EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

Letter of Intent to the ISOLDE and Neutron Time-of-Flight Committee

Metals in Medicine Project: Investigation of the Treatment of Leishmaniases with Antimony Containing Drug Compounds Using Perturbed Angular Correlation Spectroscopy with Parent Isotopes ^{116}Sb, ^{118}Sb, ^{120}Sb, (^{128}Sb), ^{130}Sb

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Abstract: Leishmaniasis is a parasitic disease which can be treated with the drug N-methylglucamine antimonate. Perturbed Angular Correlation studies can provide information of the antimony local structure within the biological environment. We hope to obtain more detailed information of the drug's mechanism. A set of parent antimony isotopes for Perturbed Angular Correlation is available.

Requested shifts: 3 shifts, flexible divisible

1 Introduction

Leishmaniasis is a parasitic disease transmitted by the bite of a certain species of the sandfly. Worldwide about 350 million people considered at risk of contracting leishmaniasis, and about 2 million new cases occur yearly. The Worlth Health Organization (WHO) is in process to establish control programs [1]. Till today there is no full healing possible and the treatment concentrates to enforce the immune system. Several drugs are available. The most commonly used one contains antimony as N-methylglucamine antimonate. The drug disturbs the parasite fatty acid and glycolysis metabolism. Died parasites stimulate the immune system. However, this drug is painful in the inoculation site and cardiotoxic. Improving the understanding of the mechanism of N-methylglucamine antimonate by investigating the local environment around the antimony in its biological environment with Perturbed Angular Correlation (PAC) using antimony PAC isotopes can provide important information which may enhance the medication or which gives information to increase its selectivity.

2 Leishmaniasis and Treatment

The parasite causing leishmaniasis undergoes a complex life cycle which is shown in detail by Figure 1. Leishmaniasis is transmitted by the bite of female phlebotomine sandflies. The sandflies inject the infective stage, metacyclic promastigotes, during blood meals (1). Metacyclic promastigotes that reach the puncture wound are phagocytized by macrophages (2) and transform into amastigotes (3). Amastigotes multiply in infected cells and affect different tissues, depending in part on which Leishmania species is involved (4). These differing tissue specificities cause the differing clinical manifestations of the various forms of leishmaniasis. Sandflies become infected during blood meals on infected hosts when they ingest macrophages infected with amastigotes (5,6). In the sandfly's midgut, the parasites differentiate into promastigotes (7), which multiply, differentiate into metacyclic promastigotes and migrate to the proboscis (8).
Leishmaniasis is caused by infection with the pathogen Leishmania. The genomes of three Leishmania species (L. major, L. infantum and L. braziliensis) have been sequenced and this has provided much information about the biology of the parasite. For example, in Leishmania, protein-coding genes are understood to be organized as large polycistronic units in a head-to-head or tail-to-tail manner; RNA polymerase II transcribes long polycistronic messages in the absence of defined RNA pol II promoters, and Leishmania has unique features with respect to the regulation of gene expression in response to changes in the environment. The new knowledge from these studies may help identify new targets for urgently needed drugs, and aid the development of vaccines [2].
Till today a full healing is not possible. The treatment concentrates to enforce the immune system. Several drugs are available. The most commonly used one contains antimony as N-methylglucamine antimonate, see Figure 2. The drug disturbs the parasite fatty acid and glycolysis metabolism. Died parasites stimulate the immune system. The treatment with N-methylglucamine antimonate has to be about 20 to 30 consecutive days and causes unpleasant and painful site effects.

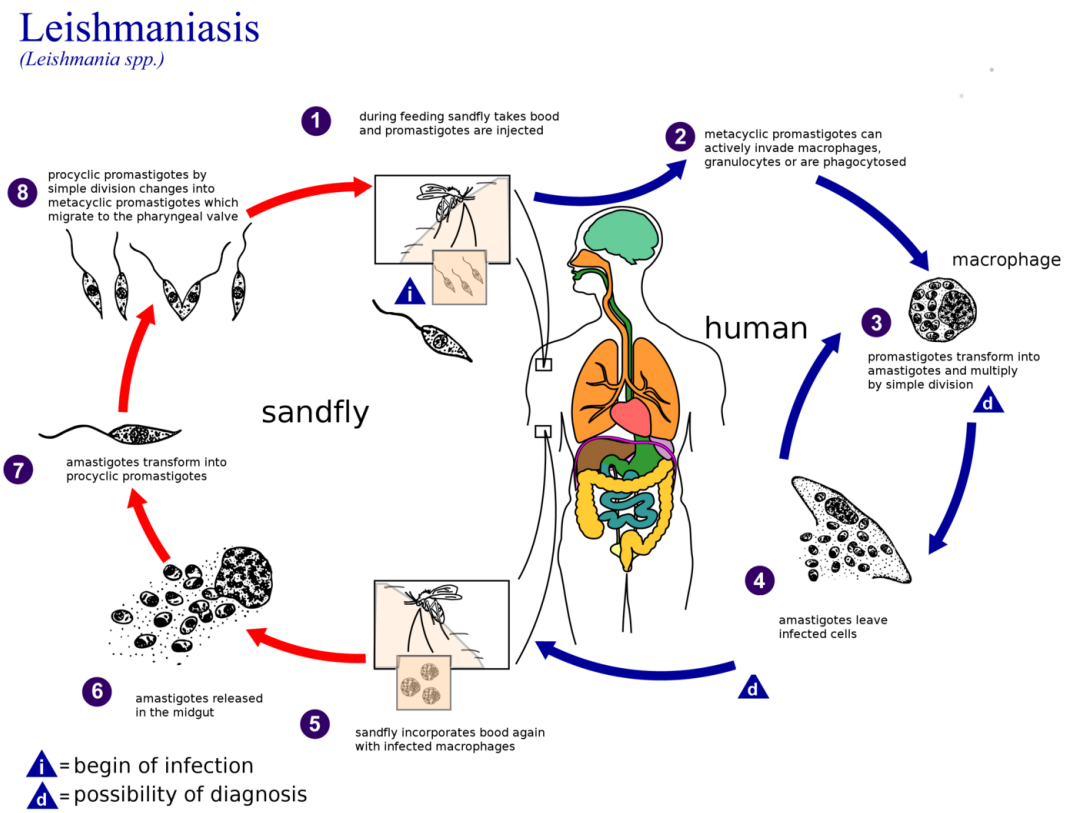

Figure 1: Life cycle of leishmaniasis parasite.

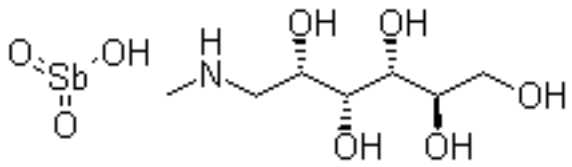

Figure 2: Structure of N-methylglucamine antimonate.

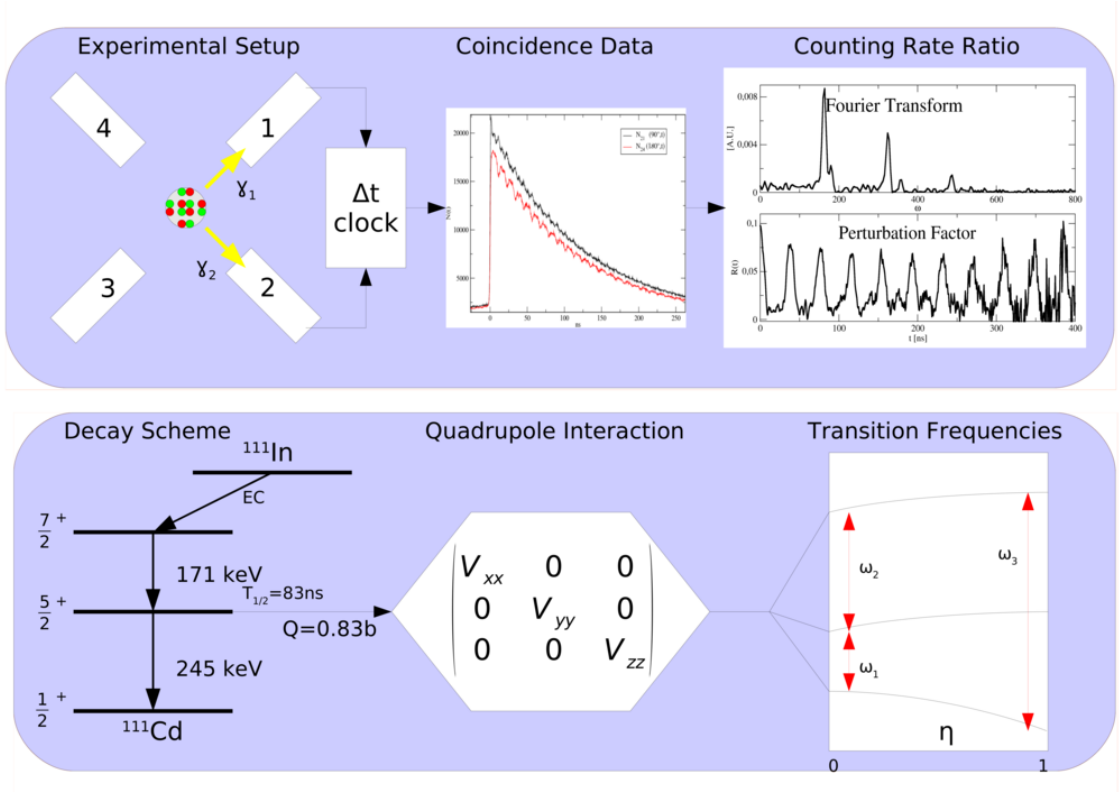

Figure 3: PAC Schema for example ^{111}In/^{111}Cd.

3 Experimental

One challenging advantage of PAC spectroscopy is the investigation of the local structure of probe atoms. A simple scheme of PAC is shown in Figure 3. Local electric fields or magnetism can provide important information about structural properties or their changes, which can be directly measured with PAC. While PAC is mainly used in condensed matter research, it has been shown to be a useful tool also in biological research [3, 4]. In biology the functional center of proteins contain metal ions which can be replaced by radioactive PAC isotopes. In the current case the drug N-methylglucamine antimonate has antimony as functional active part which disturbs the parasite fatty acid and glycolysis metabolism. We hope to obtain with PAC information about the stability or changes of the antimony of N-methylglucamine antimonate within the biological environment.
Fortunately, there are six different antimony PAC isotopes providing eight PAC sensitive levels as shown in Table 1. Decay schemes are shown in Figures 4 to 8. The large number of possible PAC isotopes provides an exceptional case for systematic studies with different time scales of the intermediate level, e.g. when dynamic effects occur in those cases when exchange rates play an important role in the biological processes. However, the half life of the parent isotope is short for ^{116}Sb and ^{130}Sb which requires a repetition of the experiment every 3-4 hours to obtain sufficient statistic for a PAC experiment. Whereas ^{128}Sb has a rather short half life of the intermediate state. However, PAC experiments on antimony isotopes are rare [5] which will require some measurement to test the usability.

Table 1: Antimony PAC Isotopes

I_{parent}	$I_{trans.}$	half life	start [keV]	rate [%]	stop [keV]	rate [%]	inter. [ns]	spin	Q [barn]
^{116}Sb	^{116}Sn	60.3 m	407	38.5	1072	25.5	348	5^-	-0.26
^{118}Sb	^{118}Sn	5.00 h	254	99	1050	97	21.7	5^-	0.16
^{118}Sb	^{118}Sn	5.00 h	984	1.5	254	99	230	7^-	0.32
^{120}Sb	^{120}Sn	5.76 d	197	87	90; 1023	80; 99.4	5.55	5^-	0.033
^{128}Sb	^{128}Te	9 h	814	13	527	45	2.4	7^-	
^{130}Sb	^{130}Te	6.3 m	1018	30	182	41	9.8	6^+	
^{130}Sb	^{130}Te	39.5 m	732; 935	22; 19	331	78	115	7^-	
^{130}Sb	^{130}Te	39.5 m	331	78	182	65	9.8	6^+	

First measurements will be therefore performed with the longer living ^{120}Sb/^{120}Sn and ^{118}Sb/^{118}Sn implanting into ice and exchange radioactive Sb and with Sb in N-methylglucamine antimonate. The measurement will probe N-methylglucamine antimonate in pure water. In a second step N-methylglucamine antimonate will be mixed with uninfected blood and isolated uninfected macrophages. In case of successful experiments, detailed experiments in a further proposal will follow with infected blood and macrophages samples. At security: Sample risk is low due to absence of disease vectorizing factors.
Using digital PAC will provide some advantages in the ^{118}Sb/^{118}Sn and ^{130}Sb/^{130}Te of the 39 m half life isotope, which have each two PAC sensitive levels with half lives of 21.7 ns and 230 ns for ^{118}Sn and 9.8 ns and 115 ns for ^{130}Te.
The ISOLDE yield database shows $6 \cdot 10^7$ ions/s for ^{114}Sb and $3.2 \cdot 10^9$ ions/s for ^{131}Sb.
The experiments do not require to be in one block. Especially the first experiments can be arranged during calibration of other experiments or use other experimental dead times as samples are only required one at a time.

4 Perspectives

Leishmaniasis is a parasitic disease which affects the life of millions of people in tropical and Mediterranean regions in the world. However the vectorizing sandfly is already also expanding new territory in south Europe due to climate changes. More understanding of the treatment mechanism using N-methylglucamine antimonate or other antimony compounds is still required.
With this study we want to examine the possibility using nuclear spectroscopy for medical research and we hope to improve the understanding of the mechanism of antimony containing drugs for leishmaniasis treatment using PAC spectroscopy that may result in new or better optimized drugs.
We hope, that this Metals in Medicine Project may be the start for a series of measurements in medical research publicizing perturbed angular correlation as a useful method.

Summary of requested shifts: 3, flexible divisible, standard UC_x target

References

[1] WHO Expert Committee: Ashford, R.; et al.: Control of the Leishmaniases, WHO Technical Report (2010), Series 949

[2] Myler, P.; Fasel Nhirf: Leishmania: After The Genome. Caister Academic Press (2008), ISBN 978-1-904455-28-8,978-1-904455-28-8

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[4] Chain, C.Y.; Ceolin, M.; Pasquevich, A.F.: PAC research in biology, Hyperfine Interactions 181 (2008), 99-106

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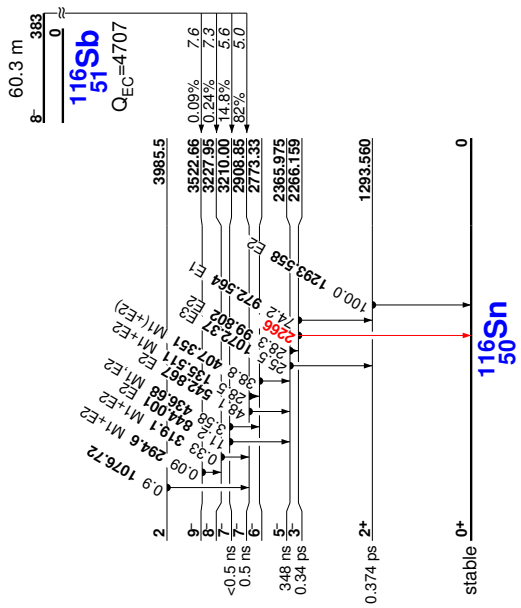

Figure 4: Decay Scheme of ^{116}Sn

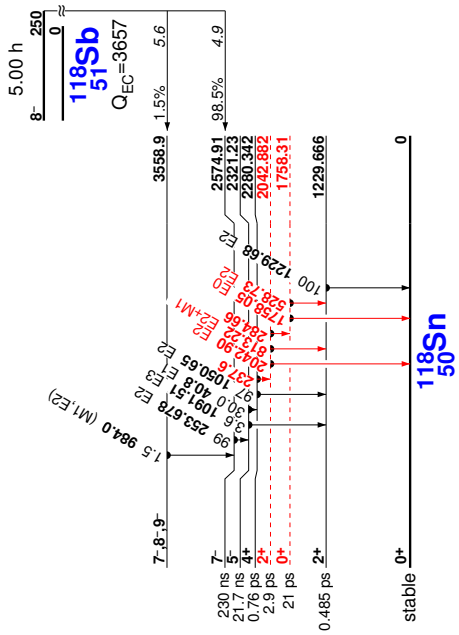

Figure 5: Decay Scheme of ^{118}Sn

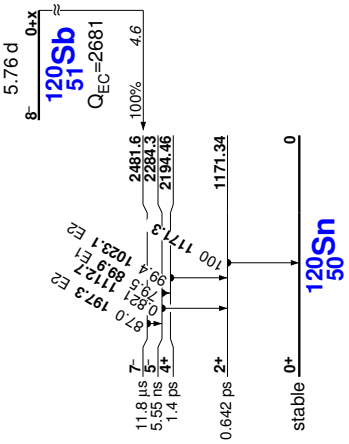

Figure 6: Decay Scheme of ^{120}Sn

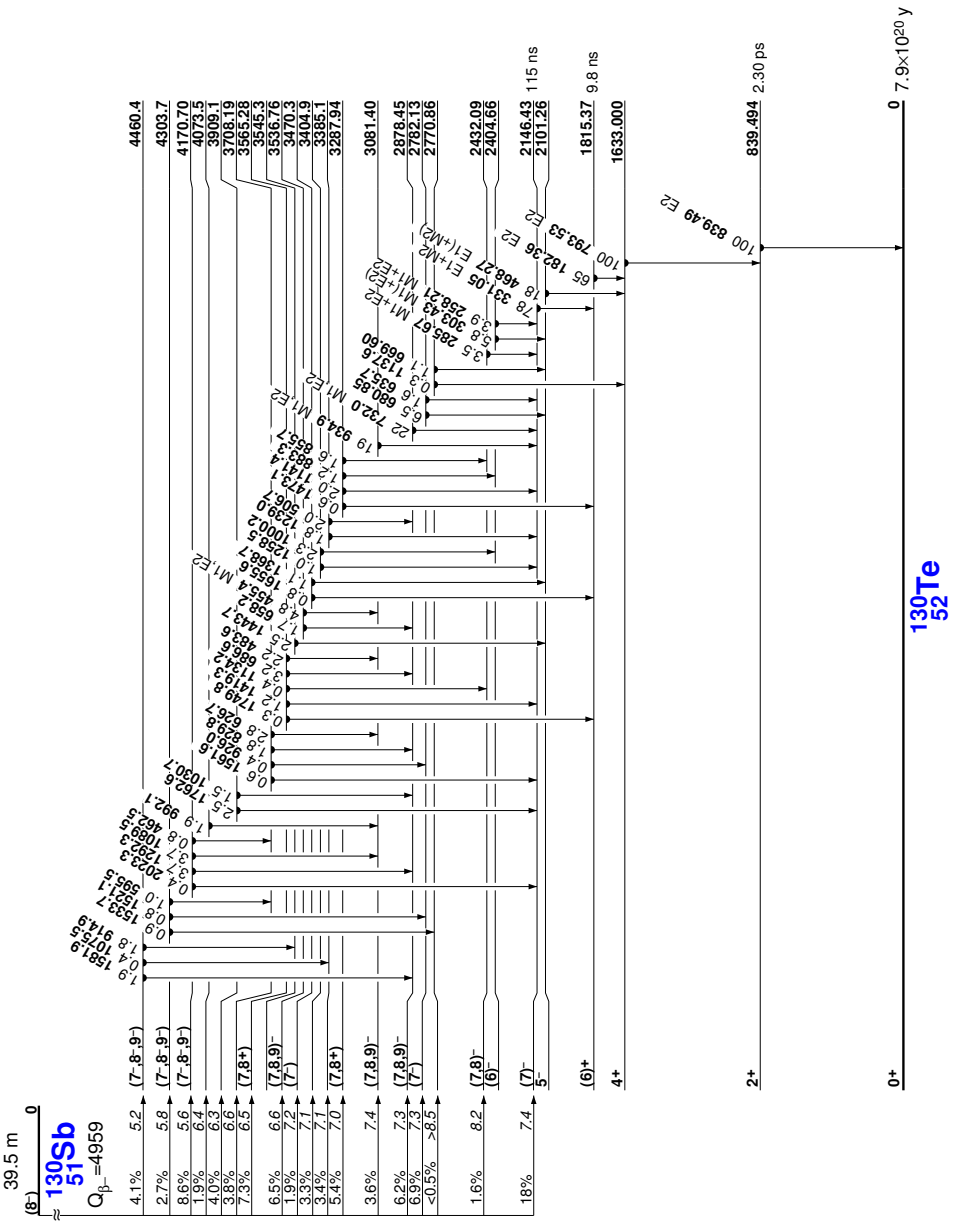

Figure 7: Decay Scheme of ^{130}Te

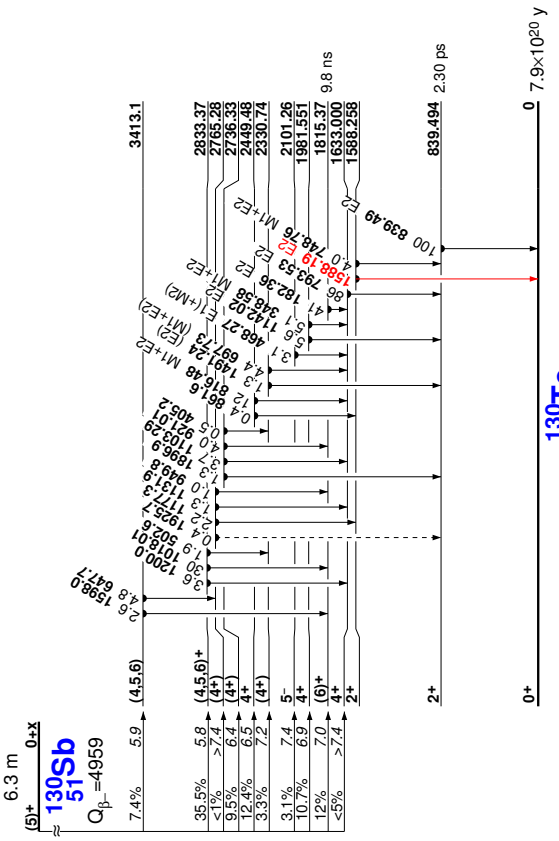

Figure 8: Decay Scheme of ^{130}Te

Appendix

DESCRIPTION OF THE PROPOSED EXPERIMENT

The experimental setup comprises: (*name the fixed-ISOLDE installations, as well as flexible elements of the experiment*)

Part of the	Availability	Design and manufacturing
SSP-GLM , SSP-GHM	☒ Existing	☒ To be used without any modification
[Part 1 of experiment/ equipment]	☐ Existing	☐ To be used without any modification ☐ To be modified
	☐ New	☐ Standard equipment supplied by a manufacturer ☐ CERN/collaboration responsible for the design and/or manufacturing
[Part 2 of experiment/ equipment]	☐ Existing	☐ To be used without any modification ☐ To be modified
	☐ New	☐ Standard equipment supplied by a manufacturer ☐ CERN/collaboration responsible for the design and/or manufacturing
[insert lines if needed]		

HAZARDS GENERATED BY THE EXPERIMENT (if using fixed installation:) Hazards named in the document relevant for the fixed [COLLAPS, CRIS, ISOLTRAP, MINIBALL + only CD, MINIBALL + T-REX, NICOLE, SSP-GLM chamber, SSP-GHM chamber, or WITCH] installation.

Additional hazards:

Hazards	[Part 1 of experiment/ equipment]	[Part 2 of experiment/ equipment]	[Part 3 of experiment/ equipment]
Thermodynamic and fluidic			
Pressure	[pressure][Bar], [volume][l]		
Vacuum			
Temperature	[temperature] [K]		
Heat transfer			
Thermal properties of materials			
Cryogenic fluid	[fluid], [pressure][Bar], [volume][l]		
Electrical and electromagnetic			
Electricity	[voltage] [V], [current][A]		
Static electricity			
Magnetic field	[magnetic field] [T]		

Batteries	☐		
Capacitors	☐		
Ionizing radiation			
Target material [material]			
Beam particle type (e, p, ions, etc)			
Beam intensity			
Beam energy			
Cooling liquids	[liquid]		
Gases	[gas]		
Calibration sources:	☐		
• Open source	☒		
• Sealed source	☐ [ISO standard]		
• Isotope			
• Number of atoms			
• Activity			
Use of activated material:			
• Description	☐		
• Dose rate on contact and in 10 cm distance	[dose][mSV]		
• Isotope			
• Activity			
Non-ionizing radiation			
Laser			
UV light			
Microwaves (300MHz-30 GHz)			
Radiofrequency (1-300 MHz)			
Chemical			
Toxic	[chemical agent], [quantity]		
Harmful	[chem. agent], [quant.]		
CMR (carcinogens, mutagens and substances toxic to reproduction)	[chem. agent], [quant.]		
Corrosive	[chem. agent], [quant.]		
Irritant	[chem. agent], [quant.]		
Flammable	[chem. agent], [quant.]		
Oxidizing	[chem. agent], [quant.]		
Explosiveness	[chem. agent], [quant.]		
Asphyxiant	[chem. agent], [quant.]		

Dangerous for the environment	[chem. agent], [quant.]		
Mechanical			
Physical impact or mechanical energy (moving parts)	[location]		
Mechanical properties (Sharp, rough, slippery)	[location]		
Vibration	[location]		
Vehicles and Means of Transport	[location]		
Noise			
Frequency	[frequency],[Hz]		
Intensity			
Physical			
Confined spaces	[location]		
High workplaces	[location]		
Access to high workplaces	[location]		
Obstructions in passageways	[location]		
Manual handling	[location]		
Poor ergonomics	[location]		

Hazard identification:

Average electrical power requirements (excluding fixed ISOLDE-installation mentioned above): [make a rough estimate of the total power consumption of the additional equipment used in the experiment]