ARSENIC HEALTH EFFECTS RESEARCH

Consulting Report

Case: Mr. Nibaldo Araya Pérez

Requested by:

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TABLE OF CONTENTS

I. SUMMARY OF FINDINGS

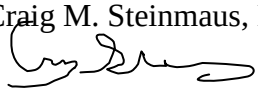
Mr. Nibaldo Araya Pérez was a 50 year old male contractor worker at the Planta de Limpieza de Gases de Caletones in Rancagua who was admitted to the Regional Hospital of Rancagua on May 22nd 2009 and passed away 20 days later of acute hepatitis. Prior to his hospitalization, Mr. Araya Pérez worked in an area with arsenic-containing dusts, and the reported arsenic concentration in his blood collected at the time of the autopsy was 19.66 mg/L. However, based on my review of this case and many case-reports and studies of high arsenic blood levels, the high blood arsenic level reported for Mr. Araya Pérez is most likely erroneous, due to laboratory or reporting error, or due to some cause other than his routine activities at work.

This conclusion is based on the following factors. First, a blood arsenic level of 19.66 mg/L is much higher than is seen following the inhalation of arsenic dusts. Blood levels this high are usually only seen after a massive oral intake involving incredibly high arsenic concentrations. This type of massive oral intake could not occur as part of Mr. Araya Pérez's normal routine work activities. Second, because blood arsenic levels can fluctuate rapidly and because urine is the primary method of arsenic excretion, arsenic measurements in urine are generally the best method for measuring a person's true arsenic intake. Importantly, Mr. Araya Pérez's urine arsenic concentration measured two days prior to his death was very low (< 2 ug/gm). A level near 2 ug/gm is well within the normal range seen in people without an obvious exposure source and is many times lower than the urine arsenic levels associated with death, hepatitis, or any other arsenic-related illness or health effect. Since urine is generally the most accurate method for measuring a person's true arsenic exposure, this very low urine level is strong evidence that the high blood concentration of 19.66 mg/L measured at autopsy is erroneous. Third, arsenic is rapidly eliminated from the blood following an exposure. Because of this, it is essentially impossible that a blood measurement of 19.66 mg/L measured more than twenty days after Mr. Araya Pérez's last day of work could be directly related to an arsenic exposure that occurred while Mr. Araya Pérez was at work. Fourth, the airborne and urine levels of arsenic measured in Mr. Araya Pérez's workplace and urine arsenic level prior to his death were below Chile standards and well below those levels associated with acute arsenic-related death and acute hepatitis. In addition, I have not seen any reports that Mr. Araya Pérez was involved in any unusual and acute exposure incidents just prior to his hospitalization which may have resulted in exposure levels substantially higher than these. Fifth, although Mr. Araya Pérez's arsenic hair levels were somewhat elevated, this level is commonly seen in people who are chronically exposed to relatively low levels of arsenic in air and water and well below the hair arsenic levels associated with an acutely fatal arsenic exposure. In addition, hair is easily contaminated by external exposures. Because external contamination of hair is likely in Mr. Araya Pérez's work environment, this hair level is not surprising given his work and is likely a poor indicator of Mr. Araya Pérez's actual internal arsenic dose.

In summary, based on all of these factors, I conclude that the high blood level of 19.66 mg/L is most likely erroneous, due to laboratory or reporting error, or due to some cause other than Mr. Araya Pérez's activities at work. Overall. I do not see any firm evidence that Mr. Araya Pérez's death was caused by his arsenic exposures and routine work activities at the Planta de Limpieza de Gases de Caletones.

II. SUMARY OF THE CASE

Mr. Nibaldo Araya Pérez was a 50 year old male contractor worker at the Planta de Limpieza de Gases de Caletones in Rancagua who was admitted to the Regional Hospital of Rancagua on May 22nd 2009 and



passed away 20 days later of acute hepatitis (per the death certificate) on June 11th 2009. Arsenic measurements collected at the time of the autopsy in the blood and hair were 19.66 mg/L and 5 mg/kg, respectively. Arsenic measurements collected from his urine two days prior to his death were < 2 ug/gm. No other details of Mr. Araya Pérez's illness, hospitalization, or death are available to me at this time. Importantly, as discussed in detail below, urinary arsenic measurements are generally the best method for evaluating a person's true internal arsenic exposure, and the very low urine level of < 2 ug/gm provides strong evidence that Mr. Araya Pérez's arsenic exposure at the time of his death was very low, that is, orders of magnitude lower than the levels associated with a fatal illness. Arsenic levels in blood can be highly variable, and hair can be easily contaminated by external arsenic exposure. Because of these issues inaccuracies can result when arsenic is measured in hair and blood.

III. REVIEW OF MR. ARAYA PEREZ'S WORK HISTORY AND ARSENIC EXPOSURE

Mr. Araya Pérez's work history is summarized in Table 1. Since Mr. Araya Pérez passed away of an acute illness (acute hepatitis) and because arsenic is fairly rapidly eliminated from the body after it is inhaled or ingested, the greatest focus should be on Mr. Araya Pérez activities in the few days or weeks preceding his hospitalization. Just prior to his hospitalization, Mr. Araya Pérez had worked as a forklift crane operator transferring sealed bags containing calcium arsenate, a residue of the smelting process. During this activity he worked inside an enclosed cab and was reportedly required to wear a respirator. Airborne levels of arsenic in this workplace were collected at multiple times throughout Mr. Araya Pérez's employment and were well below the permissible level of 0.13 mg/m^3 (this level is adjusted for the elevation at the facility). These airborne levels of arsenic and his recorded urine levels are similar or lower than those that have been reported at other copper smelter plants in Chile and elsewhere (1-5). The air and urine and other arsenic measurements for Mr. Araya Pérez and his workplace are reviewed in Table 2. His last day of work was May 21st 2009, which was the day before he was hospitalized.

A urinary arsenic measurement collected from Mr. Araya Pérez on April 12th, 2007 while he was working at this job was 175 ug/gm of creatinine. This is higher than typically seen in unexposed Chileans (generally < 20 ug/gm) (unpublished data from our studies in northern Chile), higher than the US occupational biologic effect index for urinary arsenic (6), but lower than the Chile limit of biologic tolerance of 220 ug/gm. In addition, it is unknown if this measurement included only *inorganic* arsenic. Many laboratories will measure *total* arsenic. This is important since measurements of total arsenic include both the inorganic (toxic) and organic forms. Organic arsenic exposure typically results from eating seafood and organic arsenic is essentially non-toxic. Because of this, measurements of total arsenic can be an inaccurate indication of a person's true toxic exposure if the organic and inorganic forms are not separated out.

Mr. Araya Pérez also had a urinary arsenic measurement of 15 ug/gm on August 9th, 2007, but reportedly was working at another site where he was loading and unloading metallic copper and was not exposed to significant levels of arsenic. A urine arsenic level of 15 ug/gm is well within the normal range of urinary arsenic levels seen in people without an obvious arsenic exposure source, in Chile and elsewhere (7).

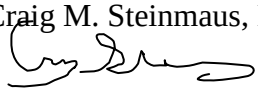
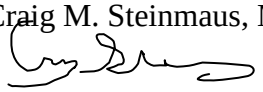


Table 1. Review of Work History

Period	Activities
October 2002-January 2007	Mr. Nibaldo Araya Pérez began working for the company contractor in 2002. His duties during this period involved working as a crane operator gathering, loading, transferring, and unloading spare parts to and from trucks.
February 2007-May 2007	Mr. Araya Pérez worked as a crane operator at the Planta de Limpieza de Gases de Caletones, in a sealed cabin, transferring bags of sealed arsenic residues between the sealing machine, storage facility, and trucks. A urinary arsenic measurement collected on April 12th 2007 was 175 ug/gm creatinine. It is unknown if this included both inorganic (toxic form) and organic arsenic (essentially non-toxic, usually from eating seafood).
June 2007-October 2008	Mr. Araya Pérez worked in another area loading and unloading metallic copper without significant arsenic exposure. A urinary arsenic measurement collected from Mr. Araya Pérez on August 9th 2007 was 15 ug/gm creatinine, which is within normal limits.
2008	Until year 2008, the wastes from the plant were neutralized, liquids were separated from solids, and the solids (consisting of 28% calcium and 8% arsenic) were dried, packaged, and eventually shipped for final disposal. In 2008, this drying process was stopped, which reportedly reduced airborne arsenic exposure to the workers.
November 2008-May 2009	Mr. Araya Pérez worked as a crane operator at the Planta de Limpiezas de Gases de Caletones in Rancagua, transferring sealed bags of arsenic residues. Again, this work was in an enclosed cab and respirators were required, and multiple airborne arsenic levels measured between 2006 and 2009 were below regulatory standards (reviewed in Table 2).

Table 2. Arsenic Exposure Records

Date	Metric	Value	Permissible limit	Notes
Sept 6th 2006	Air	0.0044 mg/m^3	0.13 mg/m^3	Inside crane cabin
April 12th 2007	Urine	175 ug/gm	220 ug/gm	--
August 9th 2007	Urine	15 ug/gm	220 ug/gm	--
June 11th 2008	Air	0.01 mg/m^3	0.13 mg/m^3	Inside crane cabin
June 11th 2008	Air	0.02 mg/m^3	0.13 mg/m^3	Personal sampling
June 9th, 2009	Urine	< 2 ug/gm	220 ug/gm	In the hospital
June 12th 2009	Air	0.026 mg/m^3	0.13 mg/m^3	Inside crane cabin
June 12th 2009	Air	0.02 mg/m^3	0.13 mg/m^3	Personal sampling
Autopsy	Blood	19.66 mg/L	--	--
Autopsy	Hair	5 mg/kg	--	--



IV. INTERPRETATION OF THE HIGH BLOOD LEVEL OF 19 MG/L AT AUTOPSY

Interpretation of arsenic measurements in blood

Mr. Araya Pérez had a reported blood arsenic level of 19.66 mg/L at autopsy. This level is extremely high, and levels this high are rarely seen in humans in the peer-reviewed literature. Normal blood arsenic levels are typically around 0.3-2.0 ug/L (7), which is about 20 thousand times lower than the levels reported for Mr. Araya Pérez. Because arsenic moves in and out of blood fairly rapidly, the half-life of arsenic in blood is fairly short and arsenic levels in blood can be highly variable (7-9). Because of this, blood is generally not the best method for assessing arsenic exposure in most people, especially when trying to assess arsenic exposures that may have occurred more than a few days prior to the blood measurement. Because blood can be a poor measure of arsenic exposure, there are very few studies of the typical blood arsenic levels seen in copper smelter workers, and most of the exposure data in this industry involves arsenic measurements collected from air or urine. Urinary arsenic measurements are usually the best method for assessing actual arsenic intake in exposed people (7). This is because urine is the primary method of arsenic excretion in humans and almost all ingested or inhaled arsenic is excreted by this route. Because of this, arsenic levels in urine usually do not fluctuate as rapidly as those in blood, and urine is the primary method most researchers and clinicians use to assess a person's true arsenic exposure (7). This is one reason why greater emphasis should be given to Mr. Araya Pérez's urine measurement than to his blood measurement. The rapid fluctuations and high variability of arsenic levels in blood make it a less than ideal metric for assessing a person's true arsenic exposure.

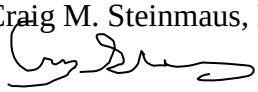
A blood level of 19.66 mg/L is incredibly high and inconsistent with inhaling arsenic-containing dusts

The arsenic level of 19.66 mg/L measured in Mr. Araya Pérez's blood is many times higher than one would expect to see in a person who is exposed to arsenic during normal routine activities at work, even in industries like smelting and mining where airborne arsenic levels have traditionally been elevated. In fact, this very high blood level is much more consistent with either a laboratory error or with a massive intentional or accidental poisoning incident. This very high level is completely inconsistent with the much lower arsenic blood levels that have been seen following inhalation exposures of arsenic-containing dusts.

Other reports of high blood arsenic levels in the current peer-reviewed literature

Table 3 provides a summary of several of the more recent case reports involving very high blood arsenic levels collected from the current peer-reviewed literature. As seen, there are only a few reports of blood arsenic levels that are close to those reported for Mr. Araya Pérez, and most importantly, all of these involve massive oral exposures or exposure situations that are much different than one would expect to occur in Mr. Araya Pérez's workplace. As seen in these case reports, even when massive doses involving very high arsenic concentrations are ingested in accidental or intentional poisonings, blood arsenic levels near 19.66 mg/L are incredibly rare. This rarity highlights the highly unusual nature of Mr. Araya Pérez's blood arsenic levels, and leads one to suspect that this high blood level was an error or due to something outside of Mr. Araya Pérez's routine work.

As seen in Table 3, most of the case reports involving blood levels of arsenic close to those of Mr. Araya Pérez's are associated with oral ingestions of many grams of arsenic in a very acute and rapid manner, such as attempted suicides or homicides or accidental ingestions in very young children. In addition, most of case reports involving high arsenic levels in blood also had very high arsenic levels in urine. The urine levels commonly associated with blood arsenic levels near 19.66 mg/L are thousands of times higher than the urine levels of < 2 ug/gm reported for Mr. Araya Pérez two days prior to his death, and 10-100 times higher than the urine level of 175 ug/gm reported for Mr. Araya Pérez while he was working at the Planta



de Limpieza de Gases de Caletones in 2007. For example, in case reports by Duenas-Laita (2005) and Lech and Trela (2005), urine arsenic levels of 67,500 ug/L and 59,400 ug/L, were reported in people with blood arsenic levels of 0.13 mg/L and 11.1 mg/L, respectively. Although these blood levels are lower than Mr. Araya Pérez's, the corresponding urine levels are over 10,000-times higher than those measured in Mr. Araya Pérez's urine while he was in the hospital. As a whole, the complete lack of consistency between his very high blood levels after his death and the arsenic levels measured in his urine (which is generally more accurate than arsenic measurements in blood) provides very strong evidence that Mr. Araya Pérez's high blood levels were erroneous, and certainly not due to his normal routine activities at work

Summary

In summary, Mr. Araya Pérez's blood levels are completely inconsistent with the description of his workplace activities, the airborne levels of arsenic reported for his workplace, his urine levels while he was working at the Planta de Limpieza de Gases de Caletones, and most importantly, the very low arsenic levels measured in his urine two days before his death. All of these major inconsistencies provide a strong body of evidence that the blood concentrations of 19.66 mg/L were not due to Mr. Araya Pérez's activities at work, and suggests that this measurement was erroneous or due to laboratory or reporting error. Normally, a blood level that is this unusually high is confirmed by a repeat measurement. Since I have no reports that a repeat measurement was done, the validity of the 19.66 mg/L reading can not be substantiated.

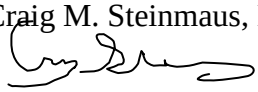
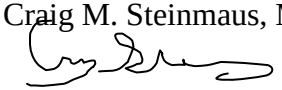


Table 3. Recent Case Reports and Studies of High Blood and Urine Arsenic Levels

Study	Scenario	Who	Dose	Blood Arsenic (Time after exposure)	Urine Arsenic (Time after exposure)[1]	Outcome	Notes
Lethal cases (sorted by highest blood arsenic)							
Lech and Trela, 2005 (10)	Accidental poisoning	38 year old male	Unknown amount of arsenic trioxide	2.29 mg/L (< 14 Hours) 20.1 mg/L (Post-mortem)	6,720 ug/L (< 14 Hours)	Death at 14 hours	
Lech and Trela, 2005 (10)	Self-poisoning	63 year old male	15 gm arsenic trioxide	2.5 mg/L (< 8 Hours) 16.2 mg/L (Post-mortem)	Unknown	Death at 8 hours	
Lech and Trela, 2005 (10)	Accidental poisoning	25 year old male	Unknown amount of 70% arsenic trioxide	11.1 mg/L (< 9 Hours) 3.0 mg/L (Post-mortem)	59,400 ug/L (< 9 Hours)	Death at 9 hours	
Jolliffe *et al.*, 1991 (11)	Self-poisoning	28 year old male	75 mg arsenic trioxide	2.3 mg/L (Post-mortem)	--	Death at 16 hours	
Saady *et al.*, 1989 (12)	Accidental poisoning	3 year old child	44% sodium arsenite	1.80 mg/L (5.5 hours, post-mortem)	--	Death at 5.5 hours	Hair arsenic = 25 mg/L (Post-mortem)
Lai *et al.*, 2005 (13)	Accidental poisoning	4 month old child	3430 mg arsenic pesticide	0.73 mg/L (Post-mortem)	9,000 ug/L (14 Hours)	Death at 36 hours	Body weight = 23 kg
Parent *et al.*, 2006 (14)	Poisoning	26 year old male	Possible 10 gm arsenic trioxide	0.35 mg/L (Post-mortem)	3,470 ug/gm (Day 6)	Death on day 26	Hair arsenic = 67 mg/kg (Post-mortem)
Non-lethal cases							
Stephanopoulos *et al*., 2002 (15)	Accidental poisoning	22 month old child	32 mg arsenic trioxide (ant bait)	1.7 mg/L (5 Hours)	2,085 ug/L (6.7 Hours)	Alive	Body weight = 14.2 kg
Kim and Abel, 2009 (16)	Self-poisoning	18 year old male	Unknown amount of arsenic trioxide	0.47 mg/L (Day 1)	18,975 ug/L (Day 1)	Alive	Multisystem organ failure
Kamijo *et al.*, 1998 (17)	Self-poisoning	23 year old male	1040 mg arsenic trioxide	0.41 mg/L (20 Hours)	51,400 ug/L (20 Hours)	Alive	
Stenehjem *et al.*, 2007 (18)	Unknown	39 year old female	Unknown	0.29 mg/L (Day 1-2)	4,000 ug/L (Day 1)	Alive	Hair arsenic = 57 mg/kg
Isbister *et al.*, 2004 (19)	Self-poisoning	28 year old male	10 mg arsenic trioxide	0.28 mg/L (< 6 Hours)	5,840 ug/gm (Day 1)	Alive	
Lai *et al.*, 2005 (13)	Accidental poisoning	2 year old child	190 mg arsenic (pesticide)	--	4,920 ug/L (Day 1)	Alive	
Duenas-Laita, 2005 (20)	Self-poisoning	43 year old male	54 gm arsenic trioxide	0.13 mg/L (Day 1) 0.16 mg/L (Day 4) 0.01 mg/L (Day 10)	67,500 ug/L (Day 1) 3,000 ug/L (Day 10)	Alive	
Isbister *et al.*, 2004 (19)	Self-poisoning	30 year old male	25 mg arsenic trioxide	0.05 mg/L (< 6 Hours)	829 ug/gm (Day 1)	Alive	
Vantroyen *et al*., 2004 (21)	Self-poisoning	27 year old female	9000 mg arsenic trioxide	--	14,000 ug/L (Day 2)	Alive	
Mathieu *et al.*, 1992 (22)	Self-poisoning	30 year old male	10 gm sodium arsenate	0.46 mg/L (Day 1)	--	Alive	

1. Since most people have about 1 gm of creatinine per liter of urine, arsenic measurements in ug/gm creatinine and ug/L are roughly equivalent in most people.



V. ANSWERS TO SPECIFC QUESTIONS ABOUT ARSENIC BLOOD LEVELS

1. What possible routes of exposure could lead to a blood arsenic level of 19.66 mg/L?

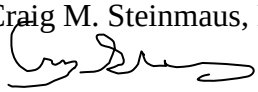
As discussed above, it is rare that arsenic exposure through any route would be associated with a blood level as high as 19.66 mg/L. Although it is theoretically possible that levels this high might occur through either inhalation or ingestion (oral intake), the highest levels in the current literature are usually associated with ingesting massive concentrations of arsenic orally, not from inhalation exposures and not from inhaling arsenic-containing dusts. None of the recent case reports with high blood arsenic levels involved the inhalation of arsenic residue dusts, which is the most likely route by which Mr. Araya Pérez would be exposed to arsenic.

2. What is the elimination pattern of arsenic in blood?

There are several reports in the literature regarding the elimination rates of arsenic in the blood of exposed laboratory animals such as rats or mice. However, these are probably not relevant to humans since the metabolism and toxicity of arsenic are much different in rats and mice than in humans (7). For example, rats tend to sequester arsenic in red blood cells, which humans do not do (7). Because of these differences, it is best to evaluate data from humans rather than laboratory animals when assessing the toxicity, kinetics, or elimination rates of arsenic. For this reason, my report focuses on data from studies in humans rather than studies in laboratory animals.

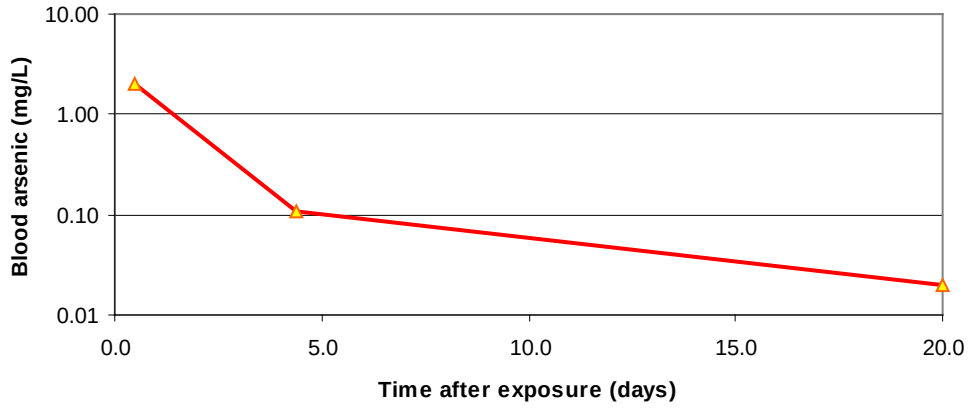
For the reasons described above, urine is generally the best method for assessing a person's exposure to arsenic, and because of this, most pharmacokinetic studies of arsenic in humans have examined arsenic concentrations in urine, not blood. The few relevant reports that have measured arsenic in blood suggest that arsenic is rapidly cleared from the blood following inhalation or oral exposure. Figure 1 shows a summary of the results of a study by Apostoli *et al.* on blood arsenic levels following an acute arsenic inhalation exposure (23). It should be noted that the vertical axis in this figure (the blood arsenic levels) is on a logarithmic scale, so the blood arsenic levels actually fall faster than they may appear at first glance at this figure. As seen, within the first few days after exposure, blood arsenic concentrations drop fairly rapidly. The half-life ($t_{1/2}$) during the first 2-3 days following exposure is 27.6 hours. This means that blood arsenic levels drop by 50% in the first 27.6 hours after the exposure. After about 3-4 days, blood arsenic concentrations continue to decline, but at a somewhat slower rate ($t_{1/2}$ = 59.4 hours). These fairly rapid elimination rates mean that arsenic levels in blood are usually only a good indication of an exposure that occurred within a few days from the time the blood was collected, but are a very poor representation of exposures that may have occurred weeks or months before. The arsenic level in Mr. Araya Pérez's blood was measured after his death on June 11th 2009, which was about 20 days after he was hospitalized and more than 21 days after his last day at work. Given this timeline, the clearance rates shown in Figure 1 suggest that any arsenic that Mr. Araya Pérez's had in his blood as a result of his exposure at work should have been more than 98% eliminated by the time his blood sample was collected. This would mean that if the reading of 19.66 mg/L was correct, the arsenic levels in his blood 20 days before he was hospitalized should have been many times higher. However, given that this level is already among the highest reported in the current literature, this seems essentially impossible. For this reason, I have not attempted to back-calculate what his estimated blood levels were prior to his hospitalization.

In summary, even if Mr. Araya Pérez had a massive inhalation exposure at work 1-2 days before he was hospitalized, it is virtually impossible that his blood arsenic levels could have been as high as 19.66 mg/L more than twenty days after this exposure. This suggests that Mr. Araya Pérez's high blood levels either came from some source other than his workplace or they were a result of a laboratory or reporting error and were erroneous.



It should be noted that in a few case reports, arsenic levels measured in blood samples collected post-mortem (after death) were higher than arsenic levels in blood samples collected before death. For example, in two of the cases reviewed by Lech *et al.* (shown in Table 3), blood arsenic levels were below 3 mg/L prior to death, but over 15 mg/L after death (10). The exact cause of this is unknown but could be related to the release of arsenic into the blood serum from dying cells or dying tissues. Regardless of the cause, these findings mean that arsenic levels collected in blood after death may not provide an accurate measure of a person's true arsenic exposure, and raises even further concern about the validity and interpretability of the very high blood arsenic level measured at Mr. Araya Pérez's autopsy.

Figure 1. Decline in Blood Arsenic Levels after Acute Inhalation Exposure (Apostoli *et al.*, 1997)



3. What arsenic levels in blood did Mr. Araya Pérez likely have 20 days before passing away?

As discussed above, based on the normal elimination rates of arsenic in blood, if the measurement at the time of autopsy is accurate then Mr. Araya Pérez's blood level when he was first admitted to the hospital should have been many times higher than 19.66 mg/L. However, given that a level of 19.66 mg/L is already among the highest reported in the recent literature, it is essentially impossible that it was many times higher at any point in time. Based on my review of the recent case-reports, a level equal to or greater than 19.66 mg/L would have assuredly caused death within a few hours of exposure. For example, Jolliffe *et al.*, Lech and Trela, Lai *et al*., and Saady *et al*. (Table 3) all provide case-reports of people with blood levels similar or lower than Mr. Araya Pérez's who all passed away within 36 hours of their exposure (10-12). The fact that Mr. Araya Pérez was alive for 20 days in the hospital suggests that his blood arsenic level of 19.66 mg/L was either erroneous or it was related to a post-mortem release of arsenic after death and was therefore not indicative of his true arsenic exposure.

4. Are there other cases in the literature of arsenic blood levels this high?

As seen in Table 3, reports of blood levels as high as those reported for Mr. Araya Pérez are very rare in the published literature and always associated with incidents of massive exposure that are unlike anything Mr. Araya Pérez would be expected to encounter in his normal course of work or even in an industrial accident.

5. How many days could a person live with blood levels this high?

Based on the published case reports in the literature (Table 3), it would be expected that someone with the blood levels of 19.66 mg/L would pass away within 36 hours of exposure. Examples of this can be seen in the case reports presented by Lech *et al.*, where three of the cases with blood arsenic levels similar or

below those of Mr. Araya Pérez all passed away within 14 hours of their arsenic exposure (10). The fact that Mr. Araya Pérez remained alive for over twenty days following his initial hospitalization raises serous doubts about the validity of his blood arsenic measurement.

6. Could these blood levels be attributable to inhalation of arsenic residues at work?

No. There is no evidence that arsenic dusts could cause a blood level of 19.66 mg/L. As shown in Table 3, most exposures resulting in blood levels similar to those of Mr. Araya Pérez were in people who ingested massive doses of arsenic by mouth in an attempted suicide or homicide or in young children who accidentally ingested arsenic. They are not seen in industrial accidents involving arsenic dusts or in the course of normal work activities such as those seen in a copper smelter.

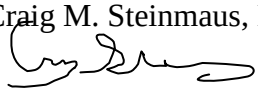
VI. INTERPRETATION OF THE ARSENIC LEVELS IN HAIR

The accuracy of arsenic measurements in hair

Several studies have used arsenic levels in hair as a biomarker of arsenic exposure. Arsenic has a high affinity to bind to sulfhydryl groups which are abundant in keratin in hair. The advantage of hair as a biomarker of exposure to arsenic, compared to urine or blood, is that hair levels are thought to reflect a longer period of past exposure (approximately 2.5 months) (9). However, there is a major problem with assessing arsenic exposure using hair: the potential for external contamination. Arsenic in water or air that comes into contact with hair can become externally bound to the sulfhydryl groups on the hair. In other words, hair may be contaminated externally through air, water, or dust, rather than from actual intake and internal absorption. Importantly, once the external arsenic is bound to the hair, most of it can not be removed by routine washing, even by washing the hair in the laboratory (8). In addition, externally bound arsenic can not be distinguished from arsenic that is absorbed internally. Because of these issues, a high arsenic measurement in hair could be caused by someone washing their hair with arsenic contaminated water or walking through a room with arsenic contaminated dust. In these situations, arsenic levels in hair may not represent how much arsenic a person has actually taken into their bodies. Since the *internal* dose is the key determinant of toxicity, a hair sample that is externally contaminated could provide a very inaccurate measure of the true toxic dose a person has had.

Other problems with hair measurements

Several other issues can limit the interpretability of arsenic measurements in hair. First, different laboratories may use different techniques to wash hair and this can lead to variability in hair arsenic levels. Second, there is strong evidence that different people absorb arsenic into their hair at different rates. This means that two people who are exposed to the same level of arsenic can have markedly different arsenic levels in their hair. For example, in Kurttio *et al.* (24), two subjects with the same concentrations of arsenic in their water and urine were found to have arsenic levels in their hair that differed by over 3 to 5 fold. Similar results have been seen in other studies (25, 26). Third, differences in arsenic levels can occur between different hairs, or between different parts of the same hair (e.g. closer vs. farther away from the scalp), and these factors can also lead to major differences in arsenic levels in hair (8). Fourth, because hair grows fairly slowly, any internal arsenic exposure that occurred within the last few days may not be reflected in a person's hair level. This is particularly important in Mr. Araya Pérez's case since the high arsenic levels in his blood and his rapid death would lead one to suspect a more immediate (e.g. 1-2 days before he was hospitalized), rather than distant, exposure. If Mr. Araya Pérez was heavily exposed a few days prior to his admission to the hospital, this high exposure may not have been fully reflected in the hair measurement that was collected at the time of his autopsy.



In summary, because of all of these issues, although hair measurements may give some indication that a person was in an environment containing some arsenic, the exact extent of this exposure, and whether or not it was internal or external, can not be conclusively determined by a hair arsenic measurement (8, 9, 25).

Interpreting Mr. Araya Pérez's hair measurement

Mr. Araya Pérez had a hair level of 5 mg/kg (or 5 ug/g), which is higher than normal reference ranges (0.02-0.2 mg/kg) (7). However, a level of 5 mg/kg is similar to the hair levels seen in people who are chronically exposed to levels of arsenic at work or in their water that are relatively low and not associated with acute toxicity and acute severe illness (7). As such, a hair level of 5 mg/kg is not indicative of an arsenic exposure that would cause acute hepatitis or rapid death. In his review of the usefulness of arsenic hair analyses, Hindmarsh produced a chart describing the approximate hair levels that are associated with various levels of arsenic toxicity (Table 4) (8). As seen, lethality is usually associated with a hair level > 45 mg/kg, which is many times higher than Mr. Araya Pérez's hair level of 5 mg/kg.

In summary, although it should be kept in mind that the chart developed by Hindmarsh is just an approximation, it does highlight the point that even though Mr. Araya Pérez's hair level indicates that he may have had some arsenic exposure, his hair level does not indicate an arsenic exposure level that would cause acute hepatitis and fairly rapid death. It also highlights the point that the level seen in Mr. Araya Pérez's hair is well within the range that could be caused by external contamination.

Table 4. Interpretation of Hair Arsenic Levels by Hindmarsh (2002)

Hair level	Effect
< 1 mg/kg	Normal
≥ 10 mg/kg	Chronic poisoning
45 mg/kg	Lethal
External contamination	Up to many thousands mg/kg

VII. ANSWERS TO SPECIFC QUESTIONS ABOUT ARSENIC HAIR LEVELS

1. Are these levels compatible with the work performed by Mr. Araya Pérez?

Yes. The arsenic levels in Mr. Araya Pérez's hair are consistent with the hair levels seen in other people exposed to arsenic at work or from other sources. Table 5 reviews the hair levels that have been seen in other exposed populations. It should be noted that the data in this table involve studies in populations that are chronically exposed to relatively low levels of arsenic, not in people who are acutely ill from arsenic toxicity. As seen, many of these hair levels are similar to those measured in Mr. Araya Pérez. These data show that although Mr. Araya Pérez's hair level is indicative of some arsenic exposure, it is not by itself indicative of an exposure that is high enough to cause acute hepatitis and acute death. In addition, as discussed above, one can not be certain whether this level of arsenic in hair is due to internal exposure or external contamination.

Table 5. Hair Levels Seen in Non-Acutely Ill Exposed Populations

Study	Exposure situation	Hair levels	Associated levels
The current case	Copper smelter	5 mg/kg (2009)	Urine: < 2 ug/g (2009) Air: 0.02 mg/m^3
Feldman *et al.*, 1979 (27)	Copper smelter	182 mg/kg[1]	Urine: 98 ug/L
Morse *et al.*, 1979 (28)	Living near a copper smelter	2.2 mg/kg	Urine: 47.5 ug/L
Clay *et al.*, 1977 (29)	Steel bronze workers	3.3-76.1 mg/kg	Air: 0.08 mg/m^3
Afridi *et al.*, 2009 (30)	Steel mill workers	3.39 mg/kg	Urine: 7.9 ug/L Blood: 5.9 ug/L
Das *et al.*, 1995 (31)	Water (Bangladesh)	2.3-9.8 mg/kg	Urine: 57-1,143 ug/L
Harrington *et al*., 1978 (32)	Water (Alaska)	1.0 mg/kg	Urine: 178 ug/L
Southwick *et al.*, 1983 (33)	Water (Utah)	0.10-4.70 mg/kg	Urine: 25-660 ug/L
Borgono and Greiber, 1971 (34)	Water (Antofagasta)	4-83.4 mg/kg	Urine: 25-770 ug/L
Kurttio *et al.*, 1998 (24)	Water (Finland)	0.06-12.5 mg/kg	Urine: 58 ug/L Water: 170 ug/L
Concha *et al*., 2006 (25)	Water (Argentina)	0.51-4.25mg/kg	Urine: 300 ug/L Water: 189 ug/L

1. External contamination is likely.

2. Are these hair levels associated with acute hepatitis?

No. There is no evidence in the current peer-reviewed literature that Mr. Araya Pérez's hair level, or his reported urine levels or the air levels in his workplace are associated with acute hepatitis. Some studies have shown an association between chronic long-term arsenic ingestion and liver cancer and chronic liver effects (NRC, 1999). But, these are chronic conditions that likely involve much different pathological process than severe acute hepatitis leading to rapid death. A few studies have identified possible links between work in a copper smelter and liver cirrhosis, but the effects seen in these studies have been very small, borderline statistically significant, and not seen in all studies (see Table 6). Therefore, these findings are not conclusive. In some case reports, very high arsenic intakes have been associated with acute liver effects. But, as discussed above in the section on blood arsenic, these have involved massive doses of arsenic completely unlike those seen in Mr. Araya Pérez's workplace, and they involve multiple organ failure which includes many different organs, not just the liver. Overall, there is no evidence in the current literature that Mr. Araya Pérez's hair levels, urine levels, or the air levels measured in his workplace are associated with severe acute hepatitis.

Table 6. Studies of Liver Disease in Copper Smelter Workers

Study	Location	Outcome	Result	Conclusion
Enterline and Marsh, 1982 (1)	Tacoma, Washington; 1940-64; n = 22	Liver cirrhosis	SMR = 1.02 (p > 0.05)	No increase
Lubin *et al*., 2000 (35)	Anaconda, Montana; 1938-89; n = 102	Liver cirrhosis	SMR = 1.21 (95% CI, 1.00-1.47)	Small borderline effect
Axelson *et al*., 1978 (36)	Ronnskar, Sweden; n = 8	Liver cirrhosis	PMR = 1.43 (p = 0.04)	Borderline effect, small study
Marsh *et al.*, 2009 (37)	Copperhill, Tenn; 1946-2000; n= 10	Liver cirrhosis	SMR = 0.41 (95% CI, 0.20-0.76)	No increase
Rencher *et al.*, 1977 (38)	Salt Lake City, Utah, USA; n = 3	Liver disease	PMR = 0.86 (p > 0.05)	No increase

CI, confidence interval; n, number of cases; PMR, proportionate mortality ratio; SMR, standardized mortality ratio. The PMR and SMR are generally well above 1.0 if an association between arsenic and liver disease exists.

3. What other conditions can produce acute sudden hepatitis?

Many factors can cause acute hepatitis. Table 7 lists some of the more common ones. Mr. Araya Pérez's medical records and history should be assessed for the possibility that one of these factors may have played a role in his illness.

Table 7. Some Common Factors Associated with Acute Hepatitis

Viral hepatitis:	Medications	Chemical exposures:
Hepatitis A	Amoxicillin-Clavulanic Acid	Carbon tetrachloride
Hepatitis B	(Augmentin)	Trichloroethylene
Hepatitis C	Isoniazid	Chloroform
Hepatitis D	Other common antibiotics	Halothane
Hepatitis E	Some seizure medications	
Cytomegalovirus	Acetaminophen (Tylenol)	Others:
Mononucleosis	Anti-inflammatory drugs (NSAIDs)	Systemic lupus erythematosus
Herpes Simplex Virus	Some diabetes medication	Other autoimmune conditions
Varicella	Some lipid medications	Multiorgan failure
	Niacin	Alcohol
Other infections:	Anti-fungal medications	Drug reactions
Typhoid	Some antiarrhythmics	Mushroom poisoning
Leptospirosis	Bupropion (Wellbutrin, Zyban)	
Parasites	Tricyclic Antidepressants	
Others	Many nutritional supplements	

VIII. OVERALL CONCLUSION

The specific conclusions of this report are summarized in Table 8. Based on my past experience and extensive research, as well as my review of many recent case-reports and studies in the current literature, and my review of Mr. Araya Pérez's workplace duties and indicators of exposure, I believe that Mr. Araya Pérez's very high blood level was most likely erroneous, and I see no evidence that his death due to acute hepatitis was caused by arsenic exposure he may have had during his work activities at Codelco.

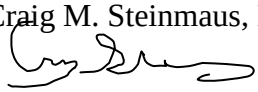
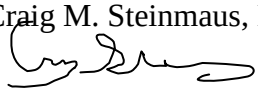


Table 8. Summary of the Conclusions of This Report

- Arsenic levels in urine are generally a more valid indicator of true arsenic exposure than arsenic levels in blood or hair.
- The urine level of < 2 ug/L collected two days before his death is within normal range and is strong evidence that Mr. Araya Pérez's illness was not due to arsenic.
- A blood level of 19.66 mg/L should cause death very rapidly (i.e. within 36 hours).
- A blood arsenic level of 19.66 mg/L is inconsistent with inhalation of arsenic-containing dusts.
- The urine, hair, and air levels measured in Mr. Araya Pérez and his workplace are inconsistent with a blood level of 19.66 mg/L and are not associated with arsenic-related acute hepatitis and death.
- Based on the normal elimination rates of arsenic in blood, the blood arsenic level of 19.66 mg/L can not be due to a workplace exposure occurring 20+ days before this measurement was taken.
- Overall, the evidence strongly suggests that the blood level of 19.66 mg/L was erroneous and that Mr. Araya Pérez's fatal illness was not due to his arsenic exposure at work.



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