# STATEMENT ON BIOLOGICAL EFFECTS OF WEAR DEBRIS GENERATED FROM METAL ON METAL BEARING SURFACES: EVIDENCE FOR GENOTOXICITY

http://www.advisorybodies.doh.gov.uk/com/hip.htm

**COM/06/S1 - July 2006**

Introduction

1. The Medicines and Healthcare products Regulatory Agency (MHRA) - Biosciences and Implants Unit have requested advice from the COM on the evidence for genotoxicity arising from biomonitoring studies of individuals who have had metal-on-metal (MoM) hip arthroplasty. In simplistic terms hip arthroplasty involves the replacement of the head of the femur with a metal prosthesis, which articulates onto a prosthesis placed in the acetabular cup.

[Throughout this statement MoM arthroplasty refers to products containing an alloy of cobalt and chromium metals (Co-Cr). (either high or low carbon) which are currently available. Metal-on-polyethylene (metal on PE) arthroplasty currently refers to one of three alloys; Co-Cr on PE, titanium-aluminium-vanadium (TiAlV) on PE or stainless steel (SS) on PE. Stainless steel contains an alloy of iron, nickel and chromium and smaller amounts of other metals. Some further information on alloys used is presented at the end of paragraph 7 below.]

2. The COM discussed a number of studies, which had been identified by the Committee on Safety of Devices (CSD), and the COM secretariat at the February 2006 meeting.[1-11] In February the Committee also heard a short presentation from the MHRA Biosciences and Implants Unit on hip replacements. Following the February 2006 COM meeting, the secretariat met with the Bristol Implant Research Centre and a number of additional studies were identified including some pre-publication research data. These were considered at the May 2006 COM meeting.[12-14]

Context of COM consideration

3. The COM agreed the following statement but noted it was important to place the evaluation and conclusions into context with regard to the unknown clinical relevance of the identified effects and the known benefits of hip replacement. In this regard the COM agreed that this statement should not be read in isolation but should be considered in conjunction with relevant advice on hip replacement from the Committee on Safety of Devices (CSD) and the MHRA. The COM was made aware of the considerable benefits to patients from hip replacement operations (eg pain relief and improved mobility).

**Background information on hip replacement and wear debris**

[Background information provided by the CSD and summarised below.]

4. Particulate debris can be generated from articulating surfaces, metal-on-metal couples and from any modular or fixation interface as a result of corrosion, abrasion and differential micromovement.

There are reports available regarding patients with particulate metal debris in the local periprosthetic tissue and in distant organs such as spleen, liver and lymph glands. Nickel, cobalt and other metal ions are released through these articulations and are subsequently found at an increased level in patient's blood, urine, hair and regional lymph glands. Larger metallic particles are associated with a foreign body giant cell reaction and smaller particles accumulate in cells and may cause histopathological damage locally in the periprosthetic tissue and systemically.

5. The generation of wear debris and the reported biological effects are dependent on various factors such as:

- types of metal used in the alloy of the prosthesis
- nature of the break-down products
- size and number of the particles generated
- the amount of metal debris in particulate form
- the amount dissolved in tissue fluids - ionic form
- prior exposure to metal components
- how long the implants are in situ
- age and activity level of patients etc.
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**Advice requested from COM**

6. The COM were asked to discuss the available information and consider the following questions:

i. Is there convincing evidence that MoM hip replacements can result in increased genotoxicity in patients? [This question refers to cobalt-chrome hip replacements ie Co-Cr on Co-Cr hip replacements.]

ii. Can any conclusions be made with regard to the chemical(s) responsible, in part, or fully for the observed responses?

iii. Is there convincing evidence that an interaction between Cr and Co may be important in the observed mutagenic responses?

7. During its discussions, the COM expanded its consideration to include metal-on-polyethylene (PE) hip replacements as relevant data were presented in the papers reviewed [ie Co-Cr on PE, TiAlV on PE and SS on PE]. In metal-on-PE hip replacements the femoral prosthesis contains a metal alloy whilst the acetabular cup prosthesis is made up of polyethylene.

[In assessing the studies members were aware that a typical alloy used for cobalt chromium prostheses would contain 63% cobalt, 26%-30% chromium, 5%-7% molybdenum, 1% nickel, 1%manganese, 1% silicon and small amounts of iron and carbon. A typical stainless steel alloy contains 65.5% iron, 17% chromium, 12% nickel, 2.5% molybdenum, 2% manganese, 1% silicon and small amounts of sulphur and carbon. It is noteworthy that SS prostheses do not contain cobalt.]

**Overview of submitted genotoxicity data**

**Doherty AT et al, The Journal of Bone and Joint Surgery (Br), 83-B, 1075-1081, 2001[2]**

8. Chromosome translocations and aneuploidy in peripheral blood lymphocytes were compared between a group of revision arthroplasty patients (n = 31, mean age = 71±13.4 y, average implantation time 11.5 years, range = 3-21 y) and controls undergoing total hip arthroplasty (n=-30, mean age = 63.9±12.7 y). All patients had osteoarthritis except two at primary arthroplasty. All took non steroidal anti inflammatory medicines (NSAIDs). 11 patients had cobalt-chromium (Co-Cr) prostheses, 13 had titanium-aluminium-vanadium (TiAlV), six had stainless steel (SS), and one a hybrid titanium-Co-Cr prosthesis. [In a subsequent paper (see paras 10-12 summarising the paper by Ladon et al 2004 below) it was reported that all these patients had metal-on-polyethylene prostheses]. Adjusted analyses reported a statistically significant five-fold increase in aneuploidy in patients with Ti (without any increase in translocations). In contrast adjusted analyses reported a 2.5 fold increase in aneuploidy and a 3.5 fold increase in translocations in patients with Co-Cr prostheses. No increase in either end point was reported for stainless steel.

9 Members considered that the number of patients included in the study was relatively small and that it would not be possible to draw any definite conclusions regarding differences between types of MoM hip replacement devices from the available results. It was agreed that the analysis using high resolution inductively-coupled mass spectrometry (ICPMS) for concentrations of metals in blood had been adequately undertaken. Members considered that the evaluation of aneuploidy and chromosomal aberrations had been generally adequately reported, although members would be interested to see full details of how the studies were undertaken and reported, so that it would be possible to consider how the aneuploid index was derived and how the results of the non-disjunction assays were reported. Thus it was noted that 300 cells were used in metaphase analysis, but it was not apparent whether this also applied to the detection of non-disjunction.

**Ladon D et al, The Journal of Arthroplasty, 19, 8 suppl 3, 78-83, 2004[3]**

10. 95 patients with total hip arthroplasty (Metasul®; head and articulation (Co-Cr high carbon), acetabular cup (large cup shaped cavity on the lateral surface of the oscoxae in which the head of the femur articulates); polyethylene; stem Protasul S30 (stainless steel)) were recruited. Patients with existing prostheses, previous radiotherapy, or chemotherapy were excluded. Blood samples (10 ml) were obtained prior to operation (95) and at 6 months (80), 1 year (89), and 2 years (54) post operation. Another 5 ml sample was taken at each time point for trace metal analysis. Cultures were set up within 24 h of collection. Post operative blood levels of Co-Cr were elevated at 2 years.

The highest level of Cr was at 2 years and the highest level of Co was at 1 year. A much smaller but statistically significant increase in Molybdenum was reported at the time points used. There was a statistically significant increase in translocations and aneuploidy at all time points after operation.

This was evident if the data from both scorers were combined and if the data from the single scorer of both translocations and aneuploidy (both chromosome gain and loss) were analysed separately. The increase in aneuploidy was much greater than that of chromosome translocation and both were progressive over time.

11. The COM agreed that more patients had been studied in this study compared to Doherty et al 2004.[2] The measurement of metal concentrations in blood had been adequately undertaken. Members noted that very few details of the determination of aneugenicity had been reported and agreed that further information should be requested from the authors. The evaluation of chromosomal aberrations had been adequately undertaken and reported.

12. Members noted that the evidence from these two studies supported the involvement of released chromium and cobalt in the observed chromosomal effects associated with MoM hip replacement, although it was not possible on these data to conclude whether this was due to release of soluble ions or particulate metals. The Chairman asked members to consider the available ex-vivo study.

**Davies AP et al, The Journal of Bone and Joint Surgery (Br), 87-B, 1439-1444, 2005[4]**

13. This study examined the proposal that there would be metal-specific DNA damage following incubation of synovial fluid from patients undergoing revision arthroplasty. It was considered appropriate to use the Comet assay to measure DNA strand breaks, cross links and alkali labile sites in primary fibroblasts from synovial fluid. 24 patients were included in the study at revision surgery. There were synovial fluid samples from six patients with Co-Cr MoM hips, six with Co-Cr metal on polyethylene knee replacements, six patients with SS-on-PE hip replacements and six control patients with no hip or knee replacements.

14. Members agreed that the Comet assays had been adequately undertaken. All six samples from Co-Cr MoM hip revisions induced a statistically significant increase in DNA damage. Four/six samples from Co-Cr-on-polyethylene knee joints induced statistically significant DNA damage. None of the samples from SS-on-PE prostheses induced statistically significant DNA damage. All samples from osteoarthritic control joints caused a low level but statistically significant increase in DNA damage.

15. The level of Cr in synovial fluid from MoM hips at revision was between 0.95-6.88 µM and Co varied from 0.92-2.64 µM. In the group with Co-Cr-on-polyethylene implants concentrations of chromium varied between 0.07-2.06 µM and those of Co between 0.01-0.62 µM. In the SS implant group, Cr levels were reported to vary between 0.07-2.76 µM whilst Co were below the detection limit in four cases and 0.05 µM in the two other patients. Low but measurable concentrations of Cr were documented in the osteoarthritic group whereas the level of Co was below the limit of detection in all individuals in the osteoarthritic group.

It was noted that the authors argued the data were consistent with an interaction between Co and Cr and this would explain why no DNA damage is seen in studies using SS implants.

A further reference[5] had been cited by Davies et al to support the proposal that there were metal-metal interactions involved in the aetiology of the observed DNA damage. Members agreed the data suggested a plausible hypothesis but no definite conclusions could be drawn.

**Daley B et al J J of Bone and Joint Surgery, 86-B, 598-606, 2004[13]**

16. This study investigated micronucleus formation in vitro for various metals extracted from wear debris from patients with different types of implant. Titanium, +/- aluminium and vanadium were reported to be correlated with the formation of centromere-positive micronuclei. The concentration of cobalt and chromium +/- nickel and molybdenum were reported to be correlated with the formation of centromere positive and negative micronuclei combined. Members expressed reservations regarding the use of primary amniotic cells for this study, and noted there were no appropriate negative and positive control data for micronucleus induction in this test system. The Committee noted that apparent positive response regarding Stainless Steel implant wear debris but observed this was based on two samples only and the magnitude of the response was small. It was concluded that there was no convincing evidence for a mutagenic response with Stainless Steel wear debris. Members also had reservations regarding the reported dose response for micronucleus induction from Co-Cr and TiVAl wear debris. It was agreed that the magnitude of response was relatively small and was suggestive of an effect at the top dose level. However overall this study had not provided convincing evidence of a metal specific effect.

**Pilger A et al, J Tox Env Health, part A, 65, 655-664, 2002[14]**

17. The COM considered that the reported results were not convincing of a mutagenic effect of metal-on-metal hip replacements. The test used was not considered the most sensitive genotoxicity assay. The association was only found with one type of sampling method. No correlation was made between two samples from the same patient.

**Additional in-confidence data submitted by BIRC[12]**

18. The COM considered that this study using the COMET assay had been adequately conducted, but provided insufficient information on interpretation of the COMET assay data. No conclusions could be drawn with regard to metal specific mutagenic effects from these data.

COM discussion

19. Members noted a preliminary study where there was evidence for a higher incidence in chromosome aberrations in bone marrow samples adjacent to the prosthesis (ie the femur) compared to iliac crest marrow from the same patients[6] but agreed that it was unclear from the paper whether MoM or metal-on-PE hip replacements had been studied.

A further preliminary report which had been published in abstract form only documented a higher incidence of 14:18 translocations in peripheral blood lymphocytes in patients undergoing revision hip arthroplasty.[7]

20. Members commented that the available information suggested that metal-on-metal hip replacement results in elevated blood levels of Co and Cr ions.[10] Post-mortem histological evaluations had shown widespread metal debris in individuals with SS and Co-Cr implants which could be detected even when there was no apparent wear of the replacement hip. Metal debris was detected in both local and distant lymph nodes, bone marrow, liver and spleen.[8] In a further post-mortem histological evaluation study metallic wear particles were more prevalent in patients who had a failed hip arthroplasty compared with patients with a primary hip or knee replacement.[9]

21. Members briefly discussed potential mechanisms by which metal ions could induce the observed effects which included effects on DNA repair and fidelity and induction of oxidative DNA damage. It was agreed that the biomonitoring and wear debris studies provided had not provided convincing evidence for an interaction between metals or for metal specific mutagenic effects (eg clastogenicity and/or aneugenicity). However the possibility of interactions between metal ions with regard to mutagenic events could not be discounted.[11]

22. In discussing the available genotoxicity data on MoM and metal on PE hip replacements, the COM was aware that several metals and metal ions investigated in the studies reviewed by the COM, were considered as possible (eg metallic cobalt and nickel) or as known human carcinogens (eg chromium VI ions, or nickel compounds) by the World Health Organisation's International Agency for Research on Cancer (IARC). (www.iarc.fr) The COM also noted the data discussed did not allow an assessment of the clinical relevance of the genotoxicity data. Any potentially increased risk of cancer associated with hip replacements needed to be balanced against the benefits resulting from hip replacement and was not considered to be part of the referral to the COM. [The risk-benefit assessment is a matter for the MHRA.] Overall, the Committee agreed there was good evidence for an association between CoCr-on-CoCr and CoCr or TiAlV on polyethylene (PE) hip replacements and increased genotoxicity in patients. It was noted that good evidence for an association does not necessarily mean there is a causal relation. There was no convincing evidence for increased genotoxicity in patients with stainless steel on polyethylene hip replacements (SS on PE).

COM conclusions

23. The COM reached the following conclusions in response to the questions considered (see paragraph 6 of this statement) during its discussions:

i. Is there convincing evidence that MoM hip replacements can result in increased genotoxicity in patients?

[This question refers to cobalt-chrome hip replacements ie CoCr on CoCr hip replacements. The Committee's discussion also included consideration of metal-on-polyethylene hip replacements. The product types currently available and considered by the COM are outlined in paragraph 1 of this statement.]

**The Committee agreed there was good evidence for an association between CoCr-on-CoCr and CoCr or TiAlV on polyethylene (PE) hip replacements and increased genotoxicity in patients. There was no convincing evidence for increased genotoxicity in patients with stainless steel on polyethylene hip replacements (SS on PE).**

ii. Can any conclusions be made with regard to the chemical(s) responsible, in part, or fully for the observed responses?

**The evidence for the increased genotoxicity observed and the increased blood levels of chromium and cobalt, in patients with Co-Cr-on-Co-Cr hip replacements or Co-Cr on polyethylene hip replacements, gave rise to concern because this may present a potential risk of carcinogenicity in humans. However, it was not possible to make any definite conclusions as to which metal ions, or interactions between metal ions or particulate metals might be responsible for the observed genotoxicity.**

iii. Is there convincing evidence that an interaction between Cr and Co may be important in the observed mutagenic responses?

**There was limited evidence available to suggest a possible interaction between chromium and cobalt ions and possible mutagenicity/DNA damage in vitro but not in vivo. There was no convincing evidence for metal-specific effects of wear debris with regard to potential for clastogenicity or aneugenicity.**

**July 2006 COM/06/S1**

**References**


1. Case et al J of Arthroplasty, 26, (2), 174-188, 2005.
2. Doherty AT et al, The Journal of Bone and Joint Surgery (Br), 83-B, 1075-1081, 2001.
3. Ladon D et al, The Journal of Arthroplasty, 19, 8 suppl 3, 78-83, 2004.
4. Davies AP et al, The Journal of Bone and Joint Surgery (Br), 87-B, 1439-1444, 2005.
5. De Boeck M et al, Mutagenesis, 18, 177-186, 2003.
6. Case CP et al, Clin Orthop Relat Res, 329 (suppl), S269-279, 1996.
7. Jenkin L et al, J of Bone and Joint Surgery, 81B (suppl III), 319, 1999.
8. Case CP et al J of Bone and Joint Surgery, 76-B, 701-712, 1994.
9. Urban RM et al, J of Bone and Joint Surgery, 82-A, 457-477, 2000.
10. Milosev I et al, J Orthop Res, 23, 526-535, 2005.
11. De Boeck et al. Mutation Research, 533, 135-152, 2003.
12. Niedzwiedz W et al In-confidence pre-publication research BIRC, 2006.
13. Daley B et al J J of Bone and Joint Surgery, 86-B, 598-606, 2004.
14. Pilger A et al, J Tox Env Health, part A, 65, 655-664, 2002.