Simulation Models To Assess Exposure Levels Of Lead In Blood Plasma And Saliva

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Research Article

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Abstract

Human exposure to metals has been among major concerns of the world and there have been links to cancer, renal failure, cardiovascular and reproductive complications. There has been conflicting information regarding the efficiency of blood plasma and saliva when used as biomarkers in biomonitoring of human exposure to lead metals. Using the Joint Expert Speciation System, the bioavailability of lead was predicted at a range of 78-93 % in blood plasma and 2-23 %. The degree of bioavailability using a net-neutral species was dependent on the total concentrations of lead within low molecular mass ligands. These models predicted more bioavailability of lead in blood plasma than saliva, indicating blood plasma to be a suitable biomarker for biomonitoring of lead exposure even at low levels. This study offers regulatory and health authorities opportunities to consider using blood bioavailability data when assessing and making decisions on lead exposure assessments.

1. Background

Chemical poisoning is among the major global health concerns (1) linked to cumulative health complications such as cancer, anemia, renal failure, cardiovascular, and reproductive problems (2–5). Repeated exposure to low levels of lead may result in bioaccumulation; a phenomenon where even low levels of lead may have adverse effects (5–8). Biomonitoring of toxicological effects of metals at low levels has been a shred of increasing interest among the scientific community and there has been needing for use of chemical speciation tools to improve diagnostic assessment of exposure risks to hazardous metals (9,10).

As the total concentration of metal may not necessarily represent the health risk; biomonitoring which involves assessment of the bioavailability (uptake) in body fluids within the low molecular mass fraction, may predict health risks linked to hazardous metals. Simulation software like Joint Expert Speciation System (JESS) allows the creation of models which are largely water-based (saliva and blood) to determine the individual chemical species present and through an evaluation of the species' charge, give a very good indication of metal uptake through passive diffusion channels. The data output from the models assumes a single uptake mechanism, that is passive diffusion.

Different pathways for human exposure may exist; the common ones include ingestion (mouthing), inhalation (nose), and/or dermal (skin) absorption (3,5,11). When considering human exposure to hazardous poisons; blood plasma and saliva are widely used as biological markers (biomarkers) for biomonitoring of human exposure to hazardous metals. Apart from the blood plasma being the most commonly used diagnostic biomarker for recent lead exposure (12), saliva has also been explored as an alternative matrix for biomonitoring of lead exposure (13,14). Different results may be expected when comparing lead exposure levels in blood and saliva as to some extent saliva lead may indirectly reflect the fraction of circulating blood plasma lead contents (8,14–16). The easiness and limitations of collecting and using blood plasma or saliva matrix for assessing lead exposure are beyond the sole focus

of this study, thus, only the bioavailability levels of lead in either of the two bio-fluids are the most important consideration in assessing metals exposure risks.

Regardless of the fact that both blood and saliva can be used in the diagnosis of lead poisoning, limited information can be retrieved in literature when evaluating the most efficient and suitable biomarker to be used in assessing lead exposure especially for low to moderate lead concentrations. Efficient biomarkers that can accurately help in describing the toxic effects of hazardous metals in the human body at low-level exposure are the potential aspect to consider (12). Therefore, ensuring the appropriate selection of efficient and suitable biomarkers for assessing early exposures to lead becomes a critical factor for consideration, hence the need for validated scientific data to help regulatory and health authorities make decisions on using suitable and appropriate biomarkers for biomonitoring of low-level lead exposures (14).

2. Methods

Simulation models are always performed in-vitro by a mimic of the physicochemical aspects of the human body to determine the fate and therefore achieve assessment of uptake of toxic elements in the human body (biofluids) at a range of concentrations. The European Commission (17) committee recommended previously the use of physiologically based fluids that may contain necessary organic and inorganic components to represent real biological systems when performing simulation models. Through simulation models, it is possible to determine specific forms of metals absorbed and hence bioavailability in the metal-ligands complex forms (9).

It is fortunate that the total concentration of metals in biological systems may not reliably provide sufficient information to use during health risk assessment for the respective metal poisoning; only a fraction of the bioavailable species can be utilized for this purpose (9,18,19). The bioavailability and toxicity of metals are dramatically affected by a slight change in their forms (species) and quantities. Thus, it is valuable to develop simulation models for blood and saliva to determine the specific portion of the lead metals that can migrate and remain significantly bioavailable for poisoning. The quantitative information (bioavailability level) on the current and post-exposure to metal (lead) species could be elucidated and be useful in toxicological biomonitoring investigations (9,12,18–20).

These simulation models were developed by relying on simulation conditions published in the previous studies for blood plasma (21,22) and saliva matrix (23). The models were optimized at pH 7.4, temperature 37°C, ionic strength of 0.15 M, and three metal concentrations. The temperature, ionic strength, and pH are important factors that affect the distribution of metals among the selected ligands, resulting in the formation of different species of metallic elements of different stability in the physicochemical system (24,25). The ligands and metal ions used in the saliva and blood plasma simulation models have been listed in the following Tables 1 and 2 respectively. Total concentrations of lead were at a range of 10^{-9}, 10^{-6}, and 10^{-3} mol/L. The JESS program simulation program was used for these models as it has been among the comprehensive and robust chemical speciation tools widely used

in toxicological studies. It can give the primary information on chemical species' relative abundances according to their thermodynamic kinetics and equilibria calculations (22).

Table 1
Total concentrations of ligands and free metal ions used in the saliva simulation models at 37°C, I = 0.15 M, and pH = 7.4

JESS ligand symbol	Ligand Concentration (M)	Metal ion symbol	Metal concentration (M)
$CO3^{2-}$	6.65E-03	Zn^{2+}	2.14E-06
Cl^{-}	2.89E-02	Ca^{2+}	1.74E-03
Cit^{3-}	5.37E-05	Mg^{2+}	4.74E-04
$PO4^{3-}$	3.68E-03	Cu^{2+}	1.62E-06
SCN^{-}	2.13E-03	K^{+}	2.05E-02
Cys^{2-}	1.00E-05	Na^{+}	1.03E-02
Tyr^{2-}	3.30E-05		
Ala^{-}	1.35E-04		
His^{-}	8.50E-05		
Histamine	1.57E-04		
$NH4^{+}$	2.63E-03		
Thr^{-}	2.52E-04		
Asc^{2-}	8.00E-06		
Asp^{2-}	1.10E-05		
Gly^{-}	1.40E-04		
Val^{-}	1.20E-04		
Ser^{-}	6.30E-05		
Pro^{-}	8.00E-05		
Arg^{-}	3.80E-04		

These are JESS species symbols input data, and not the species produced at equilibrium.

Table 2
Total concentrations of ligands and free metal ions used in the blood plasma simulation models at 37°C, I = 0.15 M, and pH = 7.4

JESS ligand symbol	Ligand Concentration (M)	Metal ion symbol	Ligand Concentration (M)
Cl^-	0.15	Ca^{2+}	1.14E-03
Na^+	0.14	Cd^{2+}	1.00E-15
K^+	0.004	Cu^{2+}	1.00E-18
$CO3^{2-}$	2.45E-02	Fe^{2+}	1.00E-23
SCN^-	1.40E-05	Pb^{2+}	1.00E-14
$NH4^+$	2.40E-05	Mg^{2+}	5.20E-04
$PO4^{3-}$	3.81E-04	Mn^{2+}	1.00E-12
$SiH2O4^{2-}$	1.38E-04	Ni^{2+}	1.00E-17
$SO4^{2-}$	2.11E-04	Zn^{2+}	1.00E-09
$2AmButan^-$	2.40E-05		
Ala^-	3.70E-04		
Arg	9.50E-05		
Asn^-	5.50E-05		
Asp^{2-}	5.00E-06		
Cis^{2-}	4.00E-05		
$Citric^{3-}$	1.13E-04		
$Citrul^-$	2.70E-05		
Cys^{2-}	2.30E-05		
Gln^-	5.21E-04		
Glu^{2-}	4.80E-05		
Gly^-	2.43E-04		
His^-	8.50E-05		

These are JESS species symbols input data, and not the species produced at equilibrium.

JESS ligand symbol	Ligand Concentration (M)	Metal ion symbol	Ligand Concentration (M)
Histamine	3.00E-08		
Hyp^{-}	7.00E-06		
Ile^{-}	6.50E-05		
$Lactic^{-}$	1.82E-03		
Leu^{-}	1.24E-04		
Lys^{-}	1.78E-04		
$Malic^{2-}$	3.50E-05		
Met^{-}	2.90E-05		
Orn^{-}	5.80E-05		
$Oxalic^{2-}$	1.20E-05		
Phe^{-}	6.40E-05		
Pro^{-}	2.11E-04		
$Pyruvic^{-}$	9.50E-05		
$Salicylic^{2-}$	5.00E-06		
Ser^{-}	1.22E-04		
$Succinic^{2-}$	4.20E-05		
Thr^{-}	1.50E-04		
Trp^{-}	1.00E-05		
Tyr^{2-}	5.80E-05		
Val^{-}	2.27E-04		
H^{+}_$Ascorbic^{2-}$	4.30E-05		

These are JESS species symbols input data, and not the species produced at equilibrium.

3. Results And Discussion

Based on these simulation models, the bioavailability levels of lead in biological fluids were dependent on the metal (lead) total concentrations, as indicated in the following.

Table 3

Net-neutral species of lead formed in the simulation models at total concentrations of 10^{-9}, 10^{-6}, and 10^{-3} mol/L at pH 7.4, and I = 0.15 M.

Total lead concentration	**10^{-9} mol/L**		**10^{-6} mol/L**		**10^{-3} mol/L**	
Net-neutral species	% bioavailability of net-neutral lead species in					
	Blood plasma	Saliva	Blood plasma	Saliva	Blood plasma	Saliva
$Pb^{2+}\_Cys^{2-}$	91	2	91	2	2	23
$Pb^{2+}\_CO3^{2-}$	2	0	2	0	74	0
$Pb^{2+}\_H^{+(2)}\_CO3^{2-(2)}$	0	0	0	0	2	0
TOTAL	**93**	**2**	**93**	**2**	**78**	**23**

There were high variations in the bioavailability levels of lead species formed on different concentrations of saliva and blood plasma at the same conditions. Lead species seem to be more bioavailable in blood plasma than saliva both at low, moderate, and high concentrations.

Figure 1 below shows bioavailability of lead remained unchanged at 93% in blood plasma when the total metal concentration increased from 10^{-9} to 10^{-6} mol/L while an abrupt decrease of bioavailability level was observed when the total concentration of lead increased further to 10^{-3} mol/L. On the other hand, there was poor bioavailability of lead in saliva at 2% even after the total metal concentration increased from 10^{-9} to 10^{-6} mol/L. Contrary to the bioavailability levels in blood plasma; there was a significant increase to 23% bioavailability level when the total metal concentration increased further to 10^{-3} mol/L in saliva.

Results of a similar trend were also reported in previous studies which concluded detection of high lead contents in blood plasma than saliva when comparison performed especially at low to moderate lead contents (8,11,13,16,26). The high bioavailability of lead in blood plasma may be contributed to the continuous release of stored lead from bones that may cause increased levels of lead in blood plasma than saliva (12). It has also been suggested that blood plasma lead (metal) as the most rapidly exchangeable form in the human circulatory system; may represent a more fraction of the toxicological index for lead exposure assessment (12). Lead seems poorly bioavailable in the saliva matrix, especially in a low level of exposure as previously reported in other studies (11,27). The poor bioavailability levels of lead at different concentrations in saliva may be resulting from the diffusible fraction component of

blood plasma lead than whole blood lead contents as there may be a different rate of diffusion at varying lead levels exposure (8).

Therefore, bioavailability data of lead in blood plasma seems a reliable indicator for biomonitoring of lead exposure as it can remain bioavailable even at low levels of lead. Previous studies (8,13,15,28) cautioned (discouraged) the use of saliva matrix as a suitable biomarker for diagnosing low to moderate lead exposures. However, lead seems moderately bioavailable in the saliva, especially when considering exposure to high levels, thus, the use of saliva as an alternative biomarker may need quantitative justification only after deep investigations to verify the correlation between blood plasma and saliva lead levels at the same conditions (10,29). Findings from this study, therefore, indicate blood plasma matrix as an efficient biomarker for diagnosis of lead exposure (poisoning) even at low levels which may still pose more toxic effects to humans.

4. Conclusions

The use of efficient biomarkers would provide vital scientific evidence when implementing biomonitoring of exposures from low-level hazardous materials. Blood plasma was found to be efficient and therefore, recommended as a suitable biomarker for use in biomonitoring of lead exposure both at low and moderate as well as high levels of lead exposure. Based on findings from this study, however, saliva may only be relatively used as a biomarker when assessing exposure to high levels of lead.

Whilst appreciate the results and conclusions drawn from this study based solely on the predicted thermodynamic behaviors and stability constants of the formed low molecular mass complexes, and the models were based on ‘average’ concentration input details; the reality may be slightly different in terms of the actual chemical species formed but should be broadly in line with the predictions from the JESS program.

As there are limited studies comparing the efficiency between the blood plasma and saliva when used as biomarkers at different metal concentrations, the author recommends further research on investigating actual blood plasma and saliva samples to determine the bioavailability levels of hazardous metals, hence establishing the reliable and efficient biomarkers to be used in biomonitoring of lead exposures (poisoning).

5. List Of Abbreviations

JESS=Joint Expert Speciation System

Mol/L=Molarity per Litre

6. Declarations

- **Ethics approval and consent to participate**

Not applicable as there was no human involvement in the study.

- **Consent for publication.**

Not applicable as there was no human involvement in the study.

- **Availability of data and materials.**

All data generated and analyzed during this study are included in this published article [and its supplementary information files].

- **Competing Interests.**

There is no conflict of interest to disclose.

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- **Author's contributions.**

I, the only author of this article, carried out all activities from conceptualization to finalization of this manuscript.

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Figures

Figure 1

Bioavailability levels of total net-neutral species of lead in blood plasma and saliva models at the total lead concentrations of 10^{-9}, 10^{-6}, and 10^{-3} mol/L at pH 7.4, and I=0.15 M.