Silver nanoparticles biokinetics study by mathematical modelling of the their transport in living organism

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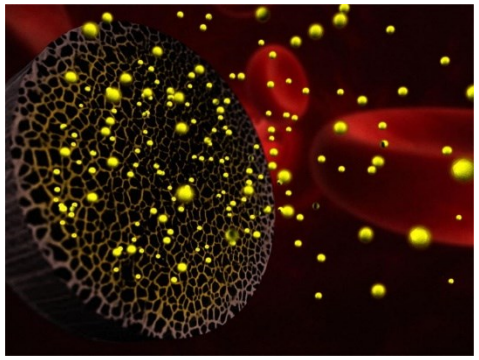
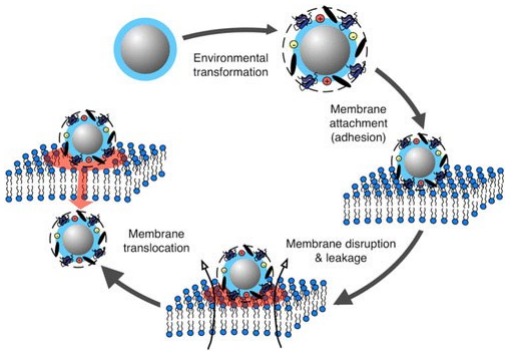
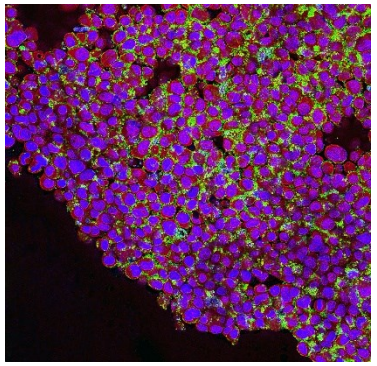
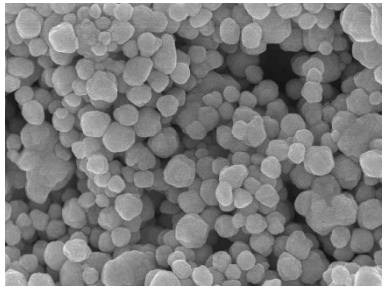






Nanotoxicity and Nanopharmaceutics Research: Aims and Problems



➢**Nanomaterials (NMs) and, more specifically, Nanoparticles (NPs) potentially have new, emergent properties and unknown impact on living organisms.**

➢**Most of nanotoxicity research is implemented on cells cultures *in vitro.***

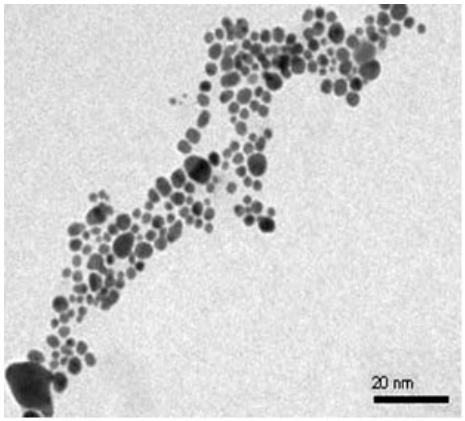
➢**The experimental investigation of NPs impact on living beings is expensive and limited in literature.**

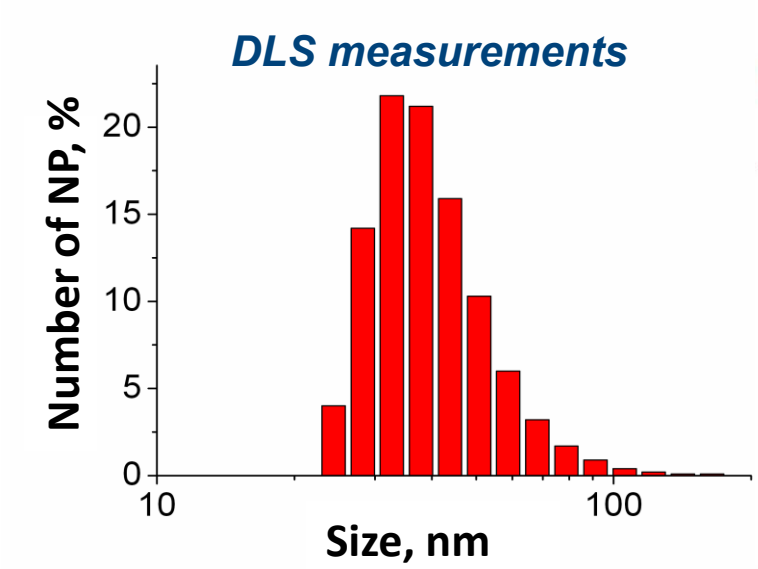
✓Alternative: to investigate the Adsorbtion, Distribution, Metabolism and Excretion (ADME) of NPs by mathematical modelling of their transport in living organisms due to building of NPs impact prognostic scenarios based on limited experimental data.

The purpose of current study

➢**The development and application of mathematical "chamber" model for adsorption, distribution and excretion of non-metabolizable NMs in the laboratory rat's organism on the example of silver NPs.**

Silver NPs: ARGOVIT-S™ (Biologically active food supplement; Russian production) – Ag NPs in PVP stabilizing shell with Average Diameter of 35±15 nm





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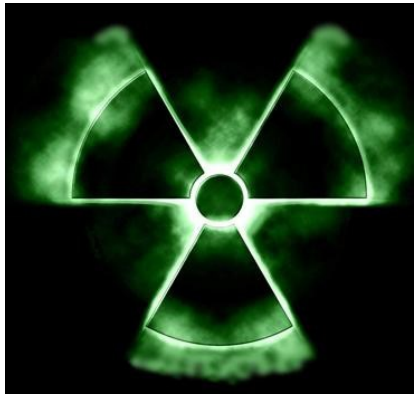
Experiment on rats with Ag NP acute insertion through the gastrointestinal tract

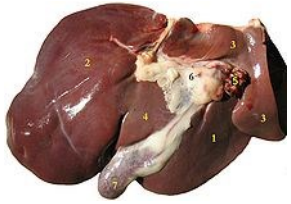
Ag NPs colloids

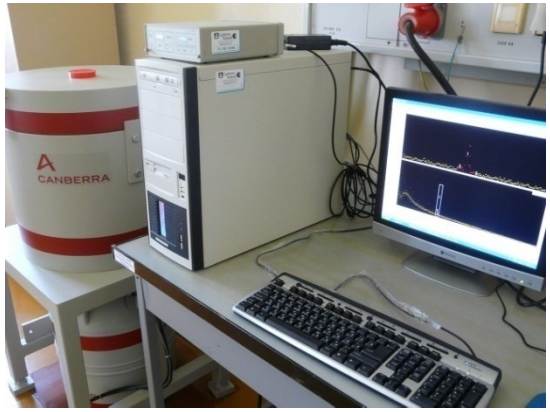
Activation by neutrons in nuclear reactor IR-8 (Kurchatov Institute): Ag → ^{110m}Ag



Insertion of radioactively labelled Ag NPs through a stomach pump into the rats' GIT

Organs and bioliquids removal at 24, 48 and 72 hours after NPs insertion





γ-radiation measurements of radioactively labelled Ag NPs in organs and bioliquids ⇒ Ag NPs content determination

Experimental results and specifications to the model

Organ / tissue / bioliquid*	Time after NP insertion, hours		
	24	48	72
GIT+feces (in total)	>98	>99	>99
GIT (calculated value [Pinna K. et al, J.Nutr., 2001])	65	6,2	0,2
Bone-muscular carcass	0,36±0,17	<0,6	0,23±0,09
Liver	0,60±0,18	0,8±0,3	0,18±0,10
Kidneys	0,014±0,002	0,029±0,008	0,007±0,003
Blood	0,13±0,05	0,20±0,05	0,05±0,02
Lungs	0,009±0,003	0,016±0,003	0,006±0,003
Heart	0,0042±0,0016	0,0060±0,0015	0,0032±0,0007
Pancreas	0,0079±0,0015	0,012±0,005	0,0039±0,0013
Spleen	0,05±0,02	0,06±0,03	0,010±0,004
Gonads	0,016±0,003	0,033±0,007	0,010±0,004
Brain	0,0029±0,0010	0,0123±0,0023	0,0053±0,0017
Urine (increasing total)	0,012±0,002	0,032±0,009	0,05±0,04

*Values are in % of inserted dose of Ag NPs

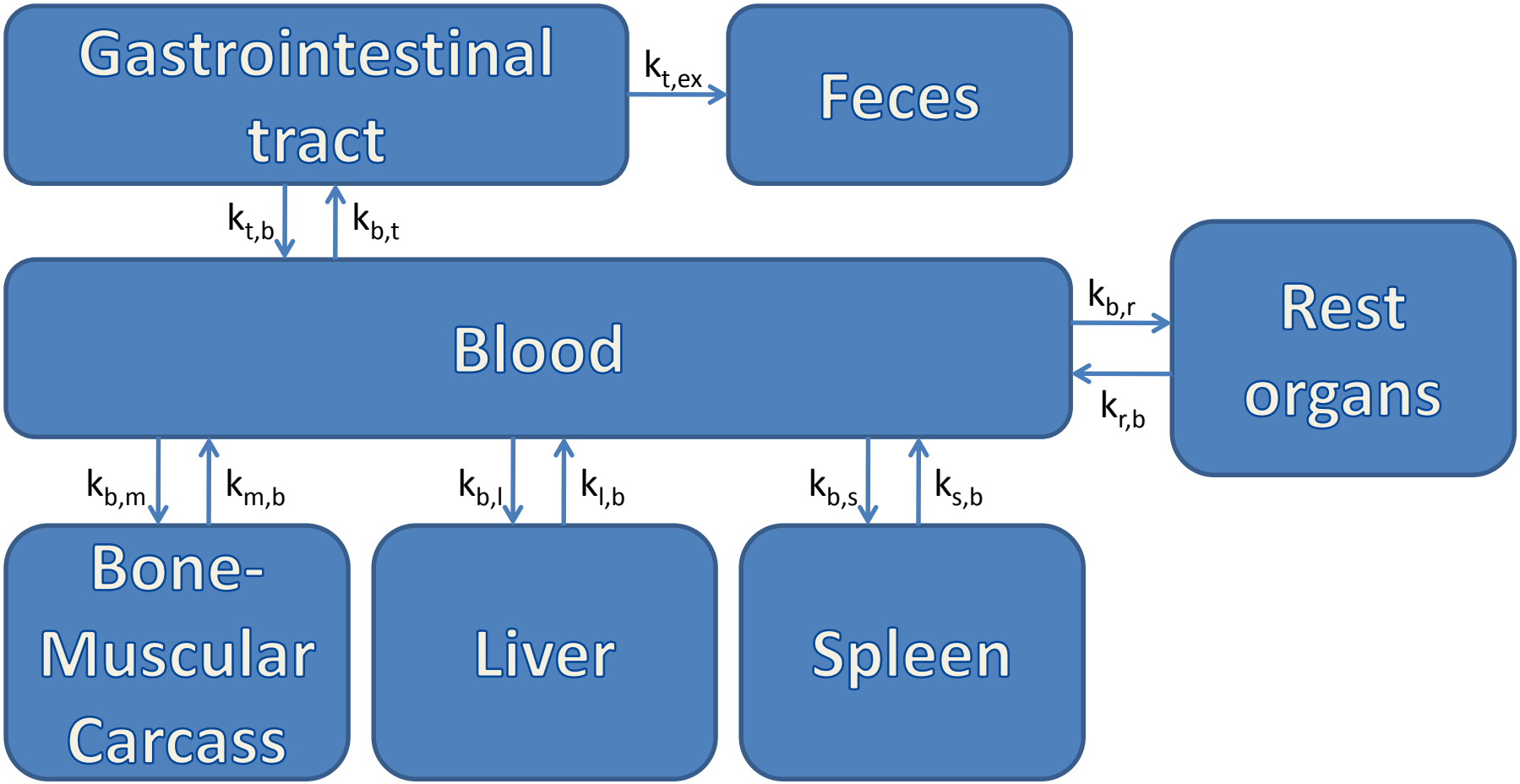
Specifications (simplifications) to the model:

✓Only those organs should be accounted for, the content of Ag NPs in which is not less than 20% of blood NPs content during the whole experiment.

Chambers for the model:

- Gastrointestinal tract
- Blood
- Bone-muscular carcass
- Liver
- Spleen

Chamber Model Scheme



Chamber Model System of Differential Equations

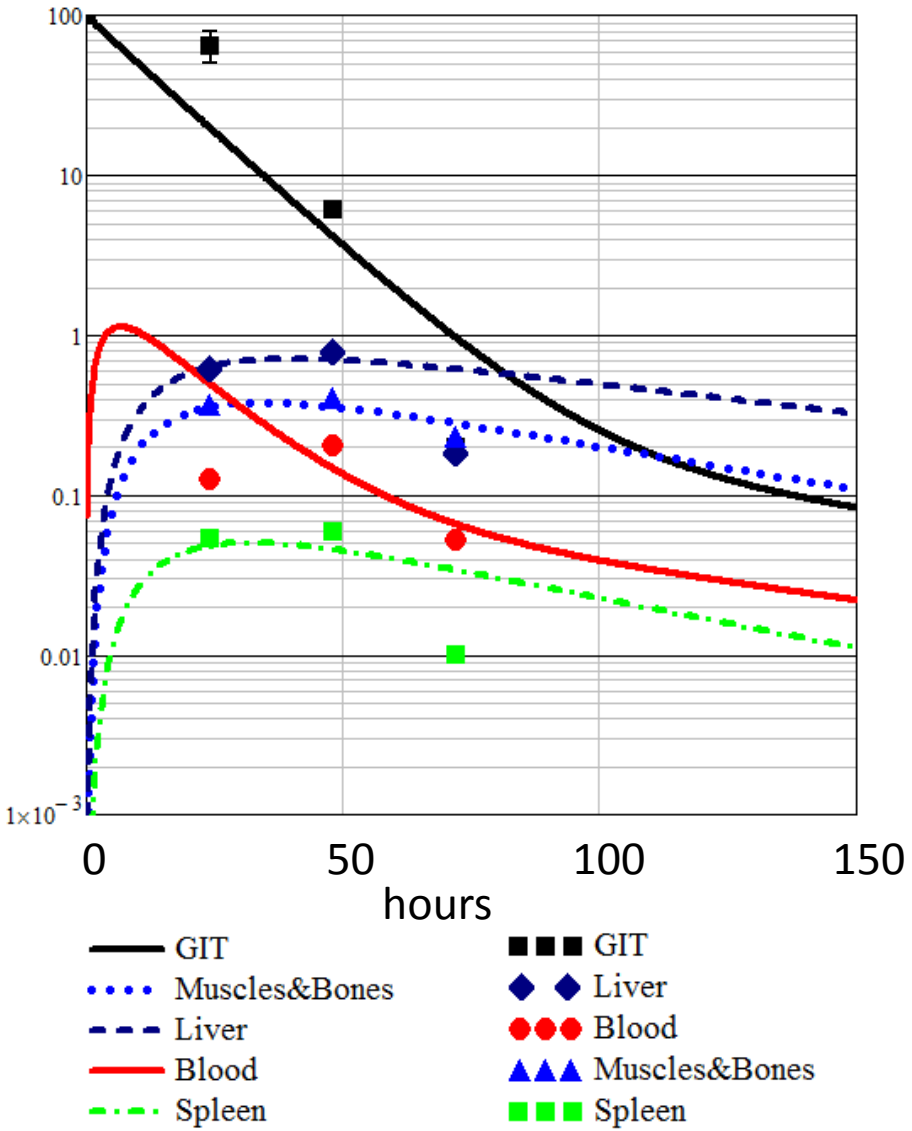
$$
\begin{cases}
\dfrac{dM_t}{dt} = -k_{t,b}M_t + k_{b,t}M_b - k_{t,ex}M_t, \\
\dfrac{dM_m}{dt} = -k_{m,b}M_m + k_{b,m}M_b, \\
\dfrac{dM_l}{dt} = -k_{l,b}M_l + k_{b,l}M_b, \\
\dfrac{dM_s}{dt} = -k_{s,b}M_s + k_{b,s}M_b, \\
\dfrac{dM_b}{dt} = k_{t,b}M_t + k_{m,b}M_m + k_{l,b}M_l + k_{s,b}M_s - \\
-\left(k_{b,t} + k_{b,m} + k_{b,l} + k_{b,s}\right)M_b + k_{r,b}M_r - k_{b,r}M_b, \\
\dfrac{dM_r}{dt} = -k_{r,b}M_r + k_{b,r}M_b,
\end{cases}
$$

where $M_t, M_m, M_l, M_s, M_b, M_r$ are the NPs mass or percentage contents in the GIT, bone-muscular carcass, liver, spleen, blood and rest organs.

According to the assumptions made above about the chambers that should be accounted for, we can suppose that $k_{b,r} \approx 0$.
Consequently, $M_r \approx 0$, and we can neglect by the 2 terms of the last but one of equation and by the last equation as a whole.

This system of 5 ODE cannot be solved analytically, so the numerical methods should be used, along with a fitting of the biokinetics parameters set such that solutions would approximate the experimental data minimizing some optimization (e.g. the error least square) functional.

Chamber Model Solutions



Results of biokinetics parameters fit:

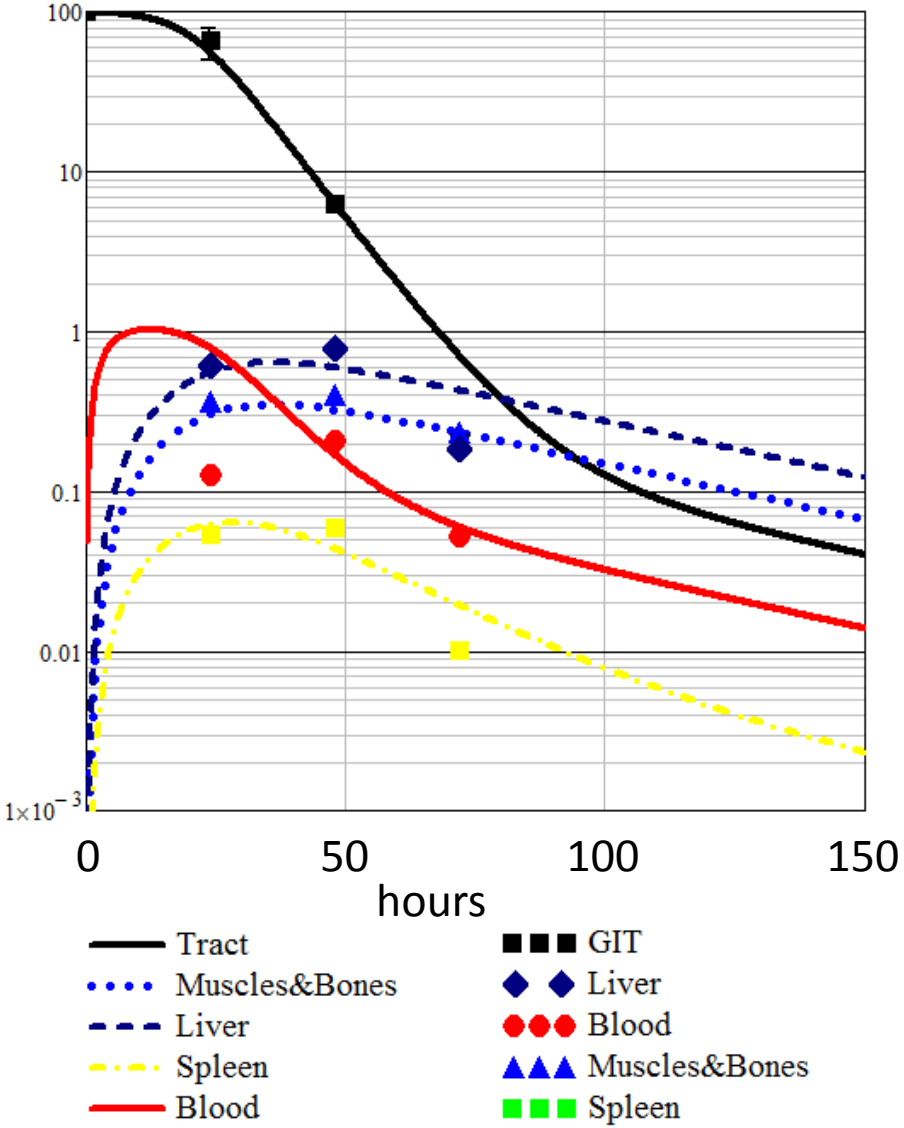
$$\begin{pmatrix} k_{t,b} & k_{b,t} \\ k_{m,b} & k_{b,m} \\ k_{l,b} & k_{b,l} \\ k_{s,b} & k_{b,s} \\ k_{t,ex} & 0 \end{pmatrix} = \begin{pmatrix} 1/200 & 1/4.5 \\ 1/60 & 1/45 \\ 1/90 & 1/45 \\ 1/90 & 1/27 \\ 1/15 & 0 \end{pmatrix} hour^{-1}$$

The model does not satisfactorily approximate the GIT biokinetcs ⇒

The physiological timing of NPs excretion from GIT shall be accounted for in the case of acute NPs insertion: digestion process lasts from 18 to 25 hours, so

$$k_{t,ex}(t) = k_{t,ex}^{(\infty)}\sigma(t) = \frac{k_{t,ex}^{(\infty)}}{1+\exp\left(-\frac{t-20}{5}\right)}.$$

Chamber Model Solutions



New results of biokinetics parameters fit:

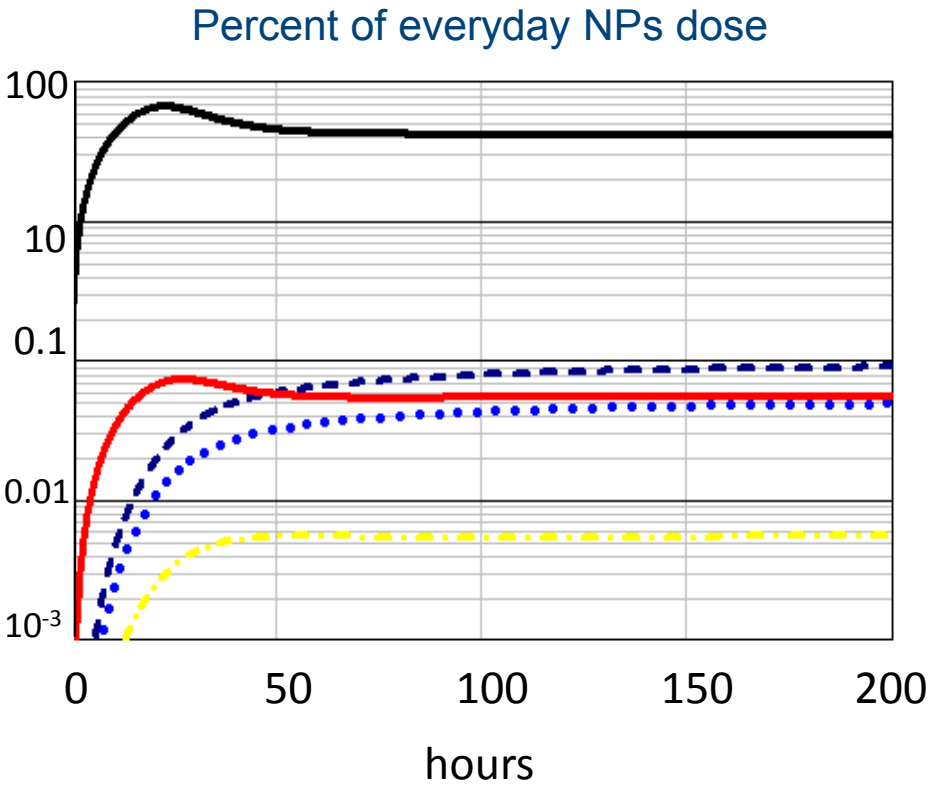
$$\begin{pmatrix} k_{t,b} & k_{b,t} \\ k_{m,b} & k_{b,m} \\ k_{l,b} & k_{b,l} \\ k_{s,b} & k_{b,s} \\ k_{t,ex}^{(\infty)} & 0 \end{pmatrix} = \begin{pmatrix} 1/300 & 1/4 \\ 1/50 & 1/55 \\ 1/50 & 1/30 \\ 1/20 & 1/200 \\ 1/10 & 0 \end{pmatrix} (hour^{-1})$$

$$k_{t,ex}(t) = k_{t,ex}^{(\infty)}\sigma(t) = \frac{k_{t,ex}^{(\infty)}}{1+\exp\left(-\frac{t-20}{5}\right)}.$$

The corrected model does satisfactorily approximate the GIT and other organs biokinetcs.

Chamber Model Prediction Capabilities

1. Stationary values of Ag NPs content in organs of rats reached under a sub-chronic nutrition can be evaluated.



$$\begin{pmatrix} M_t \\ M_m \\ M_l \\ M_s \\ M_b \end{pmatrix} = \frac{m}{k_{t,ex}} \frac{k_{t,b}}{k_{b,t}} \begin{pmatrix} k_{b,t}/k_{t,b} \\ k_{b,m}/k_{m,b} \\ k_{b,l}/k_{l,b} \\ k_{b,s}/k_{s,b} \\ 1 \end{pmatrix} = m[ng/day]* \begin{pmatrix} 417 \\ 5 \\ 9 \\ 0.4 \\ 5 \end{pmatrix} (ng)$$

where *m* is an everyday NPs dose in nanogramms.

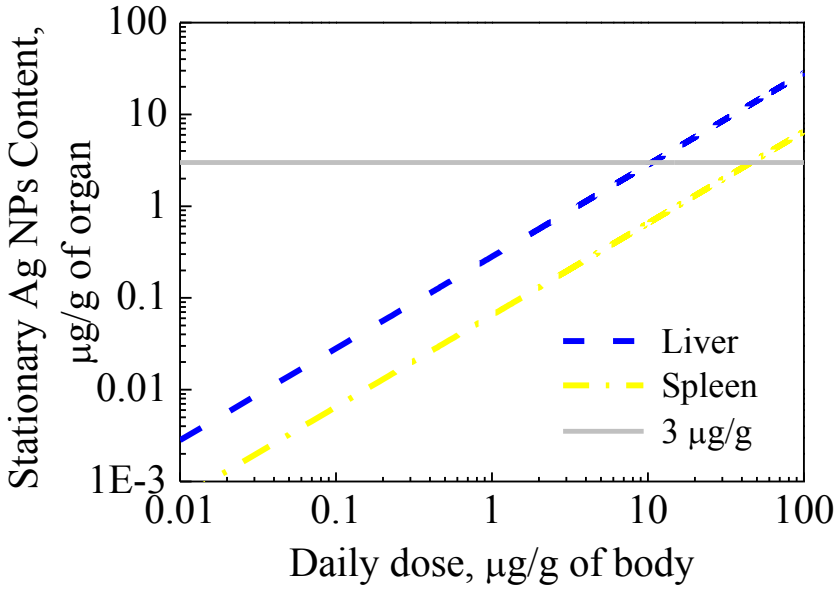
2. Maximum (peak) dose evaluation of Ag NPs content in organ (indexed "o") of rat, reached under the acute nutrition can be done.

$$M_{o,\max} = \frac{k_{b,o}}{k_{o,b}} M_b(t_{o,\max}) \le \frac{k_{b,o}}{k_{o,b}} M_{b,\max} \approx 0{,}011 \frac{k_{b,o}}{k_{o,b}} M_0,$$

Chamber Model Prediction Capabilities

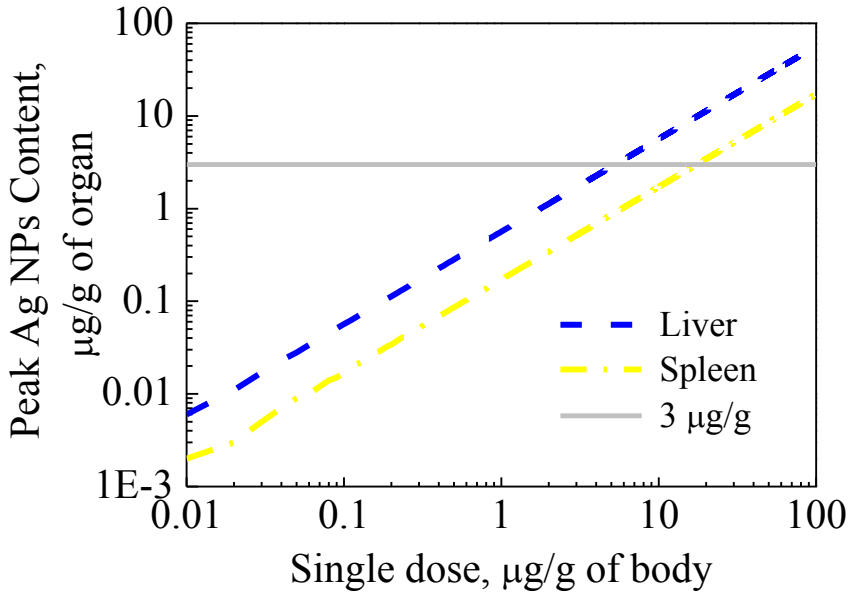
According to the most of literature sources [*Hussain S.M., et al.,* Toxicol. In vitro. 2005; *Arora S., et al.,* Toxicol. Appl. Pharmacol. 2009; *Haase A., et al.,* Toxicol. Sci. 2012; etc.**] any effects on cells cultures were observed at the Ag NPs concentration ≥ 3 μg/g.**

Sub-chronic nutrition of Ag NPs



Possible toxicity-emerging daily dose (for liver): 10.6 μg/g of body

Acute nutrition of Ag NPs



Possible toxicity-emerging daily dose (for liver): 5.3 μg/g of body

These results qualitatively correspond to the experiments on rats and mices with Ag NPs:

[*Kim Y.S., et al.,* Part. Fibre Toxicol. 2010; *Shumakova A.A.*, et al., Voprosy pitaniia 2011]

Conclusions and the nearest perspectives

✓**Chamber model of silver NPs transport in the organism of rat can be used to predict the possible time dependent mass content and the concentration of NM in different organs and tissues of animal, using for that only the limited experimental ADME data for acute intake of NPs.**

✓**Chamber model can establish the probabilistic connection between NPs exposition dose and toxic effects on tissues and organs under acute and sub-chronic insertion of NM, using for that all known *in vitro* and *in vivo* experimental data for hazardous effects. It is even possible to evaluate the NM impact on human health making a correction on different metabolism by methods of pre-clinical trial.**

✓**The development of the model should account for the minor ("rest") organs, in which the NPs content is negligible at the sub-chronic scale but can become determinative at chronic exposures and following excretion of NPs. Some of the such organs (like brain, heart, gonades) have the significant meaning for the whole organism and the possible NPs impact on them shall be analyzed.**

Thank you for attention!