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# Cobalt Determinations in Hair of Patients after Metal-on-Metal Hip Implant by Instrumental Neutron Activation Analysis

G. D'Agostino<sup>(1)</sup>, M. Di Luzio<sup>(1)</sup>, M. Oddone<sup>(2,1)</sup> and S. Stea<sup>(3)</sup>

(1) Istituto Nazionale di Ricerca Metrologica (INRIM), Unit of Radiochemistry and Spectroscopy, c/o Department of Chemistry, University of Pavia, via Taramelli 12, 27100 Pavia, Italy

(2) Department of Chemistry, University of Pavia, via Taramelli 12, 27100 Pavia, Italy

(3) Istituto Ortopedico Rizzoli, via di Barbiano 1/10, 40136 Bologna, Italy

Email of the corresponding author: [g.dagostino@inrim.it](mailto:g.dagostino@inrim.it)

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**Abstract:** In these years, following the alert of possible problems of toxicity issued by national medicine authorities, thousands of patients with hip implants are recalled for a set of analysis, including cobalt determinations in blood and urine. In this framework, additional measurements of cobalt in hair are recommended to monitor the release of metals in the body after surgery. Aiming at a clinical application, the standardization of the hair washing protocol used to remove possible external contamination is essential. To this aim, a method suggested by the International Atomic Energy Agency and based on repeated washings with acetone and deionized water was tested. Specifically, hair samples of two healthy subjects and three patients were measured at different steps of the washing sequence to observe the decrease in the level of cobalt to the plateau corresponding to the bound component. The data confirmed the suitability of the washing method and proved high levels of bound cobalt in hair of two patients requiring revision hip surgery. Moreover, the cobalt bound component was not affected by the neutron exposure of hair. As a result, use of Instrumental Neutron Activation Analysis might be advantageous compared to other analytical techniques.

## 1. Introduction

Measurements of trace element levels in human hair have been widely used in environmental and occupational studies to determine the degree of contamination of man by pollutants [1-4], and in biomedical studies to investigate neurodegenerative [5,6], and neoplastic diseases [7].

Additional hair analyses have been carried out after the evidence that blood and urine levels of Co are increased in patients who had metal-on-metal (MoM) hip resurfacing arthroplasties compared to those in the control group subjects [8]. Specifically, the Co mass fraction in hair samples of these patients was measured at  $10^{-5}$  g g<sup>-1</sup> level during a follow-up of 1 year, compared to the  $10^{-6}$  g g<sup>-1</sup> level before surgery [9]. Later, a study extended the follow-up period from 1 to 6 years and reported a Co mass fraction at  $10^{-5}$  g g<sup>-1</sup> level in hair after MoM hip implant. Furthermore, the collected data proved a consistency between Co variations in blood and serum with those in hair [10].

Although the outcomes of these studies are encouraging to use Co in hair as a biologic marker in periodic checkups of patients after MoM hip implant, the significance of the results might be questioned due to their dependence on the washing protocol adopted to remove possible exogenous contamination.

The need for standardization was already acknowledged during proficiency testing among clinical laboratories claiming the capabilities of performing hair analysis [11]. Experimental tests proved that, in some cases, sample washing failed in separating the exogenous from the endogenous component of the trace element [12]. This is the main reason of controversy on the use of hair to monitor the internal body status [13,14].

It is understood that the washing effect is in fact the removal of the unbound component of a trace element. The bound component, still attached to the hair, might be assumed to be largely dependent on (but not equal to) the endogenous component. Evidently, the result is strongly influenced by the choice of the liquid solutions, the washing sequence and the washing time.

Several protocols have been applied, compared and reported in literature [15-19]. Among them, the method suggested by the International Atomic Energy Agency (IAEA) [1] is promising because most protein-bound trace element levels are expected to be little changed. It consists of five washings performed in three consecutive steps: (i) one 10 min washing with acetone, (ii) three 10 min washings with water and (iii) one 10 min washing with acetone. The liquid solution is decanted off and renewed after each 10 min washing.

Recently, following a request from the European Commission, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) gave an opinion on potential risks associated with MoM hip implants [20]. Based on the experimental indication that metals deposited in body fluids and tissues by MoM hip implants lead to adverse health effects, SCENIHR recommended the systematic follow-up for all patients. Among the diagnostic tools suggested in the ultimate decision of implant revision, the determination of metal levels in hair are recommended.

In this framework, the aim of our study was to assess the use of the IAEA washing method as a standard protocol in hair analysis of patients after MoM hip implant. To this aim, the variation of Co levels in hair samples following single washing steps was determined by Instrumental Neutron Activation Analysis (INAA) to observe the removal of the unbound component. In addition, the effect of neutrons on the bound component was also investigated to check the possibility of performing hair washing after irradiation.

## **2. Materials**

Hair bunches of about 2 cm in length were collected using cleaned ceramic scissors from the nape of the neck of two (healthy) control subjects, hereafter referred as C1 and C2, and of three patients after MoM hip implant, hereafter referred P1, P2 and P3; at the time of hair collection, patients P1 and P2 required revision hip surgery while patient P3 required only monitoring. Hair samples were stored separately in cellophane packets at room temperature.

Weighed aliquots of a Co standard solution ( $1000 \text{ mg L}^{-1}$ , Merck) pipetted on high purity cellulose filter papers were used as comparators for the application of the relative-INAA standardization method. Polyethylene (PE) vials and tube vessels were used for the neutron irradiation of the samples.

Hair washing was performed with ultra-pure acetone and deionized water in a Teflon container using a magnetic bar and a stirrer. The PE tweezers used to handle hair samples, the PE irradiation vials and vessels, the Teflon container and magnetic bar were cleaned in an ultrasonic bath with 10% ultra-pure nitric acid.

### 3. First experiment

Hair samples collected from C1, C2, P1, P2 and P3, called  $H_{C1}$ ,  $H_{1,C2}$ ,  $H_{P1}$ ,  $H_{P2}$ , and  $H_{P3}$ , respectively, were sealed in five PE vials and used in a first experiment. Sample masses ranged between 10 mg to 150 mg, depending on the total amount of hair available.

Seven Co comparators, called  $C_{1,1}$ ,  $C_{1,2}$ ,  $C_{1,3}$ ,  $C_{2,1}$ ,  $C_{2,2}$ ,  $C_{2,3}$  and  $C_{2,4}$  were prepared by pipetting aliquots of the Co standard solution in seven PE vials and weighted with a digital balance. Before sealing, the pipetted aliquots were dried out using an infrared lamp.

Hair samples and comparators were closed in two tube vessels for irradiation in the order  $C_{1,1}$ - $H_{C1}$ - $C_{1,2}$ - $H_{1,C2}$ - $C_{1,3}$  and  $C_{2,1}$ - $H_{P1}$ - $C_{2,2}$ - $H_{P2}$ - $C_{2,3}$ - $H_{P3}$ - $C_{2,4}$ , respectively. The neutron irradiation lasted 6 h and was performed in the central channel of the 250 kW TRIGA Mark reactor operated by the University of Pavia ( $6.11(16) \times 10^{12} \text{ cm}^{-2} \text{ s}^{-1}$  thermal neutron flux, 15.6(3) thermal to epithermal neutron flux [21]).

After irradiation, hairs were removed from their vial, equally distributed on a 45 mm diameter surface and pressed between two filter paper disks in a plastic container for  $\gamma$ -counting.

Six  $\gamma$ -spectra per sample were consecutively acquired with a high purity germanium (HPGe) detector, ORTEC GEM50P4-83 (relative efficiency 50 %, resolution 1.90 keV FWHM at 1332 keV) connected to a digital signal processor ORTEC DSPEC 502. The  $\gamma$ -counting lasted at least 48 h and was performed with the hair sample in contact with the endcap of the detector.

After each acquisition, the hairs were (i) removed from their container, (ii) weighed, (iii) washed according to a scheduled sequence, (iv) dried and (v) pressed again between two new filter paper disks in the container for the next  $\gamma$ -counting. After the last acquisition, hairs were only removed from their container and weighed.

The number of completed washing steps, the scheduled washing sequence and the  $\gamma$ -counting number of a hair sample are summarized in Table 1. Here and hereafter, a single washing step is either one 10 min acetone washing, called a, or three 10 min water washings, called w. Three completed steps, i.e. -a-w-a, correspond to the washing protocol suggested by IAEA as a pre-treatment of the sample prior to analysis.

Steps	Washing	$\gamma$ -counting
0	-	1
1	-a	2
2	-w	3
3	-a	4
7	-w-a-w-a	5
9	-w-a	6

**Table 1.** Number of completed acetone, a, and water, w, steps, the scheduled washing sequence and the  $\gamma$ -counting number of a hair sample.

The Co comparators were successively measured in contact with the endcap of the GEM50P4-83 detector.

A few strands of H<sub>1,C1</sub> were selected at steps 0, 1, 2, 3 to inspect the external hair surface by a Scanning Electron Microscope (SEM).

#### 4. Second experiment

Hairs collected from C2 were used in a second experiment. A first hair sample, called H<sub>2,C2</sub>, was subjected to nine washing steps, i.e. -a-w-a-w-a-w-a-w-a, and sealed in a PE vial. A second hair sample, called H<sub>3,C2</sub>, was sealed in a PE vial without any washing. The mass of each sample was about 350 mg.

Three Co comparators, called C<sub>3,1</sub>, C<sub>3,2</sub>, and C<sub>3,3</sub>, were prepared according to the procedure used in the first experiment.

The hair samples and the comparators were closed in a tube vessel in the order C<sub>3,1</sub>-H<sub>2,C2</sub>-C<sub>3,2</sub>-H<sub>3,C2</sub>-C<sub>3,3</sub> and irradiated for 6 h in the central channel with a neutron flux equal to the first experiment.

After irradiation, hairs of the (pre-washed) sample H<sub>2,C2</sub> were removed from their vial, placed in a container, counted and weighed. The  $\gamma$ -spectrum was recorded in 48 h with the sample in contact with the endcap of a HPGe detector CANBERRA GC3518 (relative efficiency 35 %, resolution 1.80 keV FWHM at 1332 keV) connected to the DSPEC 502 digital signal processor.

Afterwards, hairs of sample H<sub>3,C2</sub> were removed from their vial and subjected to the recursive procedure performed in the first experiment, including  $\gamma$ -countings before washing and between consecutive steps (see Table 1). Six  $\gamma$ -spectra were sequentially acquired with the sample in contact with the endcap of the GC3515 detector.

The Co comparators were successively measured in contact with the endcap of the GC3518 detector.

#### 5. Results and discussion

The mass of Co was determined by applying the relative-INAA standardization method. The results were normalized to the mass of the hair sample measured after each  $\gamma$ -counting to calculate the corresponding mass fractions corrected for hairs lost during washing.

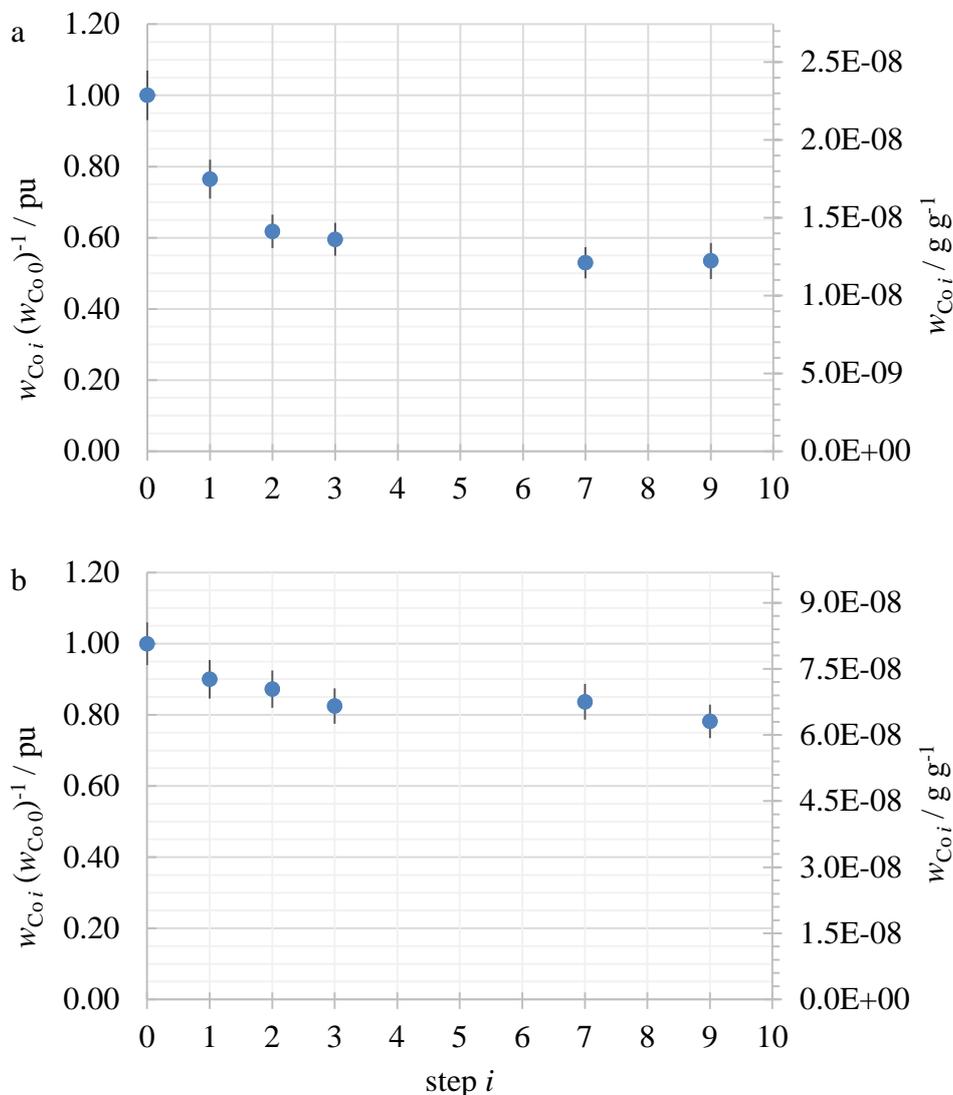
The recorded  $\gamma$ -spectra were processed using the Hyperlab software [22] to measure the number of counts in the 1173.2 keV and 1332.5 keV <sup>60</sup>Co full-energy  $\gamma$ -peaks adopted to quantify the Co level in hair. The effect of the neutron flux vertical gradient was limited by averaging the data collected with the comparators located above and below the hair sample.

The Co mass detection limit reached the 10<sup>-10</sup> g level, corresponding to a mass fraction detection limit at 10<sup>-9</sup> g g<sup>-1</sup> level for a 100 mg mass hair sample. This makes the applied method suitable for monitoring patients after MoM hip implant.

Preliminary tests carried out using the (strong) 1115.5 keV <sup>65</sup>Zn  $\gamma$ -emission produced from Zn in hair showed a 3% relative standard deviation due to variations in sample geometry and  $\gamma$ -counting position after successive washing steps. In the following, quoted uncertainties include this contribution combined to the uncertainties from counting statistics.

The data of the first experiment were used to determine the Co mass fraction at the washing step  $i$ ,  $w_{\text{Co } i}$ , in hairs of C1, C2, P1, P2 and P3.

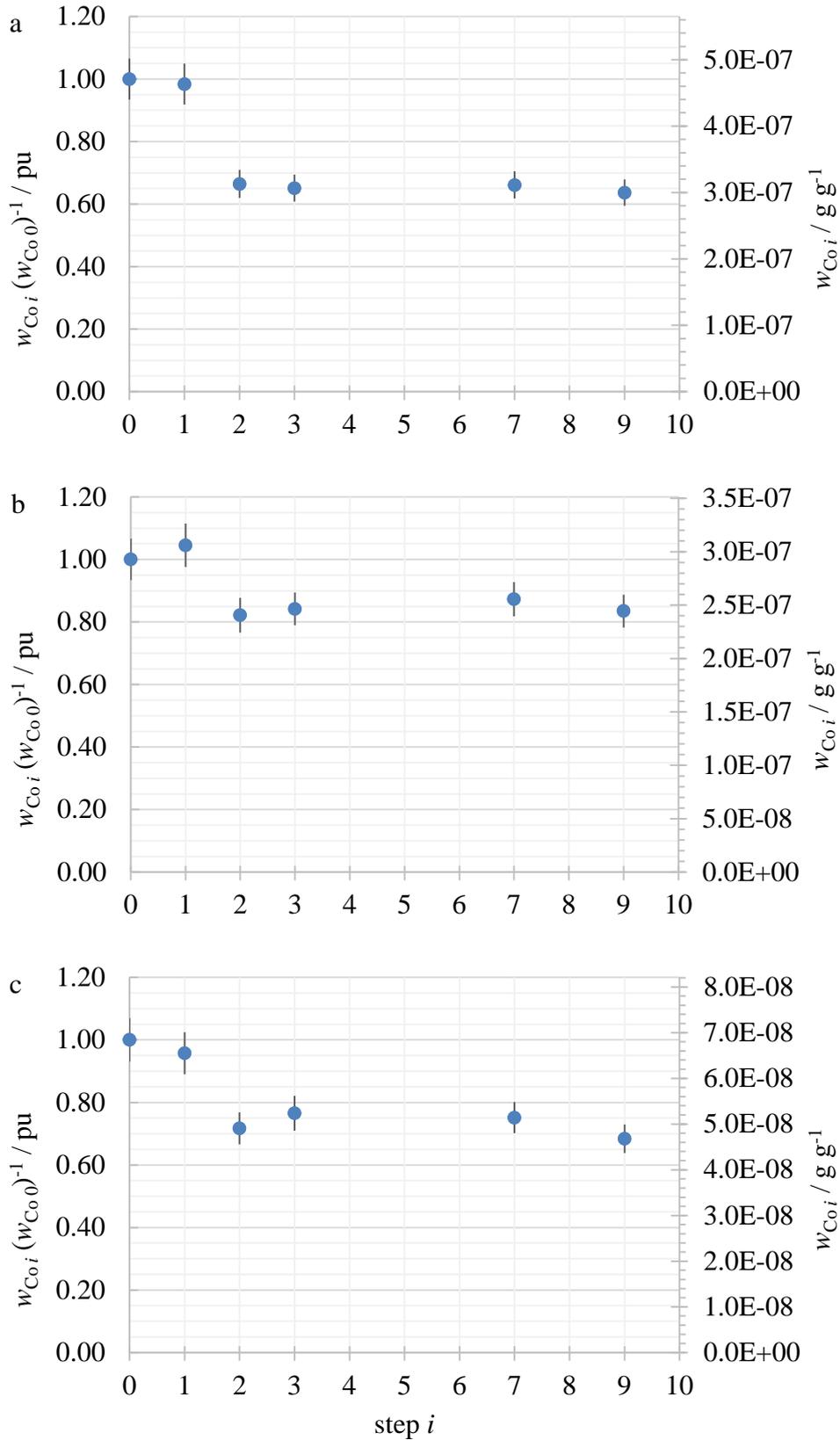
The values in samples of the two healthy subjects,  $H_{\text{C1}}$  and  $H_{1,\text{C2}}$ , absolute and relative to the Co mass fraction at step 0,  $w_{\text{Co } 0}$ , are plotted in Figure 1a and 1b, respectively.



**Figure 1.** Variations of Co levels in hairs of C1 and C2 (healthy subjects) during washings. The closed dots show the Co mass fraction (absolute right y axis and relative left y axis) at step  $i$  in a)  $H_{\text{C1}}$  and b)  $H_{1,\text{C2}}$ . The error bars indicate the expanded uncertainty ( $k = 2$ ).

The level of Co decreased by 40% in  $H_{\text{C1}}$  from the initial  $2.29(16) \times 10^{-8} \text{ g g}^{-1}$  (unwashed, step 0) to  $1.36(11) \times 10^{-8} \text{ g g}^{-1}$  (step 3) and by 18% in  $H_{1,\text{C2}}$  from  $8.07(49) \times 10^{-8} \text{ g g}^{-1}$  (step 0) to  $6.66(40) \times 10^{-8} \text{ g g}^{-1}$  (step 3). Here and hereafter the expanded uncertainty ( $k = 2$ ) in parentheses applies to the last respective digits.

The Co mass fractions in hair samples of the three MoM patients,  $H_{\text{P1}}$ ,  $H_{\text{P2}}$ , and  $H_{\text{P3}}$ , absolute and relative, are plotted in Figure 2a, 2b and 2c, respectively.

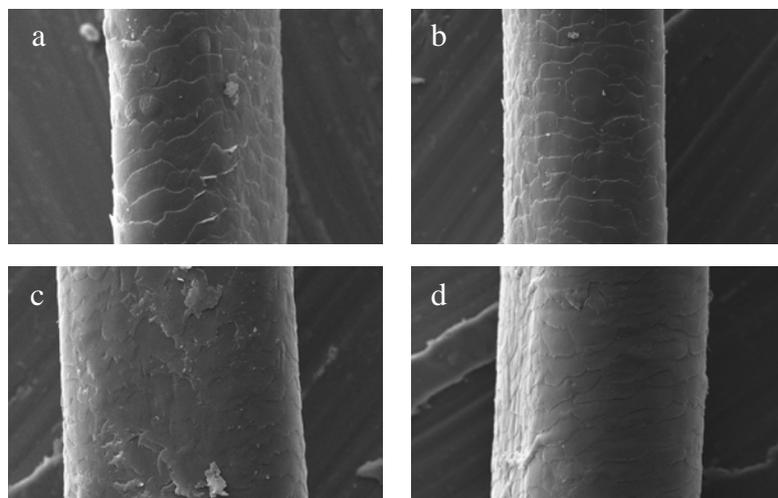


**Figure 2.** Variations of Co levels in hairs of P1, P2 and P3 (MoM patients) during washings. The closed dots show the Co mass fraction (absolute right y axis and relative left y axis) at step  $i$  in a)  $H_{P1}$ , b)  $H_{P2}$ , and c)  $H_{P3}$ . The error bars indicate the expanded uncertainty ( $k = 2$ ).

The level of Co decreased by 35% in  $H_{P1}$  from  $4.71(31) \times 10^{-7} \text{ g g}^{-1}$  (step 0) to  $3.07(20) \times 10^{-7} \text{ g g}^{-1}$  (step 3), by 16% in  $H_{P2}$  from  $2.93(19) \times 10^{-7} \text{ g g}^{-1}$  (step 0) to  $2.46(15) \times 10^{-7} \text{ g g}^{-1}$  (step 3) and by 23% in  $H_{P3}$  from  $6.84(47) \times 10^{-8} \text{ g g}^{-1}$  (step 0) to  $5.24(38) \times 10^{-8} \text{ g g}^{-1}$  (step 3).

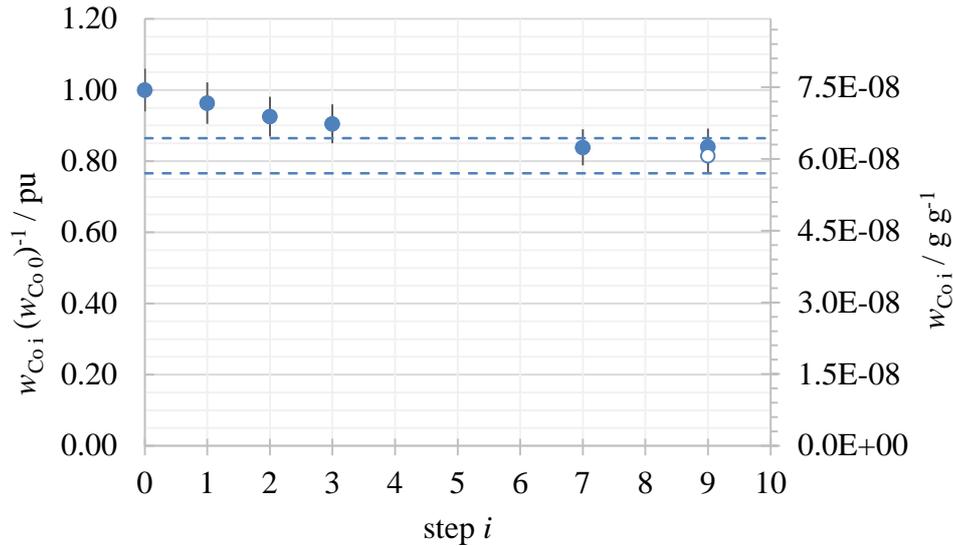
The first acetone washing removed a significant amount of Co only in  $H_{C1}$  and  $H_{1,C2}$ . In the case of  $H_{P1}$ ,  $H_{P2}$ , and  $H_{P3}$  most of the Co was removed by water following the first acetone step. Additional washings succeeding step 3 did not decrease the Co level, with the exception of a (small) reduction observed in  $H_{C1}$ .

The external surface of a hair strand of  $H_{C1}$  at steps 0, 1, 2 and 3 is displayed in Figure 3a, 3b, 3c and 3d, respectively. The scales of the cuticle appears to be damaged after two completed steps, i.e. -a-w. The damaged scales are later removed in the next -a step because they appear again intact after 3 completed steps, i.e. -a-w-a. Therefore, the -w-a-w sequence seems to act as a kind of hair peeling which takes away possible dust residues attached to the surface as well. Furthermore, a general embrittlement of the hair shaft was observed during consecutive washings.



**Figure 3.** SEM images of hairs selected from sample  $H_{C1}$  recorded at steps a) 0, b) 1, c) 2 and d) 3.

The data of the second experiment were used to determine  $w_{Co_i}$  in the sample  $H_{3,C2}$  and  $w_{Co_0}$  in the (pre-washed) sample  $H_{2,C2}$  of the healthy subject C2. The values, absolute and relative to  $w_{Co_0}$  in  $H_{3,C2}$ , are plotted in Figure 4.

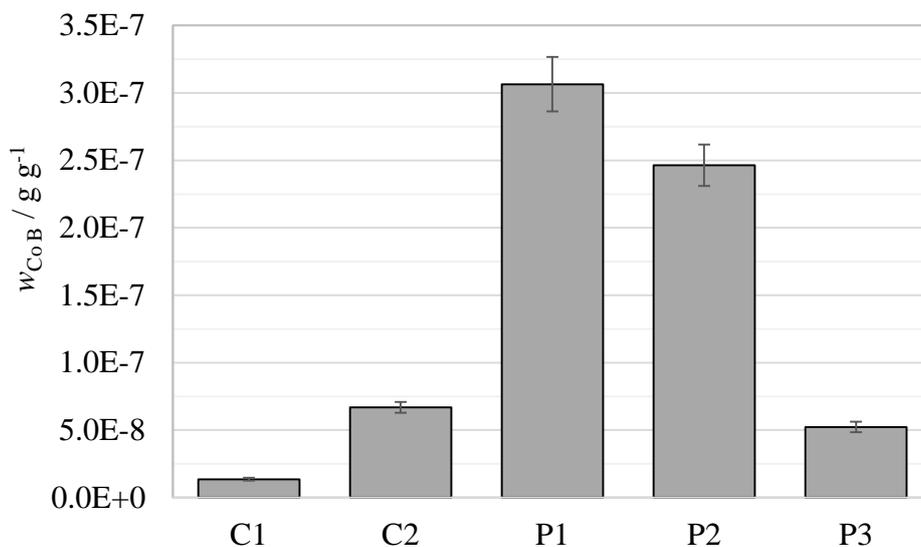


**Figure 4.** Variations of Co levels in hairs of C2 (healthy subject) during washings. The closed and open dots show the Co mass fraction (absolute right y axis and relative left y axis) at step  $i$  in sample  $H_{3,C2}$  and in the (pre-washed) sample  $H_{2,C2}$ , respectively. The error bars indicate the expanded uncertainty ( $k = 2$ ). The horizontal dashed lines show the expanded uncertainty ( $k = 2$ ) associated with Co level in  $H_{2,C2}$ .

The level of Co in  $H_{3,C2}$  decreased by 9% from  $7.44(45) \times 10^{-8} \text{ g g}^{-1}$  (step 0) to  $6.74(41) \times 10^{-8} \text{ g g}^{-1}$  (step 3). A (small) decrease was observed at steps 7 and 9.

Based on the Co variations shown in Figures 1, 2 and 4, the Co level reaches a plateau. Specifically, the level at step 3, i.e. after the IAEA washing protocol, can be considered as a good upper-bound estimate (say at percent level) of the bound Co mass fraction,  $w_{Co,B}$ . In a few cases, best accuracy might be reached with additional washing steps.

The  $w_{Co,B}$  values (i.e.  $w_{Co,3}$ ) in hair of C1, C2, P1, P2 and P3 are plotted in Figure 5.



**Figure 5.** The bound Co mass fraction,  $w_{Co,B}$ , in hair of healthy subjects (C1 and C2) and MoM patients (P1, P2 and P3). The error bars indicate the expanded uncertainty.

It is worth to observe that the  $w_{\text{CoB}}$  value measured in patient P3, requiring only monitoring, is similar to the values measured in healthy subjects C1 and C2 while the values measured in patients P1 and P2, requiring revision hip surgery, are significantly higher.

In addition, the agreement between the  $6.07(38) \times 10^{-8} \text{ g g}^{-1}$  value measured at step 9 in the (pre-washed) sample H<sub>2,C2</sub> and the  $6.26(37) \times 10^{-8} \text{ g g}^{-1}$  value measured at step 9 in the (post-washed) sample H<sub>3,C2</sub> (see Figure 4) proves that the bound component of Co was not affected by the 6 h irradiation at the neutron flux used in this study.

The opportunity of washing after the irradiation opens a straightforward way to measure both the unbound and bound components of Co in hair by INAA. Specifically, hair samples can be (i) irradiated, (ii) measured (first  $\gamma$ -counting), (iii) washed up to the plateau and (iv) measured again (second  $\gamma$ -counting). Since the result of the first  $\gamma$ -counting is the sum of bound and unbound component, the latter is obtained by difference.

## 6. Conclusions

This study investigated the application of the IAEA washing method for the measurement of Co in hairs of patients after MoM hip implant via INAA.

The possibility of performing repeated Co determinations in the same sample after successive washing steps allowed reaching a measurement reproducibility suitable to observe the removal of the unbound component.

The data showed that the three -a-w-a steps sequence proposed by IAEA and suggested as a standard washing protocol removes amounts of Co close to a plateau corresponding to the bound component. Supplementary washing steps might assure best accuracy, if required.

The agreement between the Co levels measured in hair samples after the application of a nine steps washing sequence performed prior and subsequent to the irradiation demonstrated that the bound component of Co is unaffected by the 6 h exposure to neutrons in the central channel of the Pavia TRIGA Mark reactor. This offers the unique possibility of determining the bound and unbound components by irradiating the hair sample and, consecutively, measuring the Co mass fraction before and after the application of the washing sequence. It is worth to note that the neutron effect should be tested again if longer irradiation times are required or other nuclear reactors with higher neutron flux, different neutron spectrum and higher gamma-ray field are used.

In conclusion, the adoption of a three steps -a-w-a washing sequence for the standardization of hair analysis carried out to determine the Co level is recommended in clinical applications for the mid- and long- term follow-up of patients after MoM hip resurfacing arthroplasties.

Moreover, the high Co levels obtained in hairs of two patients requiring revision hip surgery with respect to two control subjects and one patient requiring only monitoring are promising for use of Co in hair as a biologic marker in clinical surveillance.

The optional use of INAA might have some advantages compared to other analytical techniques, e.g. Inductively Coupled Plasma-Mass Spectrometry (ICP-MS), because the measurement of both the unbound and bound components of Co is straightforward. Moreover, the possibility of performing hair washing after irradiation and measuring solid samples avoids the losses of analyte and the

contaminations affecting the data collected by liquid sampling techniques requiring hair decomposition.

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