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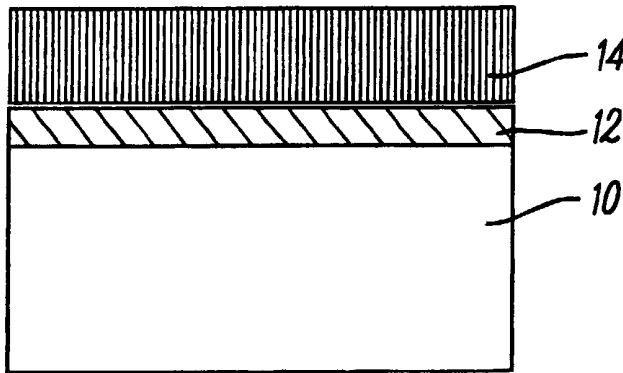
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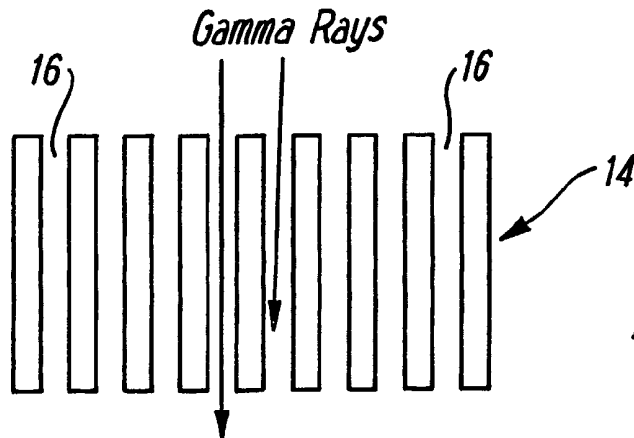
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(54) Title: DEVICES FOR IMAGING RADIONUCLIDE EMISSIONS



**a**

(57) Abstract: There is disclosed a device for imaging radionuclide emissions comprising: a charge coupled device or CMOS active pixel sensor device; and a scintillator layer in direct contact with the charge coupled device or CMOS active pixel sensor device; in which the thickness of the scintillator layer is greater than 200 μm, preferably greater than 400 μm, most preferably about 500 μm.



**b**



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### Devices for Imaging Radionuclide Emissions

This invention relates to devices for imaging radionuclide emissions.

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Imaging of radiolabeled tracers in tissues (commonly referred to as autoradiography) has traditionally been performed using film to record the image. The use of film has the disadvantages of being time consuming, and having limited dynamic range and non-linear response. Furthermore, the technique is limited to the imaging of excised tissues.

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A competing technology is known as a "gamma-camera", and comprises an array of small photomultiplier tubes equipped with a single crystal NaI scintillator. However, this device has the disadvantage of having a relatively limited intrinsic spatial resolution of ca. 3 to 4mm. Furthermore, in practice the device requires a collimator in order to produce an image, which reduces the resolution to ca. 8 to 15mm. Another competing technology utilises room temperature semiconductor arrays. However, such arrays are not routinely available and thus are expensive. Furthermore, the spatial resolution of the such arrays is no better than that obtained with gamma-cameras.

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Karellas *et al* (IEEE Transactions on Nuclear Science, 40 (1993) 979) reports on imaging using charge coupled devices (CCDs) and a polycrystalline  $Gd_2O_2S(Tb)$  scintillator.  $Gd_2O_2S(Tb)$  is also known as "Gadox". Images were obtained using a lens to couple the Gadox scintillator to the CCD, i.e, the scintillator was physically separated from the CCD, although Karellas *et al* does suggest that either direct contact of the scintillator with the CCD or the use of a fibre optic reducer to couple the scintillator to the CCD may be possible. Karellas *et al* utilises relatively thin ( $< 100\mu m$ ) layers of Gadox, and notes that problems of light absorption would be very significant

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if thicknesses of greater than about  $200\mu\text{m}$  are used. In other words, Karellas *et al* directs the skilled person towards the use of thin layers of Gadox. It is noted that Karellas *et al* does provide computations which suggest that an energy resolution ( $\Delta E/E$ ) of between 0.08-0.10 might be achieved at an incident energy of 140keV, but does not  
5 provide any indication of the experimental conditions needed to achieve this energy resolution.

CCDs which are directly coated with a thin ( $100\mu\text{m}$ ) layer of Gadox are known. Such devices have been extensively used in dental applications, specifically  
10 intra-oral X-ray imaging. However, such devices are only used for transmission imaging with low energy (25 to 40keV) gamma rays and are unsuitable for imaging high energy gamma such as 140.5keV gamma ray emission from  $^{99\text{m}}\text{Tc}$ .

The present invention overcomes the abovementioned problems and  
15 disadvantages, and provides a low cost, high performance device capable of imaging small volumes of radionuclide (such as  $^{99\text{m}}\text{Tc}$ ) uptake in tissues. High performance with regard to spatial resolution and energy resolution is achieved. Furthermore, in-vivo imaging is possible.

20 According to a first aspect of the invention there is provided a device for imaging radionuclide emissions comprising:

a charge coupled device or CMOS active pixel sensor device; and

25 a scintillator layer in direct contact with the charge coupled device or CMOS active pixel sensor device;

in which the thickness of the scintillator layer is greater than  $200\mu\text{m}$ , preferably greater than  $400\mu\text{m}$ , most preferably about  $500\mu\text{m}$ .

The use of a relatively thick layer of scintillator which is in direct contact with the CCD or CMOS active pixel sensor device enables high count rates, and allows excellent energy resolution to be achieved over the range 30-160keV (although this range should not be considered to be a limiting one). This is surprising, particularly in view of Karellas et al which predicts that problems would be encountered if thick layers are used. Sub-millimetre spatial resolution is possible. Furthermore, the device is convenient and economic to produce.

The scintillator layer may comprise a rare earth phosphor, which may comprise Gd, and may comprise  $Gd_2O_2S$  units. The rare earth phosphor may be  $Gd_2O_2S(Tb)$  or  $Gd_2O_2S(Pr, Ce, F)$ .

The scintillator layer may comprise CsI.

The scintillator layer may be directly coated onto the device.

The device may further comprise a collimator. The collimator may be a coded aperture mask.

The device may further comprise means for operating the device in photon counting mode.

According to a second aspect of the invention there is provided an apparatus for imaging radionuclide emissions from a source, the apparatus comprising: a solid state pixel sensor device, a scintillator arranged between the source and the pixel sensor device, and a signal processing circuit coupled to receive an output from the pixel sensor device, which signal processing circuit is configurable to operate in a photon counting mode.



are utilised, but it is possible to use larger or smaller apertures as desired. The collimator may be fixed or detachable. In the latter case, it is possible to provide a single device having a number of associated collimators of different aperture size. In this way, the spatial resolution of the device can be varied as desired by the user. A coded aperture  
5 may be used. Such masks are well known to those skilled in the art, and permit three dimensional mapping of the radiolabeled area by image reconstruction. Such masks can have a random or a fixed pattern which might comprise an arrangement of circular, square or diagonal shaped apertures.

10 The device is operated by control means (not shown) which supplies power to the device and measures the output of the device. Preferably, the device is operated in photon counting mode. Cooling of the device, such as by Peltier cooling, is possible. Such operational techniques are well known to those skilled in the art.

15 With  $^{99m}\text{Tc}$  radionuclides (producing gamma rays of 140.5keV energy), energy resolutions  $\Delta E/E$  of 0.04 are possible, with a concomitant spatial resolution of 0.3-0.4mm.

20 Figure 3 shows a block diagram of an embodiment of an apparatus according to the present invention. The apparatus is shown in an experimental arrangement to determine the resolution of the apparatus but could equally provide an image of a radionuclide *in vivo*, for example.

25 A radionuclide source 20 comprises Americium 241 which emits gamma rays at an energy of 59.5 keV illustrated by the arrows 22. For the purposes of the resolution experiment these are applied to a lead sheet 24 having a pinhole in the centre which pinhole is 1mm in diameter.

These gamma rays impinge upon a 500 micron layer of Gadox acting as a scintillator 26. The Gadox layer is formed on a charge coupled device (CCD) 28, specifically a Mtech CCD38. The CCD and Gadox layer can be encapsulated in a suitable material, such as a plastic, in order, eg, to afford protection to the device. The  
5 CCD 28 is driven by drive electronics 36 and supplies an output to a signal processing circuitry 32 *via* low noise preamplifier 30. The drive electronics 36 are controlled at a high level by a personal computer (PC) 34 which also receives an output signal from the signal processing circuitry 32. An image of a spot (ie, the image of gamma rays travelling through the pinhole in the lead sheet 24) is shown on the screen of the PC 34.  
10 Replacing the Americium source and the lead sheet with a patient to whom a radioactive tracer has been administered provide an *in vivo* imaging function.

The signal processing circuitry 32 is configurable in a photon counting mode. This effectively means that the image from the CCD 28 is read sufficiently often  
15 to detect a single photon at a particular pixel location. The read rate required to accomplish this can be determined statistically. In this application the read rate will be 1 second or less.

While the Gadox layer is shown as being formed upon the CCD 28 it is  
20 possible to couple the photons produced in the scintillator layer to the CCD or other active pixel sensor device via a lens or via a fibre optic coupling. However, direct coupling is much preferred because of the substantially better efficiency in photon transfer compared with the other techniques. Preferably, the Gadox layer is at least 400 microns thick.

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Although not explicitly shown in the diagram, cooling (for example Peltier cooling) is applied to the CCD 28. Without cooling the noise performance of the apparatus is degraded.



The CCD 28 could be replaced by a suitable CMOS active pixel sensor device.

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Figures 2(a) and 2(b) show an image from a  $^{241}\text{Am}$  source (59.5keV). A CCD coated with a  $500\mu\text{m}$  layer of Gadox and having a 1mm diameter pinhole disposed thereon was used to obtain the image. The cross section through the spot image shown in Figure 2(b) indicates a spatial resolution of better than 0.7mm. The derivation of this  
10 resolution will be explained with reference to Figure 4.

Figure 4 illustrates the analysis of the results shown in Figure 2 to determine the resolution of the arrangement in accordance with this embodiment of the invention shown in Figure 3. Figure 4 (a) shows the radiation incident upon the scintillator (and  
15 hence the CCD) as a consequence of the Americium source and the pinhole in the lead - a 1mm wide 'flat top'. Figure 4 (b) shows a representation of the results of Figure 2 (b) ie, the measured intensity distribution.

The measured intensity distribution has spread on either side of the incident  
20 intensity distribution by an amount  $dx$ . This amount comprises the upper limit on spatial resolution (it should be noted that this comparatively crude technique provides an overestimate of the actual value). Comparison between Figure 4 (b) and Figure 2 (b), after subtraction of the background intensity, shows that  $dx$  for this experiment is  
0.7mm.

25

In place of the CCD, it is possible to utilise a CMOS active pixel sensor device. Such devices are silicon devices which comprise, essentially, arrays of silicon diodes and associated transistors.

Detectors of the present invention, with sub-mm spatial resolution and excellent energy resolution over the range 30-160 keV, could be useful in detecting small breast cancers and tumours in lymph nodes and therefore may have considerable importance in treating breast cancer and in imaging melanoma and other small lesions.

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The ability to image the 140.5keV  $\gamma$ -ray emission from  $^{99m}\text{Tc}$  with high spatial resolution could be of benefit in other areas in nuclear medicine. These include single photon animal imaging to visualise radioactive tracers, particularly for the evaluation of new drugs, where there has been much work in developing high resolution  
10 PET scanners (R. Slates *et al.*, 1999, "Design of small animal MR compatible PET scanner" IEEE Trans.Nucl. Sci. NS-46 565-570). Devices of the present invention could also provide a basis for an intra-operative probe for radio-guided cancer surgery. Mosaics of such detectors could be useful for the high resolution imaging of small organs such as the thyroid and skeletal joints (knees, ankles, elbows).

15

**CLAIMS**

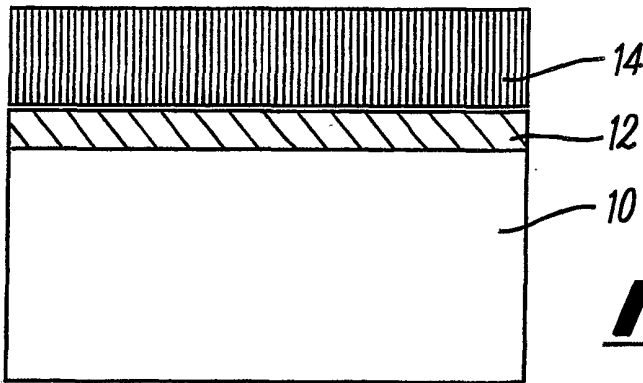
1. A device for imaging radionuclide emissions comprising:  
5 a charge coupled device or CMOS active pixel sensor device; and  
a scintillator layer in direct contact with the charge coupled device or  
CMOS active pixel sensor device;  
10 in which the thickness of the scintillator layer is greater than  $200\mu\text{m}$ ,  
preferably greater than  $400\mu\text{m}$ , most preferably about  $500\mu\text{m}$ .
2. A device according to claim 1 in which the scintillator layer comprises a  
rare earth phosphor.  
15
3. A device according to claim 2 in which the rare earth phosphor comprises  
Gd.
4. A device according to claim 3 in which the rare earth phosphor comprises  
20  $\text{Gd}_2\text{O}_2\text{S}$  units.
5. A device according to claim 4 in which the rare earth phosphor is  
 $\text{Gd}_2\text{O}_2\text{S}(\text{Tb})$ .
- 25 6. A device according to claim 4 in which the rare earth phosphor is  
 $\text{Gd}_2\text{O}_2\text{S}(\text{Pr}, \text{Ce}, \text{F})$ .
7. A device according to claim 1 in which the scintillator layer comprises CsI.

8. A device according to any previous claim in which the scintillator layer is directly coated onto the device.
9. A device according to any of the previous claims further comprising a  
5 collimator.
10. A device according to claim 9 in which the collimator comprises a coded aperture mask.
- 10
11. A device according to any previous claim further comprising means for operating the device in photon counting mode.
12. An apparatus for imaging radionuclide emissions from a source, the  
15 apparatus comprising:
- a solid state pixel sensor device;
  - a scintillator arranged between the source and the pixel sensor device; and
  - a signal processing circuit coupled to receive an output from the pixel  
20 sensor device, which signal processing circuit is configurable to operate in a photon counting mode.
13. An apparatus as claimed in claim 12, wherein the solid state pixel sensor device comprises a charge coupled device or a CMOS active pixel sensor device.
- 25
14. An apparatus as claimed in claim 12 or claim 13, wherein the signal processing circuit is configurable to operate in a photon counting mode by setting a read rate for the pixel sensor device less than a predetermined value.

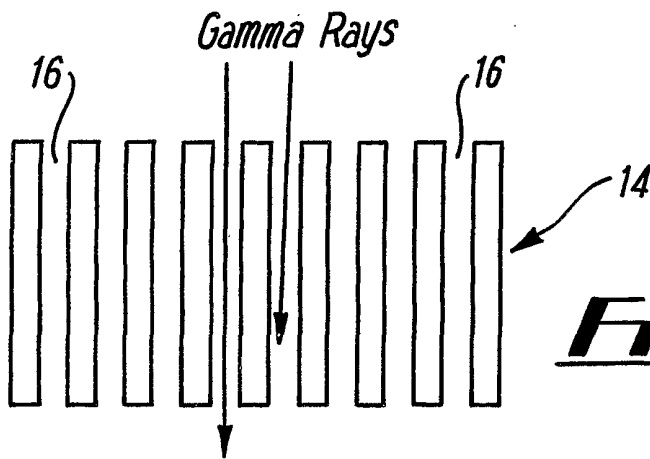
15. An apparatus as claimed in claim 14, wherein the predetermined value does not exceed 1 second.

16. An apparatus as claimed in any one of the claims 12 to 15, wherein the  
5 scintillator is at least 400 microns thick.

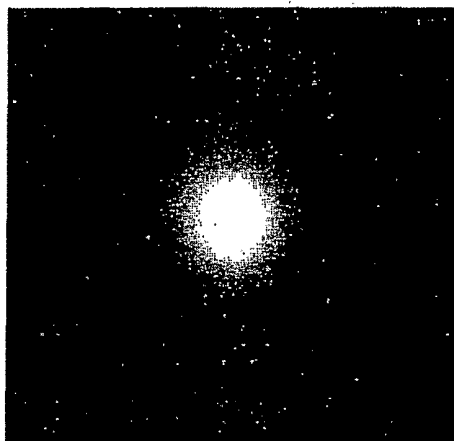
17. An apparatus as claimed in any one of the claims 12 to 16, further comprising cooling means for cooling the active pixel sensor.



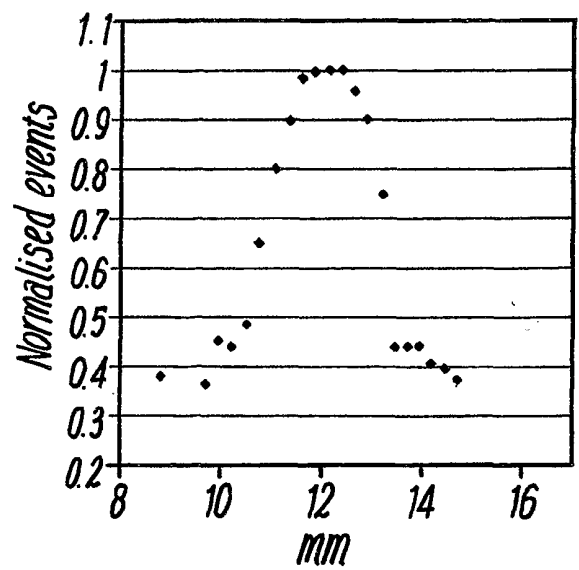
**FIG. 1(a)**



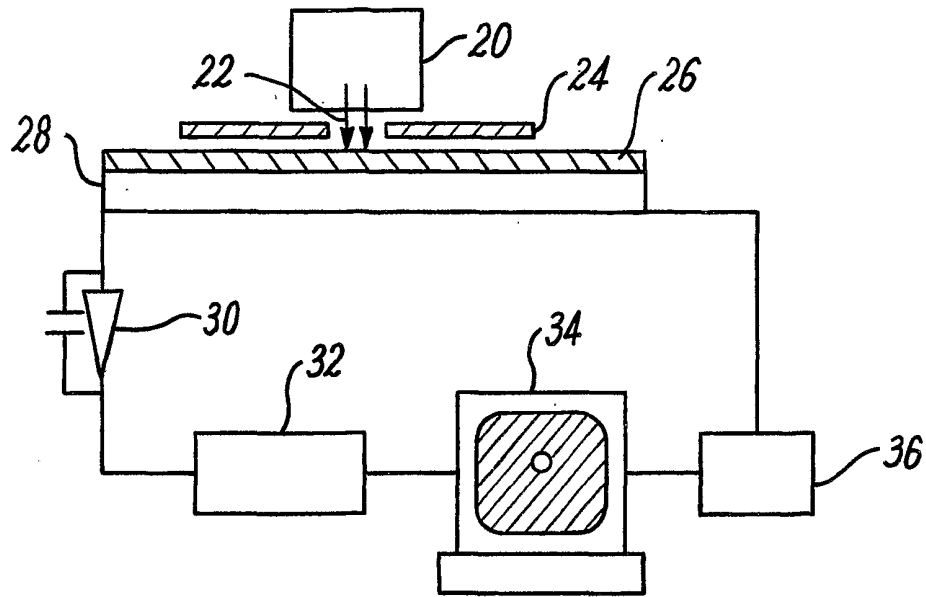
**FIG. 1(b)**



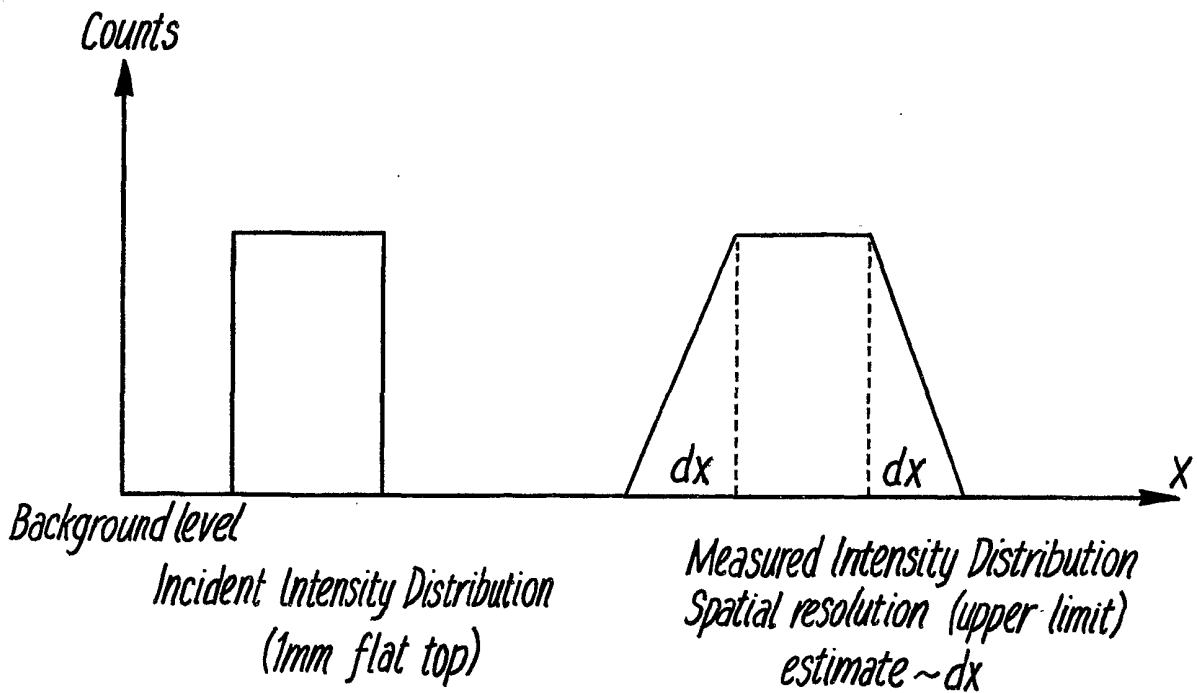
**FIG. 2(a)**



**FIG. 2(b)**



**FIG. 3**



**FIG. 4(a)**

**FIG. 4(b)**

INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 01/05345

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 G01T1/161 G01T1/29 G01T1/202

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 G01T

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 031 892 A (KARELLAS ANDREW) 29 February 2000 (2000-02-29) column 2, line 4 - line 51 column 9, line 10 - line 14 column 10, line 1 -column 11, line 6 column 15, line 53 -column 21, line 62 figures 10-12	1-9, 11-17
Y	---	10
X	GB 2 343 577 A (SIMAGE OY) 10 May 2000 (2000-05-10) page 8, line 15 -page 15, line 26	12
Y	WO 97 16746 A (BIOTRACES INC ;DRUKIER ANDRZEJ K (US); SAGDEJEV IGOR R (US)) 9 May 1997 (1997-05-09) page 39, line 5 -page 45, line 25	10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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