Application for granting new Exemption: Lead acetate marker for use in stereotactic head-frames for use with CT and MRI and in positioning systems for gamma beam and particle therapy equipment

1. Name and address of applicant

COCIR : European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry
Blvd A. Reyers 80
1020 Brussels
Contact: Mr. Riccardo Corridori
Tel: 027068966
corridori@cocir.org

2. Summary of the application

This exemption request is to allow the use of lead compounds as a marker for the precise location of small features such as tumours, particularly in patients' bodies and heads. The marker is used in a frame and must be clearly visible by both CT and MRI and no alternative substances or designs exist that provide the characteristics of lead acetate. The substance must contain a dense heavy metal that is opaque to X-rays, which eliminates metals lighter than tantalum and tungsten. The material must also emit a strong MR signal and this eliminates the use of those metals that are soluble only in acid solution and those whose compounds are incompatible with glycol solvents. Several of the potential alternative heavy metals are more hazardous than lead and so are not suitable.

3. Description of materials and equipment for which the exemption is required

The precise location of features within patients' heads and bodies is very important particularly for treatment of tumours by radiation therapy and also for brain surgery. Tumours can be destroyed by radiation using x-ray, gamma ray and particle beams for example using linear accelerators or a "gamma knife" which focuses many low dose radiation beams from cobalt 60 isotope onto the tumour usually within the head. These techniques are able to deliver radiation very precisely so that the tumour is destroyed with a minimal amount of surrounding healthy tissue affected. Radiation damage to healthy tissue can lead to other health problems including more cancerous tumours. Modern technology allows the radiation beam shape to be precisely matched to the shape of the tumour and the beam can be positioned to better than 1 mm accuracy. It is essential therefore that the position of the tumour is known with very high precision to ensure that the radiation beam is focused precisely onto the tumour.

Research has shown that the locations of tumours, etc. can be marked much more accurately by combining CT and MRI images. CT gives very good spatial resolution but is poor for imaging soft tissues. MRI is very good for imaging soft tissue and tumours but images can be distorted[1]. The marker therefore must be clearly visible at exactly the same position by both CT and MRI.

Stereotactic head-frames are used for precise brain tumour location and also for neurosurgery, such as for implanting electrodes at precise locations. Two methods of marking are used; frameless and frame marking.

Frameless marking uses adhesive pads that contain hydrogels as an MRI marker and may also contain barium sulphate as an x-ray marker. The hydrogel is inside the pad and the barium sulphate is in the external layer such that the positions seen by CT and MRI are close but not exactly identical. Adhesive pads attached to the body can move slightly in relation to the tumour and so the tumour location is not marked as accurately as with frame markers. Frameless markers may not be visible to hospital staff when the patient is being positioned for radiotherapy whereas head and body frames will be visible and allow tumours, previously located by MRI/CT, to be positioned very accurately inside the radiotherapy equipment.

Head-frames and body frames are rigid structures that contain a lead acetate glycol solution as a very clear marker for both CT and MRI. This solution is sensitive to both CT and MRI and so clearly shows exactly the same location in the combined results. Head-frames and body-frames are clamped tightly onto the head or body so that no movement can occur. This may be uncomfortable for the patient but allows more accurate marking of the location of tumours than by frameless markers. The use of lead acetate solution in head or body-frames allows the most accurate marking of tumours and other features so that radiation therapy has the least harmful side-effects.

This marker must contain a high atomic mass element such as lead and so be opaque to X-rays as well as a substance that is easily visible by MRI but not be adversely affected by the MRI (i.e. must be non-magnetic so not a magnetic metal). MRI is sensitive to hydrogen atoms in molecules such as water, fats and organic materials within the human body. Hydrogen atoms in different states behave differently in MRI scanners depending on what they are bonded to. For example, hydrogen attached to water behaves differently to hydrogen ions formed in strongly acid solution. This behaviour affects the frequency of the signal and the signal intensity so that acid hydrogen ion (H^+) signals are relatively

[1] J. N. H. Brunt, "Computed Tomography – Magnetic resonance image registration in radiotherapy treatment planning" Clinical Oncology, vol 22 (8), p 688 http://www.sciencedirect.com/science/article/pii/S0936655510002244

weak and occur at higher frequencies whereas hydrogen bonded to oxygen in hydroxyl groups is much stronger and occurs at lower frequency. Signal strength is very important for MRI markers as they have to be visible against a background of hydrogen bonded to a variety of molecules within the human body. The MRI marker therefore contains substances with hydrogen atoms that give strong signals such as glycols and acetates.

Markers to identify positions for both CT and MRI use a solution that contains a soluble and stable lead compound because lead is very opaque to X-rays. This is dissolved in a mixture of both water and 1,2-propane diol (propylene glycol) which can clearly be seen by MRI due to the hydrogen atoms in the hydroxyl groups. The diol has two hydroxyl groups per molecule. Acetate ions have hydrogen atoms in the methyl group which are also MRI sensitive. Lead is clearly visible by CT as it is a heavy and dense metal and so this solution can be seen by both MRI and CT to mark positions. Water solutions are less effective than polyols as there is also water in the human body and so water is not a good marker as it cannot easily be differentiated from water present in the human body.

No alternative combinations of substances have been identified that are suitable. High atomic mass and high density metals and their compounds would be suitable as CT markers but most cannot be used in MRI as explained below. Metals and most of their compounds are invisible to MRI (only hydrogen is visible) and some metals become very hot under the influence of the radio-frequency radiation. Magnetic materials cannot be used as they distort the MRI image. Water / glycol mixtures are good markers for MRI but are completely invisible by CT. Some high density heavy metal compounds are ideal for CT imaging and do not interfere detrimentally with the MRI but the choice of these compounds that are sufficiently soluble and stable in suitable solvents such as glycols that have high hydroxyl group content (i.e. highly polar) and also do not decompose in the MRI is very limited. Soluble lead acetate dissolved in water / glycol mixtures has been found to be the only choice.

Lead acetate is the preferred lead salt because it is stable, it has a high solubility in water and more importantly in glycol solutions. The lead concentration in these solutions is sufficiently high for clear marking of X-ray and CT images.

4. Justification for exemption – Article 5 criteria

The justification for this exemption is that there are no substitute materials or designs that are opaque to X-rays, readily visible by MRI and are not more hazardous than lead acetate. Markers located within head-frames and body-frames give the best precision which allows radiation treatment of tumours to be used with minimal damage to surrounding healthy tissue.

Some alternative heavy metals are very toxic, such as mercury and thallium and so would be unsuitable.

Some heavy metals have compounds that are soluble only in strongly acidic solution which poses a risk to patients if a leak were to occur. Acidic solutions are not suitable for MRI as they have extremely low hydroxyl ion concentrations and high hydrogen ion concentrations due to the equilibrium:

$$H^+ + OH^- = H_2O$$

The equilibrium constant $k = \frac{[H^+][OH^-]}{[H_2O]}$

Therefore in acid solution at equilibrium, the H^+ concentration is high and gives a weak signal whereas the OH^- concentration is low. Water itself cannot easily be distinguished from water in the human body and acid is even less visible as the signal strength of H^+ is weak and so compounds that are soluble only in acid solution are unsuitable.

Some heavy metals are extremely rare and so their health risks have not been fully investigated and so may pose a risk to health. One potential candidate is compounds of tungsten but the only water soluble salt is sodium tungstate which is a moderate oxidising agent and so will chemically react with glycol causing it to decompose and so this combination cannot be used.

5. Analysis of possible alternatives

Three options are considered here, implanted gold markers, framed markers and frameless markers.

5.1. Gold markers.

In the past, small gold markers were surgically implanted into the body as CT markers. There is always a risk from surgery and gold is invisible to MRI which is more useful for locating the tumour and so this is no longer used.

5.2. Frameless markers

Frameless markers are circular adhesive pads that are attached to the patient's head or body[2]. These consist of an outer layer of polymer that can be filled with barium sulphate which is fairly opaque to x-rays, inside this layer is a cavity filled with a hydrogel that containing bound water which is visible to MRI[3]. These pads are easy to use and give reasonably accurate location of features such as tumours and other medical conditions. The opacity of parts of the human body varies with bones being the most opaque and some organs such as the brain

---

[2] For example available from IZI Corporation
http://www.izimed.com/catalog.shtml?&Vl=6&Tp=2

[3] US Patent US 5469847 IZI Corporation

being more opaque than soft tissues. Plastics alone cannot easily be differentiated from internal organs as their opacity is similar and they are less opaque than bone. Barium sulphate is used as the X-ray marker because it is an inert powder that can be used as a filler in the polymer material although lead sulphate could also be used and would give better opacity so that the contrast between a lead sulphate marker and bone (e.g. the skull) is much clearer than between a barium sulphate marker and bone.

The clarity of a marker depends on the contrast between the marker and the other materials in view. The X-ray opacity of a thin layer of polymer with added barium sulphate is significantly less than is achieved by the much denser and higher atomic mass heavy metals such as lead and so when viewed against bone, this would give less precise marking than if lead were used as the marker because lead will give a clearer image with better contrast, especially when viewed against bone.

MRI visibility also varies with fats, muscle and each organ behaving differently. There are several specialist techniques used to optimise visibility of certain organs or features such as tumours. The ability to "see" hydrogel" markers therefore varied depending on what is being viewed and which technique is used.

Another limitation of frameless markers when they are attached to the skin is that they can move in relation to a tumour or other feature. Frameless markers are reported to be inherently less accurate than frame-based markers[4]. The adhesive pad markers can be attached to frames when their disadvantage is inferior contrast to lead acetate markers.

Frameless markers are used mainly for neurosurgery with an optical tracking system to determine their position. For radiotherapy treatment, the known co-ordinates of the frame are used to very accurately locate the position of a tumour, that had previously been located by MRI/CT, without the need to use other external devices.

5.3. Framed-based markers

There is a limited choice of alternative metal compounds that can be dissolved in polar solvents for embedding into body-frames and head-frames and even fewer of these metals have stable and glycol soluble acetate salts:

High atomic mass metals include: bismuth, precious metals such as gold and platinum and tungsten salts which are either soluble only in strongly acidic solution (therefore very low hydroxyl ion content) or do not dissolve in glycol

[4] L. F. Macksey "Surgical Procedures and Anesthetic implications" Jones & Bartlett Leaning, USA, ISBN 978-0-7637-9 see page 350

solutions without decomposition. Mercury and thallium are more toxic than lead and so are unsuitable. Elements lighter than tantalum and tungsten are not sufficiently opaque to X-rays due to their lower atomic mass and lower density. There are no alternative non-radioactive heavy metals other than those listed below in table 1.

Table 1. Solubility and stability of heavy metal compounds

Metal	Atomic mass (lead is 207)	Properties
Caesium	133	Metal density is only 1.9 compared to lead at 11.4g/ cm^3 and so caesium is much less effective at adsorbing x-radiation. Its acetate is only slightly soluble in glycols
Barium	137	Metal density is only 3.5 compared to lead at 11.4g/ cm^3 and so barium is much less effective at adsorbing x-radiation. Its acetate is only slightly soluble in glycols
Lanthanum (and the lanthanides)	139	Lanthanum's density is 6.2 compared to lead at 11.4g/cm^3 and so lanthanum is less effective at adsorbing x-radiation. All lanthanide compounds have too low solubility in glycols and so are unsuitable
Hafnium	178	Acetate cannot be made, hafnium salts soluble only in strong acid
Tantalum	181	Tantalum has a density of 16.6 g. /cm^3 but tantalum salts are soluble only in strong acid solution and no acetates exist.
Tungsten	184	Tungstate salts are soluble in alkali solution but is a moderately strong oxidising agent so is likely to cause diols to decompose and so is unsuitable
Rhenium	186	Very rare metal whose toxicity is not fully understood. Sodium perrhenate is very soluble in water but has a very low solubility in ethanol. Solubility in glycol not published but likely to be lower than in ethanol. Perrhenates are strong oxidising agents and so could cause glycol decomposition.
Osmium	190	Stable osmium salts are soluble with excess alkali but there is a risk of formation of very toxic osmium tetroxide (this is a dangerous volatile liquid). Osmium is a very rare metal
Iridium	192	Sodium hexachloroiridate is water soluble. This is stable in acidic and neutral solution but may precipitate or decompose with reducing agents. Most other compounds are either insoluble or unstable. Very rare metal whose toxicity is poorly understood
Platinum	195	Most compounds are insoluble in water, some only in very acidic solution. Sodium chloroplatinate is soluble in water and in alcohol.
Gold	197	Very toxic cyanide complexes are water soluble and sodium chloroaurate are soluble in water and alcohol
Mercury	201	More toxic than lead (see below)

Thallium	204	More toxic than lead (see below)
Lead	**207**	**Ideal X-ray and CT marker**
Bismuth	209	Only stable in highly acidic solutions
Uranium	238	All elements heavier than bismuth are radioactive

The table above lists a few water or alcohol soluble compounds of heavy metals. Compounds that are more toxic than lead acetate are clearly not suitable.

- Lead, mercury and thallium acetates are toxic and are compared below.
- All osmium compounds are dangerous because of the risk that they will form osmium tetroxide which is an unusual substance in that it is a fairly volatile liquid which is extremely toxic and can cause blindness if it comes into contact with the eyeball, where it decomposes to deposit a layer of osmium dioxide that cannot easily be removed.

Substance	LD50	Solubility
Lead acetate	Ipr-rat = 150 mg/kg	Soluble in water and glycols
Mercury acetate	Oral-rat = 41 mg/kg	Soluble in alcohol but not in water
Thallium acetate	Ipr-rat = 30 mg/kg	Soluble in water

- LD50 = minimum lethal dose resulting in 50% of rat deaths
- Ipr-rat = substance administered to rat via peritoneum (abdomen)
- Oral-rat = substance administered orally to rat

No LD50 values for lead acetate or Ipr-rat for mercury acetate are published but these figures confirm that mercury and thallium compounds are significantly more harmful than lead compounds and so are not suitable as substitutes on a human health basis. Mercury and thallium acetates also have too low solubility in glycols.

Of the non-toxic potential substitute metals, very few have stable soluble acetate salts which are needed as MRI / CT markers. Of the metals listed in table 1, very few have stable and high solubility acetate salts as follows:

- **Caesium, barium** and **lanthanum** acetates can be made but these metals are much less opaque to x-rays than lead. Acetate solubility in glycols will be too low.
- **Hafnium, tantalum, tungsten** and **osmium** do not form water or glycol soluble, stable acetate salts.
- **Platinum** acetate exists but is not available commercially and is relatively unstable. Platinum acetylacetonate is relatively soluble in some organic solvents but only slightly soluble in alcohol and insoluble in water; it is also thermally unstable. Platinum acetate and acetylacetonates are not typical "salts" but are "coordination complexes" and so will behave in MRI differently to lead acetate.
- **Iridium** acetate is commercially available and is moderately soluble in water and protic solvents such as alcohols. Two suppliers have been

identified (Heraeus and Daiken Chem, Japan) that ell iridium acetate solution but this has only 8% iridium which is too dilute for CT marking.

- **Rhenium acetate** - No suppliers could be identified and it may not exist as a stable compound
- **Gold** acetate exists but has very low water solubility and so is not suitable for CT marking. It is also unlikely to be soluble in alcohol or glycols although there is no quantitative data published.
- **Mercury** acetate is soluble only in alcohol as it decomposes to insoluble compounds in water
- **Thallium** acetate is soluble in water but there is no data on glycol solubility

Other essential characteristics include:

- Metals with lower atomic mass than tantalum and tungsten also have lower density than lead and so are significantly less opaque to X-rays.
- The marker solution must be non-hazardous and pH neutral or slightly alkali in order to have high hydroxyl ion concentrations. Metals whose compounds are soluble only in acid solution are unsuitable as hydrogen ions give weak. MRI signals.
- It is important that the heavy metal compounds have high solubility because solids dispersed in liquids will usually separate and can move to different regions within the device so that the solid metal compound and the polar solvent could indicate different locations by CT and MRI.
- Solutions must have relatively high concentrations of metals to be opaque to X-rays. Many of the high atomic mass metals can be converted into "complex salts" but these are usually, either insoluble or are only soluble at such low concentrations as to be ineffective.

Several other types of markers are described in publications. Gadolinium compounds are used as MRI markers that can be injected into the bloodstream to enable vessels and arteries to be viewed. These could also be used as CT/MRI markers but their x-ray contrast is inferior as shown in table 1. Copper wire and copper sulphate pentahydrate are also described where copper is opaque to X-ray and the hydration water of the sulphate is MRI-visible. Copper however has a far lower atomic mass (63.5) than lead (207) and so has poor contrast when viewed against bone which is calcium based (atomic mass 40).

6. Life cycle assessment

6.1. Extraction and refining

Although there are no alternative substances or designs available that can replace lead for this application, the other non-toxic heavy metals have been compared

Abundance of elements is one consideration:

- Tungsten has a higher abundance than lead but occurs at lower concentrations in ores and is more difficult to extract (it is also unsuitable as a substitute).
- Rhenium, osmium and iridium have an abundance of one fifth that of gold and so are available in only very limited amounts.
- Platinum and gold are relatively rare metals although widely available.

Element	Symbol	Abundance in earths crust (ppm)
Lead	Pb	14
Tantalum	Ta	2
Tungsten	W	~70 - 100
Rhenium	Re	0.0007 – 0.0026
Osmium	Os	0.0015
Iridium	Ir	0.0004 – 0.001
Platinum	Pt	0.004 – 0.005
Gold	Au	0.003 – 0.004
Bismuth	Bi	0.009 – 0.025

The above abundance data above is from Wikipedia which includes data from several sources that give different values.

Lead extraction is a simple one-stage process involving heating the sulphide ore with limited oxygen supply to produce lead metal and sulphur dioxide which is converted into sulphuric acid as a by-product.

The **rare metals and tungsten** require complex multistage extraction processes that are energy intensive and use hazardous chemical processes.

Tungsten ores often contain arsenic and a common method of removal is by roasting and there is potentially a risk of atmospheric arsenic emissions. Tungsten is produced from concentrated tungsten ores by complex multi-stage processes, typically:

- Fusion with NaOH
- Water leaching to give sodium tungstate solution
- Precipitate WO_3 by acidification
- Conversion into the required pure chemicals

Gold can be present at as low as 0.00001% of ores, the rest being waste. A variety of extraction and refining processes are used and in some there are emissions that include Pb and As. Some mines use cyanide leaching of ores to extract gold. As cyanide is very toxic, there is a risk to health and the environment should it be released accidentally. Accidents have occurred causing considerable environmental damage[5].

Gold extraction and refining is very energy intensive compared to other metals such as lead. The relative energy consumption for mining, extraction and refining are[6]:

Element	Energy Consumption
Gold (other rare metals such as platinum consume amounts similar or more energy)	143,000 MJ/tonne
Lead	168 MJ/tonne

Re, Os, Ir and Pt are all very rare metals recovered as by-products from mining other metals including gold, copper and nickel. They are extracted and refined by complex multi-stage processes[7]. Process energy consumption will be at least as much as for gold.

Bismuth occurs with other metals including lead ores and is recovered as a by-product using complex multi-stage processes. A common method used for separation of bismuth from lead is the Kroll Betterton process where various fluxes are used to extract bismuth from molten lead. Bismuth is then recovered from the flux by a series of additional process steps.

6.2. Use phase

There would be no differences in the use phase as long as the performance was adequate.

7. Re-use and recycling of materials from waste EEE

Although lead is toxic, recycling is straightforward and well controlled whereas the processes used to recycle many of the other heavy metals described above are complex requiring many process steps and use toxic chemicals such as cyanides. Recycling of all of the heavy metals including bismuth are much more complex processes than lead recycling.

As the quantity of lead present in end of life head and body frames will be very small, dedicated recycling processes would be impractical and so they would be

[5] www.ipac.ca/documents/Marcin_Ruder.ppt and http://archive.rec.org/REC/Publications/CyanideSpill/ENGCyanide.pdf
[6] From: for gold http://www.eoearth.org/article/Gold_mining_and_sustainability:_A_critical_reflection and for lead http://www.epa.gov/dfe/pubs/solder/lca/lfs-lca-final.pdf
[7] http://www.goldandsilvermines.com/platinum.htm

recycled with other waste electrical equipment. These usually involve thermal treatment causing lead acetate to decompose to lead oxide which will behave in the same way as lead from solder and other sources. Recovery of lead from WEEE by modern high efficiency processes is carried out in the EU and elsewhere with very high recovery rates (>95% according to Umicore). The recovered lead is re-used with the largest uses being in batteries and buildings.

8. Other information

It is estimated that less than 1 kg of lead is used for this application per year in the EU

9. Proposed plan to develop substitutes and timetable

This exemption request has considered all possible available alternative elements in the periodic table. No element other than lead has very high atomic mass, high density has stable and soluble glycol salts that are readily visible by both MRI and x-ray. Direct substitution with an alternative substance is therefore not feasible. Alternative markers have been developed for some medical treatments but all have limitations. However further research may eventually identify a marking technique that provides marking simultaneously for both CT and MRI with the same precision and contrast and medical equipment manufacturers will evaluate any potential substitutes if any are identified. As there are no obvious candidates, it is impossible to predict how long this will take.

10. Proposed wording for exemption

Lead and its compounds used for positioning systems and as a marker for radiotherapy, gamma-beam and particle therapy and for stereotactic head-frames and body-frames used with CT and MRI.