difference in the occurrence of detoxification enzyme activitiy between Jewish and Non-Jewish Israelis.

When it comes to pollution exposure, early medical intervention improves resistance to disease. ATSDR and other governmental agencies confirm that metal exposure is easily diagnosed. Medical intervention is recommended for the treatment of acute or chronic metal exposure. For children, different protocols for managing their care may be needed [53].

Early recognition and intervention is the key and we thus propose further studies in support of the information provided here.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Available:http://www.haaretz.com/news/israel/.premium-1.654812/ (Sept 8, 2010)
   Available:http://www.haaretz.com/news/israel/.premium-1.652003/April 4, 2015
   Available:http://www.haaretz.com/news/israel/.premium-1.648592/March 24, 2015
2. Available:http://www.ynetnews.com/articles/0,7340,L-4183013,00.html/Feb 02, 2012
3. Available:http://www.timesofisrael.com/battle-of-the-bay/April 20, 2015
4. Li X, Zhong F. Nickel induces interleukin-1β secretion via the NLPR3-ASC-caspase 1 pathway. Inflammation; 2013.
5. Jerusalem Post, May 24, 2015.
6. Opinion of the Human Biomonitoring Commission of the German Federal Environment Agency (Umweltbundesamt). Hair Analysis in Environmental Medicine. 2005;48(2):246-250.
7. Yana Chervona, Adriana Arita, Max Costa. Carcinogenic Metals and the Epigenome: Understanding the effect of nickel, arsenic, and chromium. Metallomics. 2012;4(7): 619–627.
8. Blaurock-Busch E, Busch YM, Friedle A, Parkash C, Kaur A. Comparing the metal concentration in the hair of cancer patients and healthy people living in the malwa region of Punjab, India. Clinical Med Insights: Oncology. 2014;9;8:1-13. DOI:10.4137/CMO.S13410. eCollection 2014.
9. Blaurock-Busch E, Friedle A, Godfrey M, Schulte-Uebbing CEE. Metal exposure in the children of Punjab, India. Maedica (Buchar). 2010;5(2):102–110.
10. Blaurock-Busch E, Omnia R Amin, et al. Toxic metals and essential elements in hair and severity of symptoms among children with autism. Medica. 2012:7(1):38-48.
11. Ilychova SA, Zaridze DG. Cancer mortality among female and male workers occupationally exposed to inorganic lead in the printing industry. Occup Environ Med. 2012;69(2):87-92.
12. Qu W, Tokar EJ, Kim AJ, Bell MW, Waalkes MP. Chronic cadmium exposure in vitro causes acquisition of multiple tumor cell characteristics in human pancreatic epithelial cells. Environ Health Perspect 2012;120(9):1265-71.
13. Rashed MN, Hossam F. Heavy metals in fingernails and scalp hair of children, adults and workers from environmentally exposed areas at aswan, Egypt. Environm Bioindicators. 2007;2(3):131-145.
14. Gulson B. Nails: Concern over their use in lead assessment. The Sci. Total Environ. 1996;177(1-3):323-327.
15. Mestek O, Deyl Zm Miksik I, Novatna J, Pfeifer I, Herget J. Accumulation of lead in tissues after its administration in drinking water to laboratory rats. Physiol Res. 1998; 47(3):197-202.
16. ATSDR, hair analysis panel discussion: Exploring the State of the science. Summary Report. Public Health Service, Atlanta; 2001.
17. Horn P, Pesce A. Reference intervals: An update. Clin Chim Acta. 2003;334(1-2):5-23.
18. Piomelli S. Childhood Lead Poisoning. Pediatr Clin N Am. 2002;49(6):1285-1304.
19. Horton LM, et al. What do we know of childhood exposures to metals (arsenic, cadmium, lead and mercury) in emerging market countries? Int J Pediatr 2013;2013:872596. DOI:10.1155/2013/872596. Epub 2013 Jan 8
20. Available:http://www.who.int/ceh/capacity/cancer.pdf/ (Dec 2009)
21. Anderson LM, et al. Critical windows of exposure for chidlren's health: Cancer in human epidemiological studies and neoplasms in experimental animals models. Environ Health Perspect. 2000;108(suppl 3):573-594.
22. Linet MS, Wacholder S, Zahm SH. Interpreting epidemiologic research: Lessons from studies of childhood cancer. Pediatric. 2003;112(1Pt 2):218-232.
23. Järup L. Hazards of heavy metal contamination. Br Med Bull. 2003;68:167-82.
24. Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, Carter J, Potter R, Maynard A, Ito Y, Finkelstein J, Oberdorster G. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environmental Health Perspectives. 2006;114(8):1172-1178.
25. Utell MJ, Frampton MW. Acute health effects of ambient air pollution: The ultrafine particle hypothesis. J.Aerosol Med. 2000;13(4):355-59.
26. EPA final report: Rochester PM center: Source-specific health effects of utrafine/fine particles; July 22,2013.
27. Calderón-Garcidueñas L, et al. Air pollution and children: Neural and tight junction

antibodies and combustion metals, the role of barrier breakdown and brain immunity in neurodegeneration. 2015;43(3):1039-58.
28. Oppenheim HA, Lucero J, Guyot AC, Herbert LM, McDonald JD, Mabondzo A, Lund AK. Exposure to vehicle emissions results in altered blood brain barrier permeability and expression of matrix metalloproteinases and tight junction proteins in mice. Part FibreToxicol; 2013. DOI:10.1186/1743-8977-10-62
29. Skerfving S, Nilsson U, Assessment of accumulated body burden of metals. Toxicol Lett. 1992;(64-65):17-24.
30. Batzevich V. Hair trace element analysis in human ecology studies. Sci Total Environ. 1995;164(2):89-98.
31. Ionescu J, Novotny J, Stejskal V, Lätsch A, Blaurock-Busch E, Eisenmann-Klein M. Increased levels of transition metals in breast cancer tissue. Neuro Endocrinol Lett. 2006;27(Suppl 1):36-9.
32. Dow EC, Stanbury JB. Strontium and calcium metabolism in metabolic bone disease. J of Clin Investigation. J Clin Invest. 1960;39(6):885–903.
33. Available:http://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=655&tid=120/ (April 2004.Last upd March 26, 2014)
34. Shanker AK, Venkateswarlu B. Chromium: Environmental pollution, health effects and mode of action. In encycl of environm health. Edited by Niragu JO. 2011:650-659.
35. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for chromium. (draft for public comment). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service; 2008.
36. Available:http://water.epa.gov/drink/contaminants/basicinformation/chromium.cfm#three/ (Dec13, 2013)
37. Available:http://www.atsdr.cdc.gov/toxfaqs/TF.asp?id=101&tid=23/ (Last upd Mar 20,2014)
38. Willis AW, Evanoff BA, Lian M, Galarza A, Wegrzyn A, Schootman M, Racette BA. Metal emission and urban incident Parkinson disease: a community health study of Medicare beneficiaries by using geographic information systems. American Journal of Epidemiology. Available:http://dx.doi.org/10.1093/aje/kwq303
39. Available:http://www.atsdr.cdc.gov/PHS/PHS.asp?id=100&tid=23/ (Sept 2012)
40. Cheung MR. Blood lead concentration correlates with all cause, all cancer and lung cancer mortality in adults: A population based study. Asian Pac J Cancer Prev. 2013;14:3105-8.
41. Canfield RL, Henderson CR, Cory-Slechta DA, Cox C, Juski TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 µg per Deciliter. New England Journal of Medicine. 2003;348(16):1517-1526.
42. Gerhardsson L, Lundström NG, Nordberg G, Wall S. Mortality and lead exposure: A retrospective cohort of Swedish smelter workers. Br J Ind Med. 1986;43(10):707-712.
43. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for nickel (update). Atlanta, GA: U.S. Department of Public Health and Human Services, Public Health Service; 2005.
44. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for mercury. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service; 1999.
45. Grandjean P. Landrigan PJ. Neurobehavioural effects of developmental toxicity. The Lancet Neurology. 2014; 13(3):330:338.
46. Boothe VL, Boehmer TK, et al. Residential traffic exposure and childhood leukemia: A systematic review and meta-analysis. Am J Prev Med. 2014;46(4):413.
47. Weng HH, Tsai SS, Chiu HF, Wu TN, Yang CY. Childhood leukemia and traffic air pollution in Taiwan: Petrol station density as an indicator. J. Toxicol Environ Health A. 2009;72(2):83-7.
48. Pearson RL, Wachtel H, Ebi KL. Distance-weighted traffic density in proximity to a home is a risk factor for leukemia and other childhood cancers. J Air Waste Manag Assoc. 2000;50(2):175-180.
49. Durant JL, Chen J, Hemond HF, Thilly WG. Elevated incidence of childhood leukemia in woburn, Massachusetts: NIEHS superfund basic research program searches for causes. Environmental Health Perspectives. 1995;103(6):93-98.
50. Blumer W, Cranton EM. Ninety percent reduction in cancer mortality after chelation therapy with EDTA. Journal of Advancement in Medicine. 1989;2(1&2): 183-188.
51. Available:http://www.cancerindex.org/geneweb/GSTM1.htm/last (rev 15Feb 2015)

52. Karban A, Krivoy N, Elkin H, Adler L, Chowers Y, Eliakim R, Efrati E. Non-jewish Israeli IBD patients have significantly higher glutathion s-transferase gstt1-null frequency. Digestive Diseases and Sciences. 2011;56(7):2081-2087.

53. Agency for Toxic Substances and Disease Registry (ATSDR). Medical Management for Lead (Pb). CAS. 2014;7439-92-1.

© 2015 Blaurock-Busch et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/10658