



[DEFENDANT]

**Reopening of the case ruled on by the Danish Committee on Scientific Dishonesty for Health and Medical Sciences on 18 December 2013 pertaining to charges brought against [DEFENDANT] on 19 July 2011**

28 August 2014

The Danish Agency for Science,  
Technology and Innovation  
Secretariat of the DCSD

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## 1 Introduction

On 19 July 2011, [COMPLAINANT] (Complainant) e-mailed the Danish Committees on Scientific Dishonesty (DCSD). The Complainant accused [DEFENDANT] (Defendant) of scientific dishonesty in connection with the articles:

1. [ARTICLE 1]
2. [ARTICLE 2]
3. [ARTICLE 3]
4. [ARTICLE 4]
5. [ARTICLE 5]
6. [ARTICLE 6]
7. [ARTICLE 7]
8. [ARTICLE 8]
9. [ARTICLE 9]
10. [ARTICLE 10]
11. [ARTICLE 11]
12. [ARTICLE 12]

The case has been considered by the Danish Committee on Scientific Dishonesty for Health and Medical Sciences (the Committee). A draft ruling of 25 June 2013 was sent to the parties for consultation, pursuant to section 13 (3) of executive order no. 306 of 20 April 2009 on the DCSD, as amended by order no. 144 of 20 February 2012 (the DCSD Order). The parties' comments on the draft ruling were included in the ruling of 18 December 2013 to the extent that they contained significant new information (see section 5).

Since the distribution of the draft ruling on 25 June 2013, the Defendant has been represented by the lawyer [LAWYER].

The Committee initially issued its ruling in the case on 18 December 2013. In January and February 2014, the Committee received representations from the Defendant and two co-authors, [THE TWO CO-AUTHORS], relating, among other issues, to Articles 6, 7 and 10 in the case. Their representations contained new information concerning these three articles. In this light, and after further correspondence with



the parties (see section 4), the Committee reopened the case, pursuant to section 14 of the DCSD Order.

Following the reopening of the case, a draft ruling of 9 May 2014 was sent to the parties for consultation. The Committee finds that the parties' responses to the consultation do not contain new information or anything else that gives the Committee cause to change the conclusions in its draft ruling of 9 May 2014. The points of view put forward by the parties in their responses to the consultation are reproduced in section 5.14, and any comments on these by the Committee are reproduced in the relevant subsections to section 7 of the Committee's final ruling after the re-opening of the case, which follows below. The Committee has also modified its ruling in section 7.1.

A copy of the ruling has been sent to the Complainant.

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## 2 Ruling

The Committee finds that the Defendant acted in a scientifically dishonest manner when participating in the work concerning 3, 4, 5 and 12, pursuant to section 2 of executive order no. 306 of 20 April 2009 on the Danish Committees on Scientific Dishonesty, as amended by order no. 144 of 20 February 2012 (the DCSD Order).

The Committee finds:

1. That the Defendant, in articles 4 and 5, intentionally committed a serious breach of good scientific practice corresponding to undisclosed distorted interpretation of own results, pursuant to the DCSD Order section 2, no. 4, by failing to provide information that the biopsy material stemmed from the same subjects as in Article 1 and in another article authored by the Defendant. In these specific instances, knowledge was withheld from readers that results based on the same subjects were used to support the conclusions in articles 4 and 5. See also sections 7.16.1 and 7.16.2.
2. That the Defendant, in articles 3 and 5, intentionally committed a serious breach of good scientific practice corresponding to undisclosed selective or surreptitious discarding of own undesired results, pursuant to the DCSD Order section 2, no. 2, by failing to provide information that the biopsy material stemmed from previous studies with more subjects than the number included in articles 3 and 5. As a result, knowledge was withheld from readers that a selection of subjects had taken place. See also sections 7.16.1 and 7.16.2.
3. That the Defendant, in Article 12, by gross negligence committed a serious breach of good scientific practice corresponding to undisclosed construction of data, pursuant to the DCSD Order, section 2, no. 1, by failing to provide information that eight subjects stemmed from a previous study (used in Article 8) and were therefore subject to a different research protocol than the one described in the methodology section of Article 12. See also section 7.16.4.



4. That the Defendant, in Article 4, by gross negligence, committed a serious breach of good scientific practice corresponding to undisclosed construction of data, pursuant to the DCSD Order, section 2, no. 1, by failing to respond to obvious image manipulation in the article. See also section 7.17.3.

The Committee will inform the Defendant's employer, [UNIVERSITY] and [HOSPITAL], by sending a copy of this ruling, pursuant to the DCSD Order, section 15 (1), no. 1.

Pursuant to section 15 (1), no. 2 of the DCSD Order, the Committee recommends that the following scientific article be withdrawn or the information contained in the article be corrected (for example in an erratum):

[ARTICLE 12]

The Committee notes that the Defendant has contacted the respective journals and requested the withdrawal of articles 3, 4 and 5. As a result, the Committee does not intend to pursue these matters any further.

The Committee will send copies of its rulings to the journals in which articles 3, 4, 5, 6, 7 and 12 were published, as these journals received a copy of the ruling of 18 December 2013.

This unanimous decision was reached by Lise Wogensen Bach, Ulla Feldt-Rasmussen, Palle Holmstrup, Kirsten Ohm Kyvik, Ole Haagen Nielsen and Jens Overgaard and Henrik Gunst Andersen (chairperson).

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### 3 Summary

*In July 2011, a professor at a Danish university (the Complainant) submitted a complaint to the DCSD alleging scientific dishonesty in 12 published articles (articles 1–12), the publication of all of which involved a researcher (the Defendant) employed at a Danish research centre. The complaint concerned research in the health sciences and was therefore considered by the Danish Committee on Scientific Dishonesty for Health and Medical Sciences (the Committee).*

*The Complainant alleges that the Defendant acted in a scientifically dishonest manner during the implementation and reporting of research activities in the articles, in the form of inaccurate descriptions of the subjects, the undisclosed use of the same biopsy material and subjects, manipulation of images, erroneous and misleading presentation of data, and a number of other offences.*

*The Defendant contends that there was no scientific dishonesty in the instances cited by the Complainant.*

*The Committee initially issued its ruling in the case on 18 December 2013. The initial ruling of 18 December 2013 found scientific dishonesty in six of the 12 articles (nos. 3, 4, 5, 6, 7 and 12).*

*In January and February 2014, the Defendant and two co-authors of articles 6, 7 and 10 submitted new information to the Committee stating that the Committee had, in its ruling of 18 December 2013, misunderstood facts concerning articles 6, 7 and 10. The two co-authors submitted new material to the Committee in support of their contention. In light of this new information, and of representations from the Defendant, the Committee reopened the case in February 2014.*

*In its revised ruling, and contrary to the initial ruling of 18 December 2013, the Committee found that there was no scientific dishonesty in articles 6 and 7 in the form of failure to inform the readers that a selection of subjects had taken place, and that there was no scientific dishonesty in article 4 in the form of failure to provide information that certain measurements were only made on a selected part of the study population.*

*After reopening the case, the Committee still ruled that there was scientific dishonesty in the following four instances:*



1. Lack of information in articles 4 and 5 about the fact that the biopsy material stemmed from the same subjects used in article 1 and in another article authored by the Defendant, thus concealing from the reader the knowledge that results based on the same subjects were used to support the conclusions in articles 4 and 5;
2. Lack of information in articles 3 and 5 about the fact that the biopsy material stemmed from previous studies with more subjects than the number included in articles 3 and 5, thus concealing from the reader the knowledge that a selection of subjects had taken place;
3. Lack of information in article 12 about the fact that eight subjects stemmed from a previous study (used in article 8) and had been subject to a different research protocol than the one described in the methodology section in article 12;
4. Image manipulation in article 4.

Concerning the use of biopsy material from previous studies and its inclusion in other articles, the Committee found that there is no unambiguous practice stipulating that, in general, explicit information is provided about the origin of the test material, including its use in other articles. The Committee noted, however, that the specific circumstances surrounding a given article may entail that good scientific practice would involve providing explicit information on the origin of the test material.

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**Ref 1.**

The Committee found that the lack of information in articles 4 and 5 about the fact that the biopsy material stemmed from the same subjects as previous studies represented a serious breach of good scientific practice because, in order to support the conclusions in articles 4 and 5, the discussion section refers to the results of previous articles (article 1 and another article authored by the Defendant) based on the same test material, without informing the reader that the articles were in fact based on the same material. Thus, information is withheld from the readers about the mutual interdependence of the various articles' results.

The Committee concluded that the Defendant acted intentionally in omitting this information, as the Defendant states that the Defendant did not think that, in the instances concerned, there was any requirement to provide explicit information in each article that biopsy material stemmed from a previous study. Once the case was reopened, the Defendant also stated that the practice of not disclosing the origin of the test material was a deliberate choice.

**Ref 2.**

The Committee found that the failure to inform readers of articles 3 and 5 that the biopsy material stemmed from previous studies constituted a serious breach of good scientific practice because articles 3 and 5 (the exercise study) only included 11 subjects out of an original study population of 18, and article 5 (the infusion study) only included 12 subjects out of the original study population of 18, without the reader being informed that a selection had taken place.

The Committee concluded that the Defendant acted intentionally in omitting this information, as the Defendant stated that the Defendant did not think that, in the instances concerned, there was any requirement to provide explicit information in each article that biopsy material stemmed from a previous study. Once the case was reopened, the Defendant also stated that the practice of not disclosing the origin of the test material was a deliberate choice.

**Ref 3.**

The Committee found that it constituted a serious breach of good scientific practice that information is not provided in article 12 about the origin of the test material, and thereby the article did not make it clear that a group of subjects stemmed from a previous study (used in article 8) and had been subject to a research protocol that differed from the one described in the methodology section of article 12.

The Committee concluded that the Defendant acted in a grossly negligent manner in omitting this information, because the Defendant was the lead author of article 12 and had specific knowledge of the subjects concerned, who were also included in the study for another article with the Defendant as last author (article 8). Given the Defendant's role in the production of article 12, the Defendant should have reacted to the lack of information about the subjects in the article.

**Ref 4.**

The Committee found that, in four articles (1, 3, 4 and 5), images were manipulated, which the Committee, with reference to a different ruling on the same subject concerning the same articles, found to be a serious breach of good scientific practice. The articles concerned used the same section to illustrate different proteins, and attempted to conceal this by changing the colouring and rotating the images.

The Committee noted that, in principle, all authors of a scientific article have responsibility for its overall content. In this context, the Committee was of the opinion that the lead author of the article has



particular responsibility for all of the article's content, including reading the final manuscript carefully before submitting it to a journal.

On this basis, the Committee concluded that the Defendant acted in a grossly negligent manner concerning the image manipulation in one of the four articles, as it was clear from the figure in the article that it had been manipulated. As lead author of the article, the Defendant should have noticed this and acted on it. The Committee finds that the image manipulation in the other three articles was not as clear, and therefore the Defendant did not act in a grossly negligent manner in connection with these three articles.

#### **The remaining charges**

In relation to the remaining charges, the Committee found that a number of these did not amount to serious breaches of good scientific practice, and so could not be considered scientifically dishonest, and that several of them related to the validity of scientific theories or the quality of research – matters that do not fall under the remit of the DCSD.

#### **Summary**

In summary, the Committee finds that there was scientific dishonesty in four of the 12 articles cited in the complaint submitted to the DCSD. The Committee noted that the Defendant has contacted the journals and requested that three of the four articles (3, 4 and 5) be withdrawn. The Committee has therefore decided not to take any further action regarding these articles. In relation to the remaining article (article 12), the Committee recommends that it is either withdrawn or that erroneous information be corrected in the form of an erratum.

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## **4 Process**

On 19 July 2011, the Complainant e-mailed a complaint about the Defendant to the Danish Committees on Scientific Dishonesty (DCSD). Attached to the e-mail was the report "[REPORT]", which was also sent to [UNIVERSITY]. In the report, the Complainant alleges that the Defendant acted in a scientifically dishonest manner during the implementation and reporting of research findings in 12 articles.

The complaint was considered by the Danish Committee on Scientific Dishonesty for Health and Medical Sciences (the Committee).

On 9 August 2011, the Defendant e-mailed a report to the Committee by way of an unsolicited response. On 12 August 2011, the report was also sent to the Committee by letter, accompanied by the related appendices on a USB memory stick.

On 16 August 2011, the DCSD Secretariat e-mailed the Defendant and asked for any additional comments to the Complainant's report.

On 16 August 2011, the Defendant informed the Secretariat that the Defendant had no further comments other than those mentioned in the response report.

On 17 August 2011, the Complainant sent a letter to the Secretariat containing various articles as enclosures.

Subsequent e-mail correspondence between the Defendant and the Secretariat ensued because the USB stick contained files in PZF format, which the Secretariat could not read. This correspondence ended on 31 August 2011, when the Defendant retracted the USB memory stick, as it contained original human data that the Defendant did not wish to circulate. On 7 September 2011, the Defendant sent a letter along with a new USB stick containing the appendices concerning the complaint. This time, the above-mentioned original human data was omitted, but the Defendant stressed that it was available to the Committee.



On 30 September 2011, the Secretariat sent the Defendant's response report with appendices to the Complainant for consultation. On 10 October and 7 November, the consultation period was extended by e-mail.

On 14 November 2011, the Secretariat received the Complainant's comments on the Defendant's response report by e-mail.

On 18 November 2011, the Secretariat e-mailed the Complainant's comments to the Defendant for consultation.

On 22 November 2011, the DCSD Secretariat received the Defendant's comments and attachment by e-mail.

On 24 November 2011, the Secretariat e-mailed the Defendant's comments to the Complainant for information.

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On 26 November 2011, the Secretariat received further comments by e-mail from the Defendant.

On 8 December 2011, the Secretariat e-mailed the Defendant's further comments to the Complainant for information.

On 25 June 2013, the Secretariat sent its draft ruling of 25 June 2013 to the parties for consultation, with a deadline for comments of 15 August 2013.

On 15 August 2013, the Secretariat received the Complainant's comments on the draft ruling of 25 June 2013.

On 15 August, the Secretariat received comments by e-mail from the Defendant about the draft ruling of 25 June 2013. At this point, the Defendant requested to appear before the Committee.

On 22 August 2013, the Secretariat e-mailed the Complainant's comments of 15 August 2013 to the Defendant for potential final comments. At the same time, the Secretariat also sent the Defendant's comments of 15 August 2013 to the Complainant for any potential final comments.

On 13 September 2013, the Secretariat received the Defendant's final comments by e-mail.

On 16 September 2013, the Secretariat received the Complainant's final comments by e-mail. At this point, the Complainant requested to appear before the Committee.

On 4 October 2013, the Defendant requested by e-mail and letter that a deadline be set for commenting on the Complainant's final comments.

On 16 October 2013, the Defendant requested by e-mail and letter that the Committee contact the journal [JOURNAL 1] because, the Defendant stated, it could be





assumed that such an approach would bring to light information central to the case.

On 18 October 2013, the DCSD chairperson sent a letter by e-mail to the Complainant, rejecting the request to appear before the Committee on the grounds that the Complainant had failed to identify circumstances that gave any reason to assume that an oral presentation of the case would add information or perspectives that the parties had not already had the opportunity to put forward in their written submissions. The chairperson also stipulated a deadline of no later than 8 November 2013 for the Complainant to submit any final written submissions.

On 18 October 2013, the DCSD chairperson sent a letter by e-mail to the Defendant, rejecting the request to appear before the Committee on the grounds that the Defendant had failed to identify circumstances that gave any reason to assume that an oral presentation of the case would add information or perspectives that the parties had not already had the opportunity to put forward in their written submissions. The chairperson also stipulated a deadline of no later than 2013 November 2013 for the Defendant to submit any final written submission. The chairperson also rejected the request to contact [JOURNAL 1] on the grounds that it was not clear what type of information was being referred to, or how such a request would be expected to add significant new information to the case. The chairperson also pointed out that the Defendant was welcome to contact the journal personally.

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On 23 October 2013, the Defendant requested by letter that the DCSD chairperson issue a separate ruling on which individuals were eligible to participate in the proceedings as committee members and alternate members, and upon which concept of scientific dishonesty those proceedings would be based.

On 29 October 2013, the chairperson of DCSD replied by letter to the Defendant's letter of 23 October 2013, informing the latter that the chairperson saw no grounds for addressing these issues separately and that they would be incorporated into the final ruling.

On 7 November 2013, the Committee received the Defendant's final written submissions by letter.

On 8 November 2013, the Committee received the Complainant's final written submissions by e-mail.

On 18 December 2013, the Committee made its initial ruling in the case.

On 20 December 2013, the Committee received by e-mail a copy of a letter from two co-authors of articles 6, 7 and 10 (hereinafter referred to as "the two co-authors") to the journal [JOURNAL 3], in which the two co-authors argue that the Committee made a mistake in the part of its ruling of 18 December 2013 that referred to the selection of subjects in articles 6 and 7.

On 3 January 2014, the Committee received by e-mail a copy of the letter from the two co-authors to the editors of the journals [JOURNAL 3] and [JOURNAL 4]. Attached were patient records relating to subjects referred to in articles 6, 7 and 10. In the letter, the two co-authors state that the Committee is incorrect in its under-





standing of the facts relating to articles 6, 7 and 10 in the ruling of 18 December 2013. They point out that no selection of subjects was made in articles 6 and 7, but that articles 6 and 7 feature the same seven subjects who had biopsies taken in January 2005, and that article 10 features 14 subjects, who consist of the seven featured in articles 6 and 7 plus a further seven who had biopsies taken in February/March 2006.

On 3 January 2014, the Committee received an e-mail for information from the Defendant about the ruling of 18 December 2013. The e-mail contains the Defendant's comments on the ruling of 18 December 2013, including that the Defendant is of the opinion that the Committee was mistaken about the facts relating to articles 6, 7 and 10.

On 7 January 2014, the Committee received by e-mail a letter of the same date from the two co-authors, in which they request that the Committee corrects the ruling of 18 December 2013 in relation to articles 6, 7 and 10, and that the Committee re-draws the letters it sent to the editors of [JOURNAL 3] and [JOURNAL 4].

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On 3 February 2014, the Committee e-mailed the parties and the two co-authors asking them to confirm the following understanding of the facts surrounding the subjects featured in articles 6, 7 and 10, based on the information that the Committee had received from the Defendant and the two co-authors in January 2014:

*“Articles 6 and 7 feature seven subjects (who are the same people in both articles). The biopsies from these subjects were taken on 20 and 21 January 2005, as per the patient records received by the Committee from [THE TWO CO-AUTHORS] (the record for subject no. 7 says 20-10-05 on the front page. This appears to be a typographical error because the blood samples on page 2 are dated 21/01-05. The Committee therefore assumes that the biopsies for subject no. 7 were also taken on 21/01-05). Material from only seven subjects was therefore used in the preparation of articles 6 and 7.*

*Fourteen subjects feature in article 10. These 14 subjects are made up of the seven from articles 6 and 7 plus another seven who had biopsies taken on 17 February, 20 February and 3 March 2006, as shown by the patient records, copies of which were sent to DCSD by [THE TWO CO-AUTHORS].”*

At the same time, the Committee invited the parties and the two co-authors to submit comments about the Committee's understanding of the patient records. On 3 February 2014, the Committee wrote:

*“After an initial review of the patient records, it would also appear that not all of the biopsies from the 14 subjects in article 10 were studied by histochemistry and PCR and for protein:*

- For subject no. 3, the field for protein in the vastus and soleus has not been filled in
- For subject no. 5, a minus sign has been entered in the field for protein in the triceps and in the fields for histochemistry, PCR and protein in the soleus



- For subject no. 9, the fields for histochemistry, PCR and protein in the soleus have not been filled in
- For subject no. 14, 'OK' in the field for protein in the triceps has been scored out and 'No' inserted instead."

On 9 January 2014, the two co-authors e-mailed the Committee confirming this understanding of the facts in the letter of 3 February 2014 and commenting on the Committee's reading of the patient records.

On 10 January 2014, the Defendant e-mailed and mailed a letter to the Committee confirming its understanding of the facts in the letter of 3 February 2014 and commenting on the Committee's reading of patient records, as well as a number of other factors covered by the ruling of 18 December 2013. In this letter, the Defendant also requested that the Committee reopen the case.

On 10 January 2014, the Complainant e-mailed a letter to the Committee, commenting on the Committee's interpretation of the patient records and on a number of other factors covered by the ruling of 18 December 2013.

On 26 February 2014, the Committee e-mailed the parties to announce that the case would be reopened.

On 24 March 2014, the Defendant sent a letter containing new observations by way of an unsolicited response. On 28 March 2014, the letter was e-mailed to the Complainant for information.

On 2 April 2014, the Defendant e-mailed a copy of a statement signed by 76 researchers concerning some of the complaints covered by the case.

On 8 April 2014, by way of an unsolicited response, the Complainant e-mailed a response to the Defendant's letter of 24 March 2014.

After the case was reopened, the Complainant and the Defendant requested to appear before the Committee. On 6 May 2014, these requests were rejected by letters sent by the Committee chairperson.

On 22 April 2014, the Defendant e-mailed to the Committee a copy of a blog post written by a Danish professor and editor concerning the order of authors in a scientific article. On 22 April 2014, the Defendant also e-mailed to the Committee a copy of the same professor's comments about an article on authors' responsibilities and the ICMJE<sup>1</sup> rules. On 7 May 2014, the Defendant forwarded an e-mail from the ICMJE to the professor concerned about the ICMJE's interpretation of the criteria for authorship.

On 9 May 2014, the Secretariat sent a draft ruling on the reopened case to the parties for consultation, with a deadline for comments of 1 June 2014.

On 26 May 2014, the Secretariat received an e-mail request from the Defendant to extend the deadline for the submission of responses to the consultation. In this

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<sup>1</sup> International Committee of Medical Journal Editors



light, the deadline was extended until 8 June 2014. On 6 June 2014, the Defendant e-mailed a request for a further short extension of the deadline until 10 June 2014 because of the Whitsun break. The deadline was duly extended until 10 June 2014.

On 9 June 2014, the Secretariat received the Complainant's comments on the draft ruling of 9 May 2014 on the reopened case.

On 10 June 2014, the Defendant e-mailed the Secretariat with the Defendant's comments and attachments concerning the draft ruling of 9 May 2014 on the reopened case. On 11 June 2014, the Secretariat also received two further appendices from the Defendant, which had been mentioned in the Defendant's responses of 10 June 2014.

## 5 The parties' claims and contentions

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What follows consists of the most central parts of the parties' many claims and contentions. The supplementary comments in the parties' unsolicited responses (dated 24 March and 8 April 2014) are only reproduced in so far as they add significant new information. The Committee has no comment to make on the statement submitted by the Defendant on 2 April 2014, as it is not found to have any significance to the case concerned.

Section 5.14 reproduces the points of view submitted by the parties during the consultation process concerning the draft ruling of 9 May 2014 in the reopened case.

### 5.1 General

#### 5.1.1 *The Complainant's claims and contentions*

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for 12 articles. The Complainant makes the following general assertions concerning these articles.

The Complainant asserts that the material indicates a widespread reuse of the same test populations, tissue material and data, without the reader being informed of this.

The Complainant also asserts that the reuse is consciously or unconsciously concealed from the reader.

The Complainant alleges that the histochemical data clearly indicates deception, e.g. that the same stained sections are used to illustrate the presence of different peptides or the same peptide in different situations. According to the Complainant, messenger RNA data (mRNA data) is also generally presented in such a way that the actual expression level and its alleged agreement with histochemical and other data could not really be assessed by the reader, who was therefore misled.

The Complainant alleges that data has consistently been processed to promote the Defendant's hypotheses. The Complainant cites the following examples:



- Conclusions are either not supported by data or are exaggerated
- Conflicting data from the group, which appeared in other publications, is ignored
- There are grounds to suspect that undesirable results have been excluded.

The Complainant asserts that the weaknesses in the work were so evident that all of the co-authors should have reacted to them, even if they were not directly involved in the actual work at the time. Further, the Complainant alleges that the Defendant had a special responsibility, as the Defendant was the senior author on all of the publications except for one article. The Defendant therefore had the primary responsibility for planning, implementing and publishing studies, and also assumed more credit for the work.

The Complainant further alleges that, despite the clarity of the shortcomings mentioned in the articles, the Defendant opted to turn a blind eye, which suggests deliberate deception.

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As part of the consultation on the draft ruling of 25 June 2013, the Complainant asserts that the senior author of an article bears the overall responsibility for it. The Complainant thus asserts that the Defendant should be criticised because, as senior author, the Defendant did not notice, nor correct, the many features of the articles that in Complainant's view, could give rise to suspicion of scientific dishonesty.

As part of the consultation on the draft ruling of 25 June 2013, the Complainant also asserts, with reference to the Vancouver rules<sup>2</sup>, that the authors of an article must state whether they have previously used the test subjects referred to in the article. In support of this, the Complainant states that this transparency is very much required due to the durability of the test material. In this regard, the Complainant asserts that the Defendant has herself acknowledged that the same subjects were used in articles 1, 3, 4 and 5 ("exercise study") and articles 6, 7 and 10.

As part of the consultation on the draft ruling of 25 June 2013, the Complainant also asserts that it should not affect the Committee's ruling on scientific dishonesty that a journal has agreed to correct the information in a given article by publishing an erratum.

### **5.1.2 The Defendant's claims and contentions**

The Defendant contends that she is innocent of the complaint alleging scientific dishonesty. The Defendant also presents general contentions concerning the complaint.

The Defendant contends that, given how intrusive experiments with humans may be for the individual test subjects, it would be unethical not to try to extract as much data as possible from samples of human tissue that have already been collected. In this regard, the Defendant also contends that new scientific questions can arise in the wake of the original publications for which the study was conducted. In

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<sup>2</sup> International Committee of Medical Journal Editors – Uniform Requirements for Manuscripts Submitted to Biomedical Journals (now "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals").



such cases, according to the Defendant, it is permissible to use biological material that has been stored in a freezer.

The Defendant contends that, when using the same material in several articles/studies, the standard practice is to make reference to the previously published study in the methodology section or to provide an in-depth description of the design and procedures in each article.

The Defendant agrees that the authors used biological material from the same subject in more than one article. The Defendant also states that it is true that the authors have included the same description of muscle-fibre types in three articles, because they considered that this information constituted a description of the study population.

The Defendant contends that, in some cases, the authors have failed to include a proper reference in the methodology section, but that they did usually refer to the other articles with the same material in the results and discussion sections.

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In this regard, the Defendant contends that several researchers in integrative biology, including the Complainant, have used the same material in multiple articles.

The Defendant contends that the Complainant's recurring criticism of the lack of correspondence between mRNA levels and protein levels is based on an outdated view of a central dogma in molecular biology: namely, that DNA is transcribed into RNA, which is transformed into protein. The Defendant claims that there are several ways in which protein expressions can change without major changes in mRNA.

According to the Defendant, the method used in intervention studies, by which pre-exercise Ct values are normalised to 1 and Quantitative Polymerase Chain Reaction data (qPCR data) obtained from subsequent samples is expressed as "fold changes", is common practice when looking for the effect of an intervention.

The Defendant contends that the Complainant appears to think that IHC is a quantitative technique, which according to the Defendant is not the case. The Defendant contends that IHC is not a quantitative technique *per se* and that staining intensity can vary depending on the procedure used.

The Defendant refers to the following statement by the Complainant: "In the discussion they concluded that it is likely that muscle-derived BDNF works in an autocrine and/or paracrine manner. They did not mention that this view was in conflict with the fact that they did not find any difference in release of BDNF to the medium in contraction-treated versus control C2C12 cells."

In this regard, the Defendant contends that the Complainant is confused about basic endocrinological terms. According to the Defendant, autocrine signalling is a form of signalling in which a cell secretes a hormone or chemical messenger that binds to an autocrine receptor on the same cell, leading to changes in the cell. Paracrine signalling is a form of cell signalling in which the target cell is close to the signal-releasing cell. The authors did not observe an increase in BDNF in the cell



medium or in the animals' blood circulation, and for this reason, they concluded that the effects were neither paracrine, autocrine nor endocrine.

According to the Defendant, throughout the complaint, the Complainant overlooks that proteins can be up-regulated in the muscle cell without being separated, and that they can be separated without being involved in organ-to-organ signalling.

The Defendant contends that the authors, as soon as they became aware that some IHC images had been manipulated, reported the relevant articles to the DCSD, advised the journals and withdrew the articles.

As part of the consultation on the draft ruling of 25 June 2013, the Defendant states that the same test material was used in articles 1, 3, 4 and 5 and in articles 6, 7 and 10. The Defendant contends that it does not constitute a serious breach of good scientific practice that it is not pointed out in these articles that the same test material was used in the other articles. In support of this contention, the Defendant notes the following:

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- In connection with a research project, biopsies were taken and divided into several samples, so that research could be conducted on each sample. According to the Defendant, the samples were taken at the same time, but had not previously been used. They were then made the subject of new research, in which new data was studied based on new samples obtained from the original biopsies. These samples must be described in each project, which can be done directly, or possibly indirectly, by reference to information about previous projects.
- With reference to a letter from 70 Danish researchers, which was attached to the Defendant's response to the consultation, the Defendant contends that it is not the practice in the above-mentioned procedure to refer to the use of the sample material in each article if the articles study different scientific questions. The Defendant also refers to the examples in the consultation response. According to the Defendant, these show that a number of reputable researchers use the same practice as the Defendant and do not explicitly disclose the previous use of the same sample material.
- According to the Defendant, it is not the case that the Vancouver rules contain a stipulation that information must be disclosed about previously applied test subjects, since the concept of "subjects" must be understood to mean the materials rather than the test subjects.
- According to the Defendant, it cannot be assumed that the readers of articles such as the ones referred to in this case have an expectation that "original" material has been used.
- According to the Defendant, no statistical problems nor problems in terms of mass significance arise from using the same biological material for testing various hypotheses published in different articles.
- The Defendant challenges the Committee's ruling that it is relevant to the circumstances of the experiment that information about any previous use of the biological material is provided. The Defendant responds that account is taken of the day-to-day variation in muscle biopsies for IHC and that the degradation of the material is not a problem; that the reuse of material for mRNA measurements has no methodological influence on the test results in the studies referred to in the complaint; and that it is, of course, im-



portant that biological material is stored according to the regulations, but that cross-referencing does not in itself help to provide the reader with important specific knowledge of this.

As part of the consultation on the draft ruling of 25 June 2013, the Defendant contends that, in relation to the inaccurate information that appears in articles 3 and 12, and the conflicting information in article 9, errors have been made rather than dishonesty committed. According to the Defendant, this point of view is supported by the fact that the journals concerned have accepted corrections and printed errata.

As part of the consultation on the draft ruling of 25 June 2013, the Defendant challenges the Committee's ruling that the Defendant should have noticed the image manipulation in articles 1, 3 and 4. In support of this contention, the Defendant notes the following:

- The Defendant disputes the Committee's ruling that the mention of quantitative differences in the captions to the figures should have caused the Defendant to examine the images more closely. The Defendant states that the Committee has misunderstood the Defendant's perception of the IHC method. The Defendant is of the view that the IHC method is not quantitative per se, i.e. the method does not provide a numerical (let alone accurate) quantity or concentration, but that it is possible to see, with the naked eye, e.g., "increased expression". According to the Defendant, the captions use precisely the type of vague terms commonly used in qualitative or semi-quantitative analyses, and as such do not give particular cause to study the figures more closely.
- At the time the articles were produced, the Defendant had no suspicion that [CO-AUTHOR] (hereafter referred to as "Co-author 1"), who according to the Defendant conducted the IHC for the articles, had manipulated the images concerned. Nor were the IHC results concerned inconsistent with what might have been expected in a scientific context.
- The Defendant's role was not senior to that of Co-author 1.
- The Defendant provided a chronological account of the circumstances that led to the submission to the DCSD of the articles concerned and Co-author 1's alleged scientific dishonesty. According to the Defendant, this account shows that it was incredibly difficult to spot the image manipulations, and therefore, the fact that the Defendant failed to do so cannot be characterised as gross negligence.

As part of the consultation on the draft ruling of 25 June 2013, the Defendant denies having had special responsibility as "leading senior author". The Defendant contends, in relation to the relevant articles that she was only the last author on some of them (not of all of them), and in some cases corresponding author, but that she did not have a special role as "guarantor" (the term used in the Vancouver rules). The Defendant also contends that whether she was corresponding author or not cannot be included in the assessment of liability. As such, the Defendant disputes the Committee's ruling that she acted in a grossly negligent manner.

During the consultation on the draft ruling of 25 June 2013, the Defendant contended that Ulla Feldt-Rasmussen, Palle Holmstrup, Kirsten Ohm Kyvik and Jens





Overgaard were not eligible to participate in the proceedings, as, in the Defendant's opinion, the Minister of Higher Education and Science did not have the authority to extend their membership (in Jens Overgaard's case, his alternate membership) until completion of the proceedings, which would be after the expiry of their term of office on 31 January 2012. On 16 October 2013, the Defendant instituted legal proceedings against the Minister of Higher Education and Science on the basis that these members, and the alternate member, are/were not eligible to participate in the proceedings, and requested that the Committee suspend proceedings pending the outcome of the legal case.

During the consultation on the draft decision of 25 June 2013, the Defendant also contended that, when ruling on the articles referred to in the case, the Committee must use the concept of dishonesty that was applicable at the time the articles were produced. In this respect, the Defendant contends that the concept has been made stricter, e.g. through abolishing the impropriety condition and incorporating "serious breaches of good scientific practice".

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As part of the consultation on the draft ruling of 25 June 2013, the Defendant states that the draft ruling does not include an opinion on the degree of scientific dishonesty and its importance to the scientific message conveyed by the product concerned, pursuant to the DCSD Order, section 15 (2).

## 5.2 Article 1

### 5.2.1 *The Complainant's claims and contentions*

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: "[ARTICLE 1]"

The Complainant asserts that the Interleukin-6 staining (IL-6 staining), seen after exercise, was surprisingly high considering the complete lack of staining at rest, and that it was not clear how the sections were selected to illustrate the results after exercise. The Complainant states that the caption for Figure 1 mentions that the subjects had been exercising, but that it is not right to include sections from more than one subject, as only one section is shown for each time point.

The Complainant states that, although no attempt was made to quantify the IL-6 staining, and although it was not explicitly mentioned how many sections were evaluated, it was stated in both the results section and the caption that IL-6 immunoreactivity increased significantly after exercise. The Complainant asserts that it was not stipulated whether more than one researcher studied the sections, nor whether this was done on the basis of a blind reading.

The Complainant alleges that, for IL-6 mRNA, an elevenfold increase in the response was found between pre-exercise and the end of the workout, but that values were not, unfortunately, stated for pre-exercise. The Complainant also asserts that an explanation is required for the absence of IL-6 protein in muscle fibres in the presence of the corresponding mRNA at rest, and that the need for an explanation becomes more acute once a previous article by the group is taken into account. According to the Complainant, in the previous article, the authors reported that IL-



6 mRNA could not be detected in muscle before a marathon – and only in five out of eight subjects afterwards ([REFERENCE ARTICLE 1]). These findings were not mentioned.

The Complainant also asserts that the finding of a peak in mRNA at the end of exercise fits well with a peak in intramyocellular IL-6 protein three hours later, but – again – that this finding could not be evaluated based on the sparse IHC data presented. In the Complainant's view, it is possible that the evaluation of the IL-6 stainings was influenced by knowledge of the mRNA findings in the current or previous studies.

The Complainant alleges that the above deficiencies give rise to serious doubts about the article as a whole, and that these doubts (see below) are confirmed by the fact that one of the sections shown in this article (Figure 1, Panel H) was also used to illustrate an oxidative stress marker (Nitt) in article 4 (Figure 3, Panels D and F). According to the Complainant, the group has subsequently published conflicting results regarding IL-6 protein expression in resting muscle cells and the proportion of different types of fibres (see comments on article 6 below).

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The Complainant asserts that, although the data mentioned was accurate, it did not justify the conclusion. According to the Complainant, there was an accumulation of IL-6 in muscle cells, whereas a draining would be necessary to take into account the release of IL-6 from a leg after exercise and the accompanying increase in plasma IL-6 concentrations. According to the Complainant, it ought to be common knowledge from endocrinology that, generally speaking, an endocrine gland's hormone stocks are quickly used up once hormone secretion is stimulated. The Complainant asserts that the authors' knowledge of this ought to have raised their suspicions about the data, and that they were exposed to these arguments – at the latest – at a scientific meeting at [RESEARCH CENTRE 1] on 19 June 2003, i.e. before the article was approved for publication.

The Complainant states that a one-way ANOVA was used in the article. The study included two groups, and therefore, according to the Complainant, this was either not the right approach (it should have been a two-way ANOVA) or else the analysed data (IL-6 mRNA and plasma concentrations) stems only from the post-exercise group.

### **5.2.2 The Defendant's claims and contentions**

The Defendant contends that she is exculpated of the Complainant's allegation of scientific dishonesty.

The Defendant has informed the Committee that the article has been withdrawn.

The Defendant argues, in support of her claims, that IHC is used in basic research to understand the distribution and localisation of biomarkers and differentially expressed proteins in different parts of biological tissue, but that it is not a quantitative method. The Defendant contends that, since muscle tissue expresses a low amount of IL-6 mRNA at rest, which increases with exercise, the authors were not surprised that IL-6 protein was low/absent at rest and increased with exercise.



The Defendant also contends that it was Co-author 1 who conducted the IHC analysis, evaluation and data presentation. The Defendant claims that, since IHC is not a quantitative method, it is clear that the term “significant” is used in its non-statistical sense, i.e. important, meaningful, wide-ranging, big.

The Defendant also contends that it is well known that IHC, unlike qPCR, is not a quantitative method, and that the qPCR technique was developed into an unprecedentedly sensitive method that allowed small amounts of mRNA to be identified. According to the Defendant, the authors’ assertion that they were able to identify IL-6 mRNA with qPCR while protein was low/absent when measured by IHC is not contradictory. In this connection, the Defendant also refers to her general comments.

With regard to the pre-exercise levels, the Defendant states that Ct levels for IL-6 mRNA were on average 34.2, while the levels were 30.7 in post-exercise tests. According to the Defendant, when one looks at the individual levels, the average maximum increase after exercise was a factor of 11.

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The Defendant states that [REFERENCE ARTICLE 1] is an early qPCR article. As indicated in the methodology section, the authors used, according to the Defendant, a semi-quantitative PCR method, which is less sensitive than qPCR. qPCR was introduced as a new technique to measure mRNA after the article by [THE AUTHORS OF REFERENCE ARTICLE 1] was published. According to the Defendant, this produced a quicker and far more sensitive system for determining mRNA levels, one that facilitates the detection of low-level transcripts. In this light, the Defendant claims that it is now possible to determine pre-exercise levels of cytokines. The Defendant states that the initial establishment of the fact that IL-6 mRNA increases in human skeletal muscle when measured by qPCR was performed by [RESEARCHER 1] in the group, and was also the catalyst for the collaboration between the Defendant and [RESEARCHER 1].<sup>3</sup>

The Defendant contends that the criticism is unacceptable. According to the Defendant, since IL-6 mRNA levels, up to that point, were only found in the muscle tissue, the authors wanted to assess whether IL-6 mRNA was translated into protein, and whether it was present in the muscle fibres. Since IHC, according to the Defendant, is not a quantitative technique, the authors can only state that protein data fitted well with the IL-6 mRNA levels identified in this article and in previous articles.

The Defendant also contends that the authors – once they became aware that the IHC images had been manipulated – reported this to the DCSD and the scientific journal concerned, and subsequently withdrew the articles.

As far as IHC is concerned, the Defendant refers to her comments under “General”.

The Defendant claims that it is not surprising that the sensitivity of protein expression varies between two independent studies. The quality of the staining depends, according to the Defendant, on a number of factors, including antibody dilution, colour reagent, the preparation and fixation of cells and tissues, and incubation

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<sup>3</sup> [REFERENCE ARTICLE 2]



time with antibody and colour reagents. According to the Defendant, IHC is not a quantitative method per se, and the staining intensity can vary depending on the procedure used.

The Defendant claims that it is clear that the Complainant demonstrates a significant lack of knowledge regarding the biological role of muscle-derived IL-6. According to the Defendant, myokine IL-6 has greater autocrine and/or paracrine effects inside the actual muscle itself, and this has been demonstrated in numerous publications, not least with regard to IL-6's ability to increase fat oxidation in skeletal muscle. The kinetics of exercise-induced IL-6 protein expression in the study are, according to the Defendant, fully consistent with the fact that IL-6 accumulates in the muscle cells after exercise, and after the peak in IL-6 release from the muscle.

The Defendant contends that the Defendant did not recall the discussion to which the Complainant refers at a meeting at [RESEARCH CENTRE 1].

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The Defendant also contends that, in the initial publication, only IL-6-IHC was presented, as several publications had already demonstrated that exercise induces an increase in IL-6 mRNA. However, according to the Defendant, the evaluators wanted IL-6 mRNA data to be presented in order to confirm IHC data relating to IL-6 protein, and for this reason, the authors analysed IL-6 mRNA in a subset of subjects, in order to verify several previous studies. The Defendant contends that the authors did not provide any data for the resting control group, and therefore, a one-way ANOVA statistical analysis was used.

The Defendant claims that, even if there is a suspicion that IHC data is flawed, it seems that the conclusion from the above article may actually be sound. According to the Defendant, at the same time as the authors published the first immunoblots of IL-6 protein in skeletal muscle cells after exercise, Hiscock et al. published supportive IHC data on "in situ hybridization", which showed that IL-6 mRNA expression increased in muscle cells after exercise. In the Defendant's opinion, this study concurs with the Defendant's study, and the only difference relates to the muscle fibres that express IL-6.

The Defendant contends that the most important result is that the muscle fibres express IL-6 protein in response to contraction. According to the Defendant, this difference in muscle fibres was believed to be due to a difference in exercise protocols, e.g. that the fibres recruited during exercise would also express IL-6. According to the Defendant, several subsequent studies support the idea that IL-6 is expressed and produced by muscle cells.<sup>4</sup>

As part of the consultation on the draft ruling of 25 June 2013, the Defendant contends that Co-author 1 was the first author of the article and must be considered the senior author.

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<sup>4</sup> [REFERENCES TO ARTICLES].



## 5.3 Article 2

### 5.3.1 *The Complainant's claims and contentions*

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: “[ARTICLE 2]”

The Complainant asserts that the findings presented are inconsistent with “common sense” and are mutually contradictory to an extent that should have made the authors cautious with regard to data and conclusions – all the more so because they had previously been warned, as described above. The Complainant also makes the following assertions:

- During exercise, the histochemical data showed an accumulation of IL-6 in the muscle cells of the subjects, while IL-6 was released from the leg into the venous blood. This is not in obvious accordance with the hypothesis that released IL-6 stems from muscle cells.
- During the exercise, the accumulation of IL-6 in the muscle cells was identical in the two groups, even though IL-6 was released from the leg in subjects but not in the vitamin-treated group.
- Over a three-hour period post-exercise, a corresponding marked decrease in intracellular IL-6 in the muscle cells was observed in both groups. This was accompanied by the release of IL-6 from the legs in both groups. However, the release was much higher in the control group than in the vitamin-treated patients. The difference between the groups, in terms of the relationship between IL-6 consumption and its release in the leg, was not explained further.

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The Complainant alleges that it is probably not possible to reconcile these different results within the parameters of the overall conclusion and that no attempt was made to do so.

On this point, the Complainant asserts that the objections concerning the histochemical data are the same as those described in relation to article 1. According to the Complainant, significant increases in IL-6 expression in muscle fibres as a response to exercise were reported, but the results were not based on quantification and statistical tests. According to the Complainant, no description was provided of the evaluation of sections, which should have been blind and preferably by more than one researcher. According to the Complainant, a figure presented sections from three points in time from one individual from each group, but it was not stated whether all samples representing either the control group or the vitamin-treated group were from the same person.

The Complainant alleges that, based on comparisons between neighbouring sections stained for ATPase and IL-6, respectively, the authors concluded (in contrast to the results in article 1) that, as a response to exercise, IL-6 was predominantly (albeit not exclusively) accumulated in type-1 muscle fibres. According to the Complainant, the article does not report how many fibres were evaluated, nor was any attempt made to provide a quantitative estimate of the distribution of IL-6-positive fibres among all fibre types.



According to the Complainant, following exercise, IL-6 mRNA rose identically in the two groups, and the responses were comparable to those seen in article 1. However, these results were again merely presented as what are referred to as “fold changes”, i.e. based not on the application of absolute values, but on relative ratios between the groups. According to the Complainant, this makes it impossible to assess the actual quantities in the tissue and thus whether the mRNA most likely stems from muscle cells or other less important cells. According to the Complainant, in this study – in contrast to the previous one (article 1) – IL-6 mRNA and protein levels in muscles fell in parallel after exercise. The Complainant alleges that this difference was not mentioned, even although the time between the two variables was emphasised in article 1.

The Complainant also asserts that personal characteristics in the two groups should not differ, and that, accordingly, no signs were shown of statistical differences in Table 1 concerning BMI ( $23.5 \pm 0.3$  (SE) in the vitamin group vs.  $25.9 \pm 0.3$  in the control group per kg/m<sup>2</sup> (unit incorrectly stated) and the maximum effect ( $150 \pm 3$  vs.  $140 \pm 3$  W). According to the Complainant, the values seem to vary nevertheless. The Complainant alleges that, in accordance with this assumption, blood flow in the leg also seems to be lower (20%) in the control subjects during exercise at 50% of maximum effect than in vitamin-treated subjects (Figure 1).

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### **5.3.2 The Defendant's claims and contentions**

The Defendant contends that she is exculpated of the Complainant's allegations of scientific dishonesty.

To support this position, the Defendant contends that qPCR data (Figure 3) showed that IL-6 mRNA accumulated in contracting skeletal muscle tissue, while repeated measurements of IL-6 protein concentration in arterial and femoral vein samples showed that IL-6 was released from the contracting leg, but only during exercise in the placebo-treated control group (Figure 5 in the article). According to the Defendant, these results are in accordance with the findings of several other published studies.<sup>5</sup>

The Defendant contends that the IHC data (Figure 4) suggests that the increased IL-6 mRNA corresponds to increased protein content in skeletal muscles during exercise and recovery. The observation that IL-6 protein accumulates in the tissue and is released into the circulation at the same time does not appear to be contradictory, according to the Defendant. The Defendant therefore claims, firstly, that the quantities of IL-6 in circulation can represent an effect caused by the transfer of IL-6 into the bloodstream, while the majority of IL-6 is retained in the contracted muscle. The Defendant also contends that the proposed autocrine and paracrine effects of IL-6 are consistent with this explanation. Secondly, according to the Defendant, it is possible that the stainings represent immature precursors of IL-6. Thirdly, according to the Defendant, a simple delay in the release leads to a similar result.

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<sup>5</sup> For review and meta-analysis, the Defendant refers to [REFERENCE ARTICLE 3].





The Defendant also states that it seems quite improbable that all of the IL-6 that has been translated into protein should be released immediately, without any – at least temporary – intracellular accumulation of IL-6 protein, including its precursors.

The Defendant claims that the observation that translation (IL-6 mRNA into protein) and translocation (IL-6 into the circulation) are two separate steps, regulated separately, does not appear to be contradictory either. According to the Defendant, both post-translational modifications (splitting, phosphorylation and glycosylation) and translocation are most probably regulated by mechanisms other than those that regulate translation. The Defendant claims that in vitro results suggest that antioxidants – e.g. vitamins C and E – regulate IL-6 synthesis in muscle fibres at the transcription level, but that the results for IL-6 mRNA and IHC in the article suggest that post-translational mechanisms are involved. The Defendant notes that the IHC data presented supports the qPCR data, but that the interpretation that post-translational mechanisms are involved is not solely based on IHC data. In this connection, the Defendant contends that qPCR and IHC data merely denote snapshots, which do not provide information about the actual circulation of either IL-6-mRNA or protein in muscle tissue. According to the Defendant, it does not, therefore, make a great deal of sense to try to make direct comparisons with net release of IL-6 based on repeated samples from the femoral artery and veins.

The Defendant contends that several explanations for the observed results are possible:

- Firstly, a release of IL-6 was, in fact, observed in both groups, but especially during recovery time and in the vitamin-treated group.
- Secondly, intramyocellular IL-6 degraded locally without being released.
- Thirdly, there is neither qPCR nor IHC information about the conversion of IL-6 mRNA or protein in the tissue. Accordingly, it is possible that both the synthesis and the degradation were less pronounced in the vitamin-treated group. Changes in the synthesis/degradation rate in the tissue could probably produce identical qPCR and IHC results but different IL-6 release data when comparing the two groups.

The Defendant contends that the above points could have been discussed in more detail in the article, but that this discussion should also involve several aspects in addition to translation/translocation.

The Defendant also contends that it was Co-author 1 who conducted IHC, evaluation and data presentation in this article – and, since IHC, as mentioned above, is not a quantitative method, it is clear that the term “*significant*” in connection with IHC was used in its non-statistical sense, i.e. important, meaningful, wide-ranging, big. The Defendant notes that no attempt was made to hide the fact that IHC data was qualitative rather than quantitative. In this connection, the Defendant refers to the fact that the IHC data (Figure 4) is listed as “Representative stains”. In addition, according to Defendant, it was stated in the discussion that “we could not determine whether the skeletal muscle’s IL-6 protein content was higher in the treatment group than in the control group, as the intensity of staining for IL-6 protein was not quantified.”





The Defendant states that, during the process of writing and reviewing this manuscript, only two other studies existed that evaluated IL-6 protein in contracting skeletal muscle: (Article 1 and [REFERENCE ARTICLE 4]). Although both studies, according to the Defendant, also found that IL-6 protein could be detected in skeletal muscles after exercise, the distribution of staining varied between them. The Defendant states that both the authors and the reviewers – who were selected by the journal [JOURNAL 2] – wanted the discussion to take into account these apparent differences in the IL-6 protein breakdown. According to the Defendant, possible explanations were submitted, but no final conclusions were made regarding what appeared to be fibre type-specific distribution. According to the Defendant, it was concluded that “muscle biopsies obtained during the performance of different states and intensities would add useful information to the observed differences in the finding of IL-6 protein expression in skeletal muscles in the various studies at this time point”.

The Defendant also states that, whatever the form of qPCR data analysis, IL-6 mRNA data only provides snapshots. According to the Defendant, no information was supplied about the synthesis or degradation rates of the method used, and therefore, the “true” amount of recently synthesised IL-6 in response to physical activity was not known.

The Defendant contends that the  $\delta\text{-}\delta\text{-Ct}$  method was considered a standard method of assessing the quantitative qPCR data at the time of the experimental part of the study. According to the Defendant, several other studies at the time used exactly the same method to assess quantitative qPCR data.

The Defendant claims that inconsistencies between articles 1 and 2 – in particular, with regard to IL-6 protein in skeletal muscle – are, in fact, discussed in article 2, and that it was concluded that differences in the mode and intensity may play a role.

The Defendant contends that, when the two groups were compared, there were no statistical differences in terms of age, height, BMI or maximum effect ( $P_{\max}$ ). According to the Defendant, this could have been stated more clearly, although comparisons between groups were made clear in the bottom part of Table 1, which contains the plasma vitamin concentrations. The Defendant states that the authors agree that the BMI unit is incorrectly specified (a minus is missing in the printed version of the manuscript).

With regard to femoral “blood flow”, the Defendant contends that the two-way ANOVA test showed no statistical difference between the groups, but only the influence of time. According to the Defendant, additional comparisons were later made (in [PHD THESIS]) using an “area under the curve” method, but this still showed no statistically significant difference between the groups ( $p = 0.134$ ). The Defendant claims that, when adjusted for the workload, the apparent difference in the femoral “blood flow” – when comparing the groups – was even less ( $P = 0.360$ ).



## 5.4 Article 3

### 5.4.1 *The Complainant's claims and contentions*

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: “[ARTICLE 3]”

Concerning the study population, the Complainant asserts that it is not clear whether 11, 12 or perhaps 18 subjects took part in study 1, although the methodology section does clarify that the number was 11. According to the Complainant, the caption for Figures 1 and 3 shows that six individuals were included in each of the two groups (exercising and resting). According to the Complainant, this leads to suspicion that a subject may have been excluded without this being mentioned, as it would be natural to have an equal number of subjects in the two groups.

The Complainant also asserts that in articles 1 and 4, 18 subjects (12 exercising and six resting) were subject to a protocol identical to those used in the study (exercise and repeated biopsies over 24 hours). According to the Complainant, the subjects in the three articles share remarkably similar characteristics (age, height, weight and maximum oxygen uptake) – a fact that raises the question of whether the individuals (and consequently, the tissue samples) used in this study were a subset of those who participated in the studies cited in articles 1 and 4. The Complainant alleges that the material studied in the three articles is basically identical.

On this point, the Complainant asserts that the suspicion that the three studies presented the same material is further supported by the fact that the article (p. 511) states that “IL-8 protein was not expressed in muscle tissue before exercise (n=12)”, which, according to the Complainant, indicates that the exercising group comprised a total of 12 people. The Complainant alleges that, according to the methodology section in article 4, 12 subjects exercised, while six rested. The caption for Figure 1, according to the Complainant, shows six exercising and five resting subjects, corresponding to the number stated in the methodology section in article 3.

As far as IHC is concerned, the Complainant states that data is illustrated by a section stained for IL-8 protein from each of the six points in time at which a muscle biopsy sample was taken (Figure 2). In addition, two sections are enlarged 2–4 times, and one section is stained for the different fibre types shown. The Complainant asserts that it is not specified how the sections were selected, i.e. from one or more subjects, or how they were evaluated (one study? blind?). The Complainant further alleges that the sections are all of poor quality and do not confirm the text, which states that IL-8 was expressed in cytoplasm, membranes (which?), cell nuclei, and periodically (meaning?) in endothelium.

The Complainant alleges that the text (p.511) states that 21 hours<sup>6</sup> post-exercise, there was a strong immune reaction for IL-8, while the caption to Figure 2 states

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<sup>6</sup> The Committee notes that the Complainant appears to have made a mistake here and in the opinion of the Committee it should state 24 hours and not 21 hours. During the consultation about the draft ruling, the Complainant has stated that since the “exercise” period was three



that the staining was slightly increased at that time point. The Complainant also asserts that the section representing 21 hours<sup>7</sup> post-exercise appears to be the same as the one representing 0 hours (pre-exercise). In addition, this section is, according to the Complainant, also used in article 5, Figure 3D, where it illustrates the presence of IL-6-receptor protein in muscle-fibre membranes.

The Complainant alleges that it is clear from the discussion section (p. 513) and the conclusion (p. 514) that exercise induced a significant increase in IL-8 mRNA in the muscle fibres. According to the Complainant, however, the qPCR analysis used does not allow for locating the mRNA measured.

The Complainant also asserts that only the number of times mRNA has increased compared to pre-exercise values is reported. The Complainant alleges that the critical threshold value/number of cycles necessary to achieve detection (Ct values) in the analysis should have been reported in order to enable the reader to evaluate how large a cell population would contribute to mRNA measurements. According to the Complainant, the absence of IL-8 protein (according to the histochemistry) in the presence of the corresponding mRNA while at rest also requires explanation in greater detail.

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With regard to the calculation of IL-8 release from the leg, the Complainant asserts that the differences in “femoral veno-arterial plasma concentration” (in Figure 5, with the wrong unit: ng/min) were incorrectly multiplied by blood flow in the leg, instead of plasma flow. The Complainant finds this surprising, given that the corresponding calculation for IL-6 release was properly conducted in the previous article with the same senior author (article 2).

The Complainant claims that midway through the exercise period, there had been a significant increase in IL-8 release above basic levels, but that IL-8 tends to be absorbed in the leg rather than released into the bloodstream before and after that time point, at rest and during exercise and recovery. According to the Complainant, this pattern is quite unusual but the authors have not commented on it.

The Complainant asserts that the authors’ conclusion – that muscle-derived IL-8 may “exert its effect either endocrinally or paracrinally” (p.514) – cannot be justified by their results, even though this conclusion is tentative.

During the consultation on the draft ruling of 25 June 2013, the Complainant asserted that, in connection with the reporting of mRNA as increasing by a particular factor, the variation of the basic values was not specified.

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hours, it is possible, as the Complainant did, also to describe it as taken 21 hours after (the end of) the exercise.

<sup>7</sup> The Committee notes that the Complainant appears to have made a mistake here. The Committee therefore bases its ruling on the sections referred to by the Complainant being the 24-hour section and not, as stated by the Complainant, a 21-hour section (which does not exist). During the consultation about the draft ruling, the Complainant has stated that since the “exercise” period was three hours, it is possible, as the Complainant did, also to describe it as taken 21 hours after (the end of) the exercise.



#### **5.4.2 The Defendant's claims and contentions**

The Defendant contends that she is exculpated of the Complainant's allegation of scientific dishonesty.

The Defendant has informed the Committee that the article has been withdrawn.

The Defendant refers to her comments under "General" (and Table 1) as far as the study population is concerned.

The Defendant contends that the part of the IHC study to which the complaint refers was carried out by Co-author 1.

The Defendant also contends – as mentioned above – that when the authors became aware that the IHC images had been manipulated, they reported this to the DCSD and the scientific journal and then withdrew the articles.

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The Defendant states that the authors assumed that the increase in muscular IL-8 mRNA corresponded to the IHC image, showing an increase in muscular IL-8 protein.

With regard to mRNA levels, the Defendant refers to her comments under "General". The Defendant also contends that IL-8-Ct levels went from 36 (pre-) to 31 (post-) in connection with the exercise study, and from 34 (pre-) to 27 (post-) in the two-legged knee-extensor model.

The Defendant states that, before exercise, the Ct levels would only constitute <10 mRNA copies per cell, even though the protein level would be expected to be low.

The Defendant claims that the Complainant has confused the measurement of net IL-6 release with the net IL-8 release (and the respective use of plasma and blood flow). According to the Defendant, as far as IL-6 is concerned, a study suggested that this cytokine does not interact with red blood cells ([REFERENCE ARTICLES 5]). The Defendant contends that this is why the authors use plasma flow to calculate IL-6 net release from a working leg.

The Defendant states, on the other hand, that IL-8 is known to interact closely with red blood cells ([REFERENCE TO ARTICLES]). According to the Defendant, therefore, it is appropriate to use blood flow when calculating net IL-8 release, and if plasma flow had been used, the net release would have been underestimated by a factor of about 2.

The Defendant contends that it is correct that a small net release of IL-8 across the working leg was only observed after 1.5 hours of exercise, and it is also correct that the authors used the blood flow, not plasma flow, to calculate the net release of IL-8 across the working leg – which, according to the Defendant, is the correct way to take the measurement.

The Defendant claims that there was no significant release or uptake of IL-8 across the leg at any time – except from after 1.5 hours of exercise. The Defendant contends that the Complainant's comment, that Figure 5D might suggest that IL-8 was



added to the muscle at other times, was not supported by the statistics (as also mentioned on page 513 of the article), and that the authors did not find any reason to discuss this further (an observation that the authors believe represents analytical variance).

The Defendant contends that the authors clearly concluded that IL-8 appears to exert its effects locally in the working leg (p. 514) and that it is correct that they write endocrine or paracrine mode just 17 lines above this conclusion – it should have been autocrine or paracrine (which, according to the Defendant, would be obvious to most neutral readers). According to the Defendant, the fact that the authors saw no systemic increases in plasma-IL-8 (as also observed by other groups), and only a transient and smaller net release of IL-8 across the working leg, is discussed in the article and in the overall study conclusion (the last four lines on p. 514).

The Defendant states that although there is a correlation between qPCR and IHC data in the study, the authors suspected that the IHC data might be defective, and have therefore withdrawn the article.

The Defendant contends that the IHC data was not critical to the article's conclusion.

The Defendant maintains that IL-8 data was presented and discussed in a balanced way in the light of the available literature, and that the conclusions in the article are fully justified.

As part of the consultation on the draft ruling of 25 June 2013, the Defendant contends that the lack of precision in the stipulation of the number of subjects was merely a mistake and not a serious breach of good scientific practice. The Defendant states, therefore, that it is clear from the text in the results section and in the captions to Figures 1 and 3 as well as from the figure itself, that “n=6” in the captions refers to the exercise group. The Defendant also states that the authors made a mistake when drafting the results section, where they wrote n=12 instead of n=11.

## **5.5 Article 4**

### **5.5.1 The Complainant's claims and contentions**

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: “[ARTICLE 4]”

The Complainant states that the histochemical results were presented in Figure 2 and Figure 3 as, respectively, Metallothionein expression (MT-expression) and expression of the oxidative stress marker nitrotyrosine (NITT). According to the Complainant, the figures illustrated a temporal progression by showing a section of a muscle biopsy from each time point, but in Figure 3, the section representing the muscle after 3 hours of exercise (Figure 3D) was the same as the one that showed the muscle three hours after exercise (Figure 3F), and the same section was also used in article 1 to illustrate IL-6 expression in muscles 21 hours after exercise (Figure 1H).



The Complainant also asserts that it is not clear how the sections presented were selected and assessed. According to the Complainant, no attempt was made to quantify the staining, yet the term “negligible immunoreactivity” was used nevertheless. The Complainant alleges that no examination was made of the neighbouring section to see whether the observed variation in the metallothionin content between fibres was accompanied by variation in NIT2, even though the presence of exercise-induced MT expression was attributed to oxidative stress.

The Complainant alleges that, as mentioned above (see article 3, “subject population”), there is a discrepancy between the number of participants stated in the methodology section (12 exercising and 6 resting = 18) and the caption for Figure 1 on MT mRNA (6 exercising and 5 resting = 11). The Complainant also states that there is a suspicion that the individuals and muscle biopsies were identical with those mentioned in articles 1 and 3 – and also overlapped with those in article 5 (see below). According to the Complainant, the personal data presented in the three articles is consistent with this suspicion.

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According to the Complainant, page 480 mentions that the mRNA levels were hardly detectable, i.e. they basically could not be measured quantitatively at rest, but nonetheless, the rate of increase while exercising is calculated, and therefore, according to the Complainant, Ct values should have been included.

The Complainant also asserts that the conclusions in the abstract and at the start and end of the discussion section – about MT-mRNA being expressed in both type 1 and type 2 muscle fibres after exercise – are not justified by the results, because “in situ hybridisation” was not undertaken.

During the consultation on the draft ruling of 25 June 2013, the Complainant asserted that the basic values in this article are ostensibly non-quantifiable. According to the Complainant, this means that it is obviously inadvisable to use fold changes.

### **5.5.2 The Defendant's claims and contentions**

The Defendant contends that she is exculpated of the Complainant's allegation of scientific dishonesty.

The Defendant has informed the Committee that the article has been withdrawn.

The Defendant states that once the authors became aware that the IHC images had been manipulated, they reported this to the DCSD and the scientific journal, and then withdrew the article.

The Defendant states that the authors have nothing to add about IHC because all of this work was done by Co-author 1. The authors did not have expertise in IHC, which is why they worked with Co-author 1 on this part of the study.

With regard to the study population, the Defendant refers to her comments under “General” and Table 1. According to the Defendant, the authors informed the read-



ers that mRNA measurements were only performed on a sub-group, due to “lack of material”.

The Defendant contends that MTII-mRNA data in Figure 1 was calculated and presented as MTII/glyceraldehyde 3-phosphate dehydrogenase (GAPDH) ratios, because otherwise, the exercise levels would have been barely detectable. However, according to the Defendant, the results section presented an approximate rate of increase, to make it easier for the readers to understand. The Defendant contends that readers would be fully capable, on the basis of the ratios in Figure 1, of working out the factor increase, and therefore they were not misled in any way.

According to the Defendant, the muscle biopsies were taken from the musculus quadriceps, and are therefore representative of a mixture of type 1 and type 2 fibres. The Defendant contends that, because the MT protein appeared to represent identical expressions of muscle fibres, the authors concluded that there was no difference between the types of fibres in terms of their ability to express MT.

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The Defendant states that the authors now think that the IHC data was flawed, but that they found no reason in the first instance to suspect Co-author 1’s data. According to the Defendant, the qPCR and IHC data in the article matched.

As part of the consultation on the draft ruling of 25 June 2013, the Defendant contended that it cannot be acknowledged that the information about the subjects in the article is flawed. To support this point, the Defendant states that measurements for MTmRNA expression were only performed on 11 people. In the Defendant’s view, Figure 1 clearly states that this study refers to n=6 (exercise) and n=5 (rest). The Defendant contends that this is because the material for mRNA had not been prioritised and was therefore only available for n=6 (exercise) and n=5 (rest).

As part of the consultation on the draft ruling of 25 June 2013, the Defendant also contended that Co-author 1 was the article’s first author and has a particular interest in the subject of the article. According to the Defendant, Co-author 1 was responsible for submitting the article and corresponding with the journal. In this light, it is the Defendant’s view that Co-author 1 must be regarded as senior author of the article.

## 5.6 Article 5

### 5.6.1 *The Complainant’s claims and contentions*

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: “[ARTICLE 5]”

As far as the study population is concerned, the Complainant states that one of the human studies used the same ergometer protocol and the same timetable for blood tests and biopsy of the vastus lateralis muscle as presented in articles 1, 3 and 4. According to the Complainant, this is also compatible with some of the numbers of studied subjects listed in articles 3 and 4. According to the Complainant, under this protocol, six subjects exercised while only five rested. The Complainant asserts that





the personal data presented suggests that that the study populations and tissues were identical in the four studies.

The Complainant alleges that the discussion section shows that the plasma IL-6 levels obtained were higher in the infusion-system experiment (see below) than in the exercise experiments, even though measurements of plasma concentrations had not previously been mentioned in the article. The measurements referred to are therefore, according to the Complainant, the ones presented in article 1.

If the material for the four items came from the same experimental study, this was, according to the Complainant, not referred to in article 5, while articles 3 and 4 were not cited, and the reference to article 1 does not mention a close relationship with the study covered therein.

The Complainant alleges that recombinant human IL-6 or saline was injected into the femoral artery in the second study, which, according to the Complainant, seems to be an unethical approach unless justified by a purpose other than this study.<sup>8</sup> It was not specified from where the blood samples were taken. The Complainant refers to a previous study of “FFA kinetics” by the Defendant’s laboratory, in which the femoral artery was used for infusions identical to those in this study, while blood samples were taken from the other femoral artery ([ET AL ARTICLE]). According to the Complainant, the personal characteristics and plasma IL-6 concentrations are identical in the two studies. The Complainant alleges that there is a suspicion that the two articles were based on the same study, even though this is not mentioned in the articles.

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The Complainant asserts that the sections used to illustrate the presence of the IL-6 receptor 21 hours after IL-6 infusion (Figure 3D)<sup>9</sup>, use the same section used in article 3 to illustrate the presence of IL-8 in muscles before (Figure 2A) and 21 hours after (Figure 2G) exercise. According to the Complainant, it is not specified how the sections were chosen for the illustration (e.g. whether they represent the same person at all of the points in time), nor how they were evaluated (e.g. “blind”, by more than one researcher?).

The Complainant asserts that the discussion section informs readers that the IL-6 receptor was expressed identically in both type 1 and type 2 muscle fibres, but that evidence of this was not presented and that the methodology section did not mention the staining of types of fibre. While a very prolonged increase in IL-6 receptor mRNA after exercise was offset by an increase in the staining of the receptor in the plasma membrane, an increase in receptor staining in response to IL-6 infusion did not lead to an increase in mRNA.

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<sup>8</sup> During the consultation on the draft ruling, the Complainant has stated that the Complainant did not wish to complain about the ethical aspect of Article 5. During the consultation about the draft ruling, the Complainant has stated that since the “exercise” period was three hours, it is possible, as the Complainant did, also to describe it as taken 21 hours after (the end of) the exercise.

<sup>9</sup> The Committee notes that the Complainant appears to have made a mistake here. The Committee therefore bases its ruling on the sections referred to by the Complainant being the 24-hour section and not, as stated by the Complainant, a 21-hour section (which does not exist). During the consultation about the draft ruling, the Complainant has stated that since the “exercise” period was three hours, it is possible, as the Complainant did, also to describe it as taken 21 hours after (the end of) the exercise.



The Complainant alleges that a Western blot of IL-6 protein would have been appropriate to support the histochemical findings.

As far as IL-6 receptor mRNA is concerned, the Complainant asserts that the evaluation of data in the human trials is made difficult by the fact that the values were reported as “fold changes” from unspecified base levels. The Complainant alleges that Ct values should have been presented.

The Complainant asserts that if the mouse experiment was to have been reproducible for others, the swimming conditions should have been better described (e.g. water depth and surface area, number of mice swimming simultaneously). The Complainant also asserts that, because skeletal muscle varies, the precise muscle from which the samples were taken should be specified.

With reference to the conclusion to the article, the Complainant asserts that exercise does not cause a decrease in IL-6 levels.

During the consultation on the draft ruling of 25 June 2013, the Complainant asserts that when reporting mRNA in terms of the rate of increase, the variation for base values was not specified.

During the consultation on the draft ruling of 25 June 2013, the Complainant also asserts that the subjects in the article’s “infusion study” are the same ones referred to in a previous article,<sup>10</sup> but that this earlier application is not disclosed in the article.

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### **5.6.2 The Defendant’s claims and contentions**

The Defendant contends that she is exculpated of the Complainant’s allegation of scientific dishonesty.

The Defendant has informed the Committee that the article has been withdrawn.

As far as the study population is concerned, the Defendant refers to her comments under “General” and Table 1.

The Defendant contends that, in order to avoid double-disclosure of data, the authors reported (but did not show) plasma IL-6 levels from the original study and listed the correct reference.

With reference to the Complainant’s comments concerning Figure 3D, the Defendant states that once the authors became aware that the IHC images had been manipulated, they reported this to the DCSD and the scientific journal and then withdrew the article.

The Defendant states that it is true that the authors included an earlier human study to look at a new scientific question. According to the Defendant, the authors

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<sup>10</sup> [THE ET-AL ARTICLE].



included the reference from this study in the discussion (ref. 38), but they did not mention the original study in the methodology section.

In relation to the Complainant's claim that the study was conducted in an unethical manner, the Defendant contends that the ethics committee approved the study.

According to the Defendant, muscle biopsies were taken from the musculus quadriceps, and are therefore representative of a mixture of type-1 and type-2 fibres. The Defendant contends that, because IL-6 receptor protein appears to have been identical in terms of muscle fibres, the authors concluded that there was no difference in fibre-type expression.

As far as Ct values are concerned, the Defendant refers to her comments under "General". In connection with this, the Defendant contends that the Ct value for IL-6-receptor mRNA averages 33.5 before exercise and 31.3 five hours after exercise. According to the Defendant, this shows a clear increase in the amount of IL-6 receptor mRNA.

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As far as the description of the mouse experiment is concerned, the Defendant claims that the level of detail is a matter of discretion.

The Defendant states that the authors wrote the following at the start of the discussion:

*"Increased expression of the IL-6 receptor in muscle fibers after an exercise bout suggests that the muscle is sensitized by IL-6. The peak in IL-6 receptor production occurs several hours after the end of the exercise bout, at the time when IL-6 plasma levels are decreasing (4). Expression of the IL-6 receptor may therefore be a mechanism whereby muscle is sensitized to the effects of IL-6 when IL-6 levels are sparse".*

The Defendant contends that this section is self-explanatory.

The Defendant states that the authors now think that the IHC data was flawed, but that the conclusion that exercise regulates the expression of IL-6 receptor mRNA is sound.

The Defendant notes that the authors possess unpublished data that shows that human muscle biopsies and human primary muscle cell cultures express IL-6 receptor protein measured by Western blot ([RESEARCHER 2] et al, unpublished data).

## 5.7 Article 6

### 5.7.1 The Complainant's claims and contentions

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: "[ARTICLE 6]"



The Complainant alleges that, unlike article 1, the study found IL-6 in resting muscle fibres, but the authors did not mention this significant difference between the findings in the present and previous studies, and therefore no attempt was made to explain it.

The Complainant asserts that the title, abstract and end of the discussion section all emphasise the specificity of the cytokine expression in different muscle fibre types, while the message at the start of the discussion section is more ambiguous. The Complainant alleges that it is not possible for the reader to evaluate the underlying evidence, because it is not clear how the sections were evaluated (i.e. the number of fibres per section, and whether this was done by more than one researcher), nor was any attempt made to quantify the findings.

According to the Complainant, it was proposed that the discrepancy between the content of cytokine mRNA and protein depends on a post-transcript regulation, but that, in order to justify the main conclusion about the fibre-type specificity of the cytokine expression and to clarify the discrepancy in cytokine protein and mRNA, “in situ hybridisation” should have been conducted and compared with the fibre-type composition.

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According to the Complainant, the article states that the Myosin Heavy Chain1 mRNA level (the MHC1-mRNA level) reflected the corresponding protein level based on an evaluation of the fibre types. The Complainant alleges that this is not quite correct, because the content of this protein was significantly higher in soleus compared with the vastus lateralis muscle, whereas this was not the case for mRNA content.

The Complainant refers to the comment on articles 7 and 10 about the reuse of materials and data.

### **5.7.2 The Defendant's claims and contentions**

The Defendant contends that she is exculpated of the Complainant's allegation of scientific dishonesty.

The Defendant states that – as previously pointed out – the Complainant assumes that the IHC technique is quantitative. According to the Defendant, this is incorrect. The Defendant claims that the strength of using IHC is that it provides information about the location of a given protein.

The Defendant also contends that optimal staining depends on a number of factors, including antibody dilution, dyes, preparation and/or fixation of cells/tissues and incubation of antibody/reagent staining. According to the Defendant, IHC is not a quantitative method per se, and the staining intensity can vary depending on the procedure used. Whether or not a low expression is visible in the image depends, according to the Defendant, on a variety of technical factors, including how the photography and subsequent image editing is conducted. The Defendant contends that the fact that a protein evaluated by a qualitative method is visible in a study conducted in 2005 but not in another study conducted in 2002 was not an obvious topic for discussion.



The Defendant contends that parallel sections were evaluated, and that the authors did not attempt to quantify how many muscle fibres would express a given cytokine.

With regard to the correlation between mRNA and protein, the Defendant refers to her comments under “General”.

The Defendant contends that the use of “in situ hybridisation” would have made it possible to determine whether the muscle fibres themselves produced/expressed cytokine protein, but that this technique would not allow the authors to conclude anything about the post-translational modification.

The Defendant contends that the authors have shown that the triceps, quadriceps and soleus muscles are different in terms of the relative distribution of type-1 and type-2 fibres. According to the defendant, as far as MHC2-mRNA is concerned, the authors found the expected distribution, whereas they had expected to find a slightly higher level of MHC1-mRNA in the soleus muscle. The Defendant contends that such biological variation is not rare, and that it could be argued that it would be disproportionate to discuss this in detail.

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The Defendant contends that since it was [RESEARCH CENTRE 2] staff who conducted all of the experiments, it is improbable that Co-author 1 could have influenced the conclusions in this study.

## **5.8 Article 7**

### **5.8.1 The Complainant’s claims and contentions**

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: “[ARTICLE 7]”

The Complainant also asserts that the subjects, experiment protocols and material used in the article are the same as those used in article 6 (and article 10) and that the same data was included in all three articles. According to the Complainant, this reuse is not reported in any of the articles.

According to the Complainant, the article is largely based on a correlation analysis between, on the one hand, the mRNA content in various metabolic genes, determined by muscle biopsies, and on the other hand, the percentage of type-1 fibres in the biopsies. The Complainant alleges that each analysis included measurements for the three muscles from all subjects. The Complainant asserts that this is not the correct statistical approach, as each individual can only contribute a couple of measurements to the analysis.

The Complainant also asserts that the article’s conclusion – that certain metabolic genes are fibre-type specific – is not supported by the correlation analysis. In support of this claim, the Complainant asserts that the article found significant correlations between mRNA and the percentage of type-1 fibres, which varied widely, even



though it is clear from the data plots that such a correlation did not exist in the individual muscles.

The Complainant further alleges that data from the soleus muscle of one of the seven subjects was not included in the correlation analysis, and the reasons for this were not stated in the article.

### **5.8.2 The Defendant's claims and contentions**

The Defendant contends that she is exculpated of the Complainant's allegation of scientific dishonesty.

The Defendant contends that it is clear that the same subjects were used in the three articles, and that the authors had no intentions of concealing this.

The Defendant also contends that none of the articles treated the determination of the MHC-fibre-type distribution in the three muscles as a new discovery, but that it was merely used to confirm that the samples in question could be used as a model for the study of the importance of the MHC-fibre-type distribution for the mRNA content of selected metabolic proteins.

The Defendant agrees that there are many ways in which data from different sub-groups can be visualised. In this regard, the Defendant contends that the presentation of data in the article is highly transparent, because each individual dataset is shown.

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## **5.9 Article 8**

### **5.9.1 The Complainant's claims and contentions**

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: "[ARTICLE 8]"

According to the Complainant, the description in the methodology section of the staining of the IL-8 receptor, and the subsequent study and registration, follows the same procedures as were used in the previous articles: "primary antibody against receptor, detection by secondary biotinylated antibody and streptavidin-biotin-peroxidase complex; examination by light microscopy".

The Complainant alleges that staining of the TGF- $\beta$  receptor is not described, and that these stains are not reported in the results section.

According to the Complainant, the results of a two-layer immuno-fluorescence staining of the two receptors were presented, even though neither the fluorescence marking nor the fluorescence-microscopy method had previously been described.

The Complainant asserts, therefore, that the results section is not consistent with the methodology section.



The Complainant also asserts that the choice of muscle section is not described, including whether they were from the same subject and how they were examined (e.g. by more than one person or blind).

According to the Complainant, a Western Blot should have been used on the receptor protein, particularly because of the apparent inconsistency between the absence of IHC detectable in IL-8-receptor protein and the presence of IL-8-receptor mRNA expression at rest.

The Complainant states that the authors conclude in the article that the IL-8 receptor is located primarily in activated microvascular endothelium. The Complainant asserts that this contradicts Figure 2, in which, according to the Complainant, the receptor appears to be primarily limited to the sarcolemma (the membrane that surrounds the muscle fibres) or the adjacent cytoplasm.

The Complainant also states that the article concludes that 21 hours after exercise<sup>11</sup>, the expression of receptor-protein content returned to the pre-exercise level. According to the Complainant, this contradicts Figure 2.

The Complainant asserts that the claim in the article that the IL-8 receptor was low or absent in the muscle before exercise and during the first 1 ½ hours after exercise (p. 236 in the article) is inconsistent with protein being expressed in muscle fibres and the sarcolemma at all times.

According to the Complainant, the article also concluded that “*exercise induces CXCR2 mRNA and protein expression in the vascular endothelial cells of the muscle fibers (cf. Abstract)*”. With reference to this point, the Complainant alleges that the cellular source of the observed increase in receptor-mRNA is not known because “in situ hybridisation” was not carried out.

According to the Complainant, it is clear from the discussion section that the finding of an increase in IL-8-receptor mRNA and protein in the muscle is associated with the finding in article 3 of a release of IL-8 from the muscle, and it is proposed that there is a “local role of IL-8 in muscle”. With reference to this point, the Complainant asserts that it is not mentioned in the article that the release of IL-8 was found in the middle part of the three-hour exercise session, whereas an increase in IL-8-receptor expression in muscle was only found after exercise.

The Complainant alleges that the implications of the interpretation of the claimed protein expression were not discussed. The Complainant also asserts that the low CXCR2-RNA level was not obvious to the reader, because the basic CXCR2/GAPDH-mRNA ratios in Figure 1 were close to 1. According to the Complainant, these ratios between measurements cannot be shown in absolute terms, and therefore probably reflect the use of a form of normalisation procedure that is not described in more detail.

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<sup>11</sup> The Committee notes that the Complainant appears to have made a mistake here and thinks that it should state 24 hours and not 21 hours. During the consultation about the draft ruling, the Complainant has stated that since the “exercise” period was three hours, it is possible, as the Complainant did, also to describe it as taken 21 hours after (the end of) the exercise.





The Complainant asserts that the data was presented as geometric mean values  $\pm$  SEM (*standard error of the mean*). However, according to the Complainant, the spread in Figure 1 is symmetrical around the mean values.

### **5.9.2 The Defendant's claims and contentions**

The Defendant contends that she is exculpated of the Complainant's allegation of scientific dishonesty.

The Defendant argues that Co-author 1 conducted the IHC study of skeletal muscle sections for CXCR2, as shown in Figure 2. With reference to this point, the Defendant contends that more details could have been included in the methodology section.

Regarding the Complainant's assertion that a Western Blot should have been used, the Defendant contends that their laboratory did not use Western Blots at that time.

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As far as mRNA expression is concerned, the Defendant refers to her comments under "General".

The Defendant contends that it is clear from Figure 1 that the spread is not symmetrical. According to the Defendant, this is consistent with the fact that, when the data is expressed as geometric mean values, the spread is not symmetrical.

According to the Defendant, the qPCR and IHC data in the article match. The Defendant states, however, that it is uncertain whether the IHC can be relied upon, as it was conducted by Co-author 1.

The Defendant contends that the authors are convinced that exercise up-regulates the expression of CXCR2-mRNA levels, because they have reproduced these results in mouse experiments, which demonstrate a robust increase in CXCR2 in the skeletal muscle ([DEFENDANT] et al, data not published).

## **5.10 Article 9**

### **5.10.1 The Complainant's claims and contentions**

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: "[ARTICLE 9]"

The Complainant alleges that the article repeatedly states that the controls were matched with patients by age, gender and BMI. According to the Complainant, the assertion in the methodology section indicates that control samples with a BMI higher than 30 were excluded, and therefore a genuine matching procedure was not carried out. The Complainant further alleges that the control subjects were not randomly selected, and therefore the statistical analysis for differences in age, gender and BMI between patients and control subjects was incorrect.



The Complainant asserts that the rationale in the article for including smokers in the control group – even though not smoking for at least two months was an inclusion criteria – is unclear, and that data concerning the effects of continued smoking was not discussed.

In relation to the fact that four patients, according to the Complainant, were treated with peroral steroids, the Complainant asserts that the article does not report whether the occurrence of cytokine was different for these and other patients.

The Complainant also asserts that it is confusing that the ATPase staining for fibre-type identification is described in two different parts of the article.

According to the Complainant, the article states that muscle sections were stained for IL-8 (p.164). In this regard, the Complainant asserts that it is surprising that IL-8 results, in contrast to IL-18 results, were not reported and compared with the group's previous IL-8 findings.

The Complainant alleges that there is a discrepancy between Figures 3 and 4. According to the Complainant, Figure 3 shows that IL-18 and Caspase-1 levels were very low or absent in muscle fibres from healthy subjects, whereas there was an increased expression of these peptides in patients with chronic obstructive pulmonary disease (COPD), mainly found in type-2 fibres. According to the Complainant, Figure 4 illustrates that TNF- $\alpha$  and IL-6 content were also very low in the control samples, whereas an increase in TNF- $\alpha$  was found in the patients, mainly localised in type-2 fibres. According to the Complainant, the articles states that IL-1  $\beta$  is hardly expressed in either of the groups, which is surprising, since it is stipulated that IL-1  $\beta$  and IL-18 are closely related and both are activated by Caspase-1, which increased in COPD patients.

According to the Complainant, IL-18-mRNA levels in muscle – shown in Figure 2 without units – were also higher in the patients than in the control samples. The Complainant also asserts that, in contrast to the lack of correlation between mRNA and protein, a significant difference of a similar magnitude in IL-18 mRNA between smoking and non-smoking control samples (Fig. 2) was not matched by a difference between these groups in histochemically identified IL-18 protein (Figure 3). According to the Complainant, the finding is not discussed.

According to the Complainant, a lack of correlation is also observed between mRNA and protein expressions of TNF- $\alpha$ , where mRNA levels in muscle were at least as high in the control samples as in the patients (Figure 2). According to the Complainant, it is suggested that this possibly reflects a negative *feedback* of increased TNF protein on the TNF- $\alpha$  transcription, but in the Complainant's opinion, such a mechanism would not be able to inhibit an initial increase in mRNA.

The Complainant also asserts that there was a lack of correlation between mRNA and protein findings with regard to IL-6, which the authors apparently did not notice. The Complainant claims, therefore, that IL-6-mRNA was identical between the groups (Figure 2), whereas histochemically identified IL-6 protein was described as very low in the control samples and fell below the control level for COPD patients. According to the Complainant, these findings require a more detailed description of



the evaluation of the IHC data. The Complainant also asserts that a Western Blot should have been used in order to confirm the histochemical findings.

The Complainant alleges that the reported values for the plasma levels of IL-8<sup>12</sup> are 2–4 times higher in the abstract than in Figure 1.

The Complainant also asserts that, because the increased skeletal muscle expression of IL-18 was found in COPD patients with normal weight, it was concluded (see the abstract) that IL-18 is potentially involved in COPD-associated muscle deterioration. According to the Complainant, the opposite conclusion would appear to be more obvious. The Complainant states, therefore, that, despite the increased IL-18, there was no deterioration, not even in two patients who received oxygen therapy and six patients awaiting lung transplants. According to the Complainant, it is surprising, in this context, that no comparison is made between the observed changes in various cytokine measurements and muscle histology and the patients' clinical conditions.

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The Complainant asserts that, in addition to the lack of units of measurement for mRNA (Figure 2), there is also a lack of units of measurement for BMI and BMD (Table 1) and fibre size (Table 2). In addition, according to the Complainant, there are no P-values in Table 1.

### **5.10.2 The Defendant's responses and contentions**

The Defendant contends that she is innocent of the Complainant's allegation of scientific dishonesty.

The Defendant contends that it is clear that the authors chose to exclude overweight patients. The Defendant claims that the authors decided to match the groups for BMI with a view to excluding severe end-stage COPD.

The Defendant states that the authors think it is obvious that continued smoking is a problem/issue in COPD pathophysiology.

The Defendant claims that the exclusion of the four patients had no influence on any signs of inflammation.

The Defendant contends that, although the authors did not include data from adipose tissue, they chose to inform the readers that RNA had also been isolated from this tissue.

The Defendant agrees with the Complainant that the information regarding IL-8 staining is irrelevant.

As far as the correlation between mRNA and protein is concerned, the Defendant refers to her comments under "General".

The Defendant claims that plasma IL-8 was not measured in this study.

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<sup>12</sup> The Committee notes that the Complainant appears to have made a mistake here. It is the Committee's view that this should be "IL-18" instead of "IL-8".



The Defendant acknowledges that the IL-18 levels in the abstract and Figure 1 do not match. The Defendant states that the authors are very concerned and apologetic about the fact that they did not discover this error sooner. The Defendant claims that the authors of the article conducted two analyses of plasma-IL-18 because the first analysis did not generate enough values because of a technical problem. The Defendant contends that they must have mistakenly mixed up the two analyses, such that the results from analysis no. 2 appear in the abstract, while analysis no. 1 appears in Figure 1. The Defendant states that the authors will write an erratum to the journal.<sup>13</sup>

The Defendant contends that the above-mentioned problem is an inadvertent error and does not represent active manipulation.

The Defendant claims that the conclusion is supported and balanced in relation to the purpose of the article. The Defendant contends that it is possible to argue that it would have been incorrect to analyse an association between IL-18 and, e.g. capillarisation, because the authors had not presented a hypothesis for this.

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The Defendant claims that P-values are shown in the results section.

The Defendant contends that the authors cannot completely exclude the possibility that the IHC data is erroneous, since Co-author 1 carried out some of this work.

According to the Defendant, the qPCR and IHC data in the study match. The Defendant also contends that the article's findings are consistent with another study ([REFERENCE ARTICLE 6]), which found that TNF- $\alpha$ -protein expression increased in muscle biopsies from patients with type 2 diabetes, but that TNF- $\alpha$  mRNA did not increase.

As part of the consultation on the draft ruling of 25 June 2013, the Defendant contended that the difference in specified levels of IL-18 in the abstract and Figure 1 was due to an error caused by the results of a partially unsuccessful analysis being used in Figure 1. The Defendant states that the Committee has not accurately reproduced her explanation of this. Regarding the inter-assay variation, the Defendant contends that of course this does not correspond to the levels indicated in Figure 1, as these levels stem from a discarded analysis. In relation to this, the Defendant states that the laboratory's inter-assay-variation coefficients are calculated on the basis of a large amount of material, including IL-18-ELISA-analyses that have been carried out over a long period of time and under the same experimental conditions. According to the Defendant, this error has already been corrected by an erratum to the article, which, according to the Defendant, supports the claim that it was a mistake and not an act of dishonesty.

## 5.11 Article 10

### 5.11.1 *The Complainant's claims and contentions*

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<sup>13</sup> The Committee notes that an erratum to the article was published online on 13 November 2011.



The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: “[ARTICLE 10]”

The Complainant alleges that this article reuses muscle biopsies and data from a previous study (articles 6 and 7) without the readers being informed of this. To support this allegation, the Complainant states that the protocol in study 1 is the same as in articles 6 and 7. The Complainant asserts that it is apparent from the caption to Figure 2 and the section concerning fibre-type composition in the results section (p.310) that the histochemical study was only conducted on seven subjects, as in articles 6 and 7, even though it is stated in the methodology section that 14 subjects participated in the study. The Complainant also asserts that the incidence of type-1 fibres in each of the three muscles studied (p.310) is exactly the same as in article 7.

The Complainant asserts that although MHC-mRNA-2a is not measured in the article, a negative correlation between this variable and the incidence of type-1 fibres is reported in the results section (p. 310). According to the Complainant, the same finding is reported in article 7, and Co-author 1 only provided fibre-type data, not MHC data. The Complainant claims, therefore, that it is unclear whether the original group from articles 6 and 7, consisting of seven subjects, was supplemented with seven new subjects, or whether 14 new subjects contributed to the histochemistry.

The Complainant also alleges that the illustration of histochemical findings is flawed (Figure 2).

In this connection, the Complainant asserts that a section stained for IL-15 is shown for each of the three muscles, but that how these sections were selected is not described.

According to the Complainant, the article states that adjacent sections were stained for fibre type, and identical fibres stained for IL-15 and fibre type, supposedly marked with asterisks. The Complainant alleges that this does not correspond to the two sections from the vastus lateralis muscle (C and D) and the fibres reproduced for these do not appear to be identical.

According to the Complainant, Figure 2 compares a section stained for IL-15 and negative control sections. The Complainant asserts that these sections ought to have been adjacent ones, which they clearly were not. The Complainant also asserts that the description of the evaluation of the sections is insufficient, and does not specify, e.g. the number of fibres or whether more than one researcher was involved.

The Complainant alleges that IL-15-mRNA in study 1 was significantly higher in the triceps than in the soleus muscle, and that the values in the vastus were between these, but according to the Complainant, the Western Blot and IHC showed no difference in IL-15-protein levels for the three muscles.

According to the Complainant, in study 2, the authors found an increase in IL-15-mRNA at 24 hours, whereas no change was found in IL-15 protein determined by



Western Blot (histochemistry was not carried out). The Complainant asserts that the fact that the mRNA increase happened relatively late compared to the exercise stimulus is not discussed in detail.

According to the Complainant, the lack of correlation between mRNA and protein findings in the two experiments is attributed to the presence of transcription without translation, which, in the Complainant's view, is a highly unsatisfactory explanation.

### **5.11.2 The Defendant's responses and contentions**

The Defendant contends that she is innocent of the Complainant's allegation of scientific dishonesty.

The Defendant contends that the authors included muscle biopsies from 14 individuals, as stated in the methodology section. According to the Defendant, seven of these individuals are also included in article 6. The Defendant claims that there is no reference to article 6 in the methodology section because the number of subjects (n) in this study was twice as high, and the personal details in the two articles are therefore not identical. The Defendant claims that the authors clearly indicate that the supporting data concerning fibre-type distribution and IHC relates to analyses of n=7.

The Defendant concedes that the muscle fibres in Figure 2C are slightly out of position compared to Figure 2D. Nevertheless, the Defendant contends that this does not affect the conclusion that it seems as if IL-15 is expressed identically by different fibre types and in different muscle groups.

According to the Defendant, the Complainant has misunderstood Figure 2. The Defendant contends, therefore, that the figures are included to show an image both with and without IL-15 staining (Ba, Bb, Bc).

As far as the correlation between mRNA and protein is concerned, the Defendant refers to her comments under "General".

The Defendant contends that the authors had no reason to suspect the histochemical data, but they cannot be completely certain about it, as Co-author 1 was involved.

## **5.12 Article 11**

### **5.12.1 The Complainant's claims and contentions**

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: "[ARTICLE 11]"

The Complainant alleges that the article's results are contrary to previous findings by the group, and that this is not mentioned in the article. The Complainant therefore asserts that a main conclusion in article 6 is that, in the basic stage, TNF- $\alpha$  is expressed in skeletal muscle, though only in type-2 fibres, whereas Figure 3 ap-



pears to show that, in the basic stage, it was not possible to demonstrate TNF- $\alpha$  staining in the study of control subjects.

According to the Complainant, the article concludes that TNF- $\alpha$  is increased in skeletal muscle of type 2 diabetics, especially in an undefined subset of type-2 fibres. In relation to the conclusion in article 6, the Complainant finds it surprising that the authors emphasise the presence of TNF- $\alpha$  in type-2 fibres rather than the fact that the presence of TNF- $\alpha$  in type-1 fibres in type 2 diabetics was contrary to their earlier finding that these fibres do not contain TNF- $\alpha$  in healthy subjects.

The Complainant also asserts that the significant difference in TNF- $\alpha$  staining of muscle fibres between diabetics and the control subjects, as shown in Figure 3, is contrary to the Western Blot data, according to which TNF- $\alpha$  protein content in muscle was on average no more than maximum twice as high in diabetic patients than in the control group (Figure 2). The Complainant alleges that this fact was not noticed.

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The Complainant asserts that the description of the evaluation of histochemical data is incomplete (number of fibres per section, percentage of type-2 fibres with increased TNF- $\alpha$  in diabetics, more than one researcher, and whether the tissue sections were coded for the researcher or not).

The Complainant also asserts that negative control sections were incubated without goat serum, which is used to block potentially non-specific bindings of the primary and secondary antibodies.

According to the Complainant, the article identifies a “split” form of TNF- $\alpha$  protein in muscle in addition to membrane-bound proTNF- $\alpha$ , and, according to the text and blots shown (Figure 2), the amounts of proTNF were greater than those in the split form. The Complainant alleges that this is contrary to Figures 2B and C, in which values are expressed relative to  $\beta$ -actin protein, and in which the inverse relationship appears to apply. The Complainant also asserts that the results and discussion sections show that the levels of both forms were higher in diabetic patients than in control subjects, and that TNF- $\alpha$  was higher in diabetics’ muscles compared with the control subjects, irrespective of how overweight they are. However, according to the Complainant, Figure 2B and the results section show that the difference was not significant for proTNF in subjects who are not overweight. The Complainant alleges that the caption accompanying the figure states that a one-way ANOVA was used, but that this is in contrast to the results described in the caption and in the statistical section.

The Complainant asserts that the discrepancy between TNF- $\alpha$ -mRNA and protein levels in the article is tentatively attributed to post-transcript regulation of the protein content, whereas a similar discrepancy in article 10 is attributed to negative feedback inhibition of mRNA.

According to the Complainant, the introduction and methodology section show that a “case-control” design was used. The Complainant asserts that this is not correct, as the control subjects were treated as a group and not individually matched with the patients.





The Complainant asserts that VO<sub>2</sub> max and fat-mass values are reported, but not the methods for analysing these variables.

The Complainant also asserts that the conclusion that plasma TNF- $\alpha$  is associated with insulin resistance, and possibly plays a role in the pathogenesis of chronic insulin resistance, seems daring in light of the fact that this correlation was not significant for the control group. With reference to this point, the Complainant also claims that the correlation coefficient for diabetics was only 0.3, and that, judging from the reported p-values, this is a very low estimate when adjusted for various confounders.

The Complainant asserts that the spread of several variables in the estimate was very small. The Complainant claims, therefore, that, in the light of these narrow spreads, it is surprising that it was possible to establish significant correlations, e.g. a 95% “confidence interval” for sTNFR2 less than 2% in healthy subjects, and yet this variable was significantly correlated with HOMA2-IR.

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### **5.12.2 The Defendant’s responses and contentions**

The Defendant contends that she is innocent of the Complainant’s allegation of scientific dishonesty.

The Defendant contends that the study included clinical trial material consisting of a total of 199 participants (patients and control group). According to the Defendant, it is clearly stated that mRNA from muscle biopsies was taken from 84 control subjects and 83 diabetic patients. The Defendant also contends that the authors conducted further analyses (Western Blot and IHC) in a sub-group of individuals (n=8 in each of four groups) and that this information is disclosed to the reader.

The Defendant contends that the IHC image is included to give an impression of whether muscle cells expressed TNF protein. According to the Defendant, the discussion does not include IHC data due to the many other results that were derived from this rich source of material.

The Defendant contends that the IHC technique is not quantitative, and therefore it is not relevant to discuss discrepancies between findings obtained by the quantitative Western Blot method and those obtained by IHC.

The Defendant states that the purpose of the article was not to describe how many fibres express the cytokine, but to give an impression of whether muscle cells express cytokines. According to the Defendant, the IHC figure constitutes supporting data.

The Defendant contends that lack of space meant that the authors could not provide in-depth descriptions of the sub-groups that were subjected to further analyses.

The Defendant states that the authors did not provide exhaustive details in the summary of the data at the start of the discussion section, but that Figure 2, according to the Defendant, gives the reader a clear overview of this.



With regard to the correlation between mRNA and protein levels, the Defendant refers to her comments under “General”.

The Defendant states that the study used a “case-control” design.

The Defendant contends that a multivariate analysis was conducted, and that five different models were presented. The Defendant contends that, in all of the models, plasma-TNF is significantly correlated with insulin sensitivity. According to the Defendant, the control group did not include subjects with impaired glucose tolerance, and therefore represents a homogeneous group in relation to insulin sensitivity. According to the Defendant, this means that a correlation between plasma-TNF and insulin sensitivity cannot be presupposed.

The Defendant states that the data is expressed as mean values and SEM.

The Defendant contends that the authors had no reason to suspect the histochemical data, but that they cannot be completely sure of it because Co-author 1 was involved.

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## **5.13 Article 12**

### **5.13.1 The Complainant’s claims and contentions**

The Complainant alleges that the Defendant acted in a scientifically dishonest manner when drawing up and reporting on research results for the article: “[ARTICLE 12]”

The Complainant asserts that the methodology section does not mention control subjects at rest, but that such control subjects are mentioned in the results section and in the caption to figures 1 and 2. The Complainant alleges that the analysis of the resting cohort is presented, but that the cohort’s origin and composition is not described.

The Complainant further alleges that the uncertainty regarding the origin of the study population is supported by the fact that the blood-platelet counts in Figure 2 are not expressed in absolute terms, but as a percentage of the baseline values. The Complainant asserts that in Figure 2 the number of subjects is ten, while in Figure 1 it is eight, which means that the number of subjects in Figure 2 is higher than described in the methodology section. According to the Complainant, it is strange that the age, weight and height of the eight subjects in the article are the same as those of the 15 individuals referred to in article 8.

The Complainant asserts that it is surprising in relation to the findings in the article concerning brain-derived neurotrophic factor protein (BDNF-protein) after 24 hours of exercise, that BDNF protein levels in subjects who exercised were not measured more frequently before and after the 24-hour point, and were not measured in resting individuals in the control group.

The Complainant doubts that the observed 1.5 (-3)-fold increase in BDNF-mRNA can be linked with a 50% increase of BDNF-protein, because – according to the Complainant – previous studies of rat muscles showed that a five-fold increase of



BDNF-mRNA was not followed by an increase in protein. According to the Complainant, the immunoblot that illustrates these findings does not underpin faith in the measurements, because  $\beta$ -actin content and image contrast vary considerably between pathways/times for the tissue samples.

With reference to the fact that C2C12 “myotubes” were electrically stimulated to contract in vitro in hours, the Complainant alleges that the authors do not discuss the observed difference between “myotubes” and human muscle in relation to the finding of a 70% increase in both BDNF-mRNA and protein in the final phase of the contractions. According to the Complainant, the conclusion is that it is probable that muscle-derived BDNF “works in an autocrine and/or paracrine manner”. The Complainant alleges that the authors do not mention that this contradicts the fact that they did not find a difference in the release of BDNF to the medium in contraction-treated versus control C2C12 cells. The Complainant asserts that because the data is not shown, it is not possible to assess whether a release took place at all.

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Regarding IHC for BDNF protein, the Complainant alleges that the article does not report how the sections were selected, how many fibres they represented and how they were evaluated. According to the Complainant, the staining for 24 hours after exercise looks strange, and apparently exceeds the 50% increase in BDNF found by Western Blot. The Complainant asserts that the authors do not comment on this.

The Complainant alleges that the fact that BDNF-mRNA levels in the vastus muscle in the study were presumably very low would not be apparent to the reader, because the levels presented have undergone some kind of normalisation procedure that is not described.

According to the Complainant, a significant increase in mRNA level could be demonstrated by AUC (“area under the curve”), but the calculation procedure and the calculated numbers are not reported.

The Complainant alleges that the (at best) low numerical increase in BDNF-mRNA indicated by Figure 1, which is only just above the very low baseline levels, cannot account for the massive increase in intramyocellulær BDNF indicated by the IHC findings.

With reference to the increase in palmitate oxidation in L6-myotubes stimulated with BDNF (Figure 4), which according to the Complainant is significant, the Complainant asserts that the illustration of the increase is misleading because the y-axis does not start at zero. The Complainant also alleges that the spreads are surprisingly low and varied between similar experiments (SEM was about 1.4% in panel e and up to 4.3% in panel d).

According to the Complainant, the authors suggest that BDNF increases palmitate oxidation by stimulating alternating AMPK or ACC, even though L6 myotubes-ACC was phosphorylated at a lower dose of BDNF than AMPK (Figure 4), whereas ACC in isolated rat muscle was phosphorylated earlier than AMPK when treated with BDNF (Figure 5).



### **5.13.2 The Defendant's responses and contentions**

The Defendant contends that she is innocent of the Complainant's allegation of scientific dishonesty.

The Defendant accepts the Complainant's critique that the first part of the methodology section does not contain a precise description of the study material. The Defendant argues that the authors, when adapting the article in order to comply with space requirements, mistakenly omitted the description of one of the two studies. The Defendant contends that a study was carried out only for use in this article, and that this study has not been used in other publications. According to the Defendant, the study comprised ten exercising subjects and ten who rested. According to the Defendant, muscle biopsy samples were taken from the vastus lateralis at the points in time 0, 2, 3, 5, 8, 24, 48 and 72 hours. According to the Defendant, the material led to the data shown in Figures 1A, 1B, 1D and 2.

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The Defendant states that the authors will inform the journal of this.<sup>14</sup>

The Defendant claims that, due to insufficient muscle protein (due to a freezer problem), the authors included material from a previous study (n=8, exercise only) for use in Western Blot. According to the Defendant, the description in the methodology section in the originally published article refers to the latter material.

The Defendant contends that differences in the magnitude of the changes between mRNA and protein levels are normal, because protein expression involves a balance between translational efficiency/degree of efficiency and protein turnover and stability.

The Defendant contends that the authors present the data as it is, without over-interpretation. According to the Defendant, AUC was used on the advice of their statistician.

The Defendant states that it is unclear what the Complainant means by "image contrast" in relation to the point in the complaint about variation between pathways/points in time for the tissue samples concerning  $\beta$ -actin content and image contrast, because the representative blot is the original and not composed of results from various experiments. The Defendant thus contends that there is only one image, and therefore each pathway cannot be manipulated in relation to other pathways.

With regard to autocrine and paracrine signalling, the Defendant refers to her comments under "General". The Defendant contends that data from the cell tests was not presented because the authors did not find any changes in BDNF in the medium.

The Defendant claims that IHC was only conducted in order to obtain an indication of whether BDNF expression might increase in muscle fibres. The Defendant contends that the authors chose to present the IHC image from the individual who had

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<sup>14</sup> The Committee notes that, on 10 January 2012, an erratum was published pertaining to the article's methodology section.



the most striking mRNA response. According to the Defendant, this individual apparently also had the most pronounced BDNF-protein response. The Defendant thus contends that the authors showed the IHC image that best supported the idea that the increase in BDNF expression 24 hours after exercise was actually intramyocellulær (Figure 1D).

Concerning the regulation of mRNA and protein and the presentation of mRNA levels as normalised values, the Defendant refers to her comments under “General”. With reference to this point, the Defendant contends that not all molecular biologists share the view that a Ct value of 37 is a critical value threshold. The Defendant contends that the authors describe their data without over-interpretation.

The Defendant claims that the literature includes numerous indications that the skeletal muscle of rodents expresses BDNF, and that contractions stimulate the up-regulation of this expression. The Defendant states that the authors consider it highly likely that human skeletal muscle would respond in a similar manner, and therefore conclude that their data is consistent with the published literature.

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The Defendant contends that there is nothing misleading about the fact that the y-axis in Figure 4 does not start at 0. The Defendant claims that the authors did not try to hide the fact that the axis started from 2–2.6-mg protein per hour, as clearly indicated in the figure. According to the Defendant, the measurement reflects a “rate”, not an accumulation, which suggests that the changes, though small, are consistent and statistically relevant.

According to the Defendant, one experiment was conducted on a rat muscle *ex vivo*, and one on a muscle cell line *in vitro*. According to the Defendant, it should not be surprising that two very different model systems exhibit different response kinetics.

The Defendant contends that the important thing is that the AMPK/ACC was phosphorylated when either muscle cells or whole muscle pieces were stimulated by BDNF, and that palmitate oxidation increased in both model systems separately. The Defendant also contends that the effect of BDNF on fat burning was eliminated when AMPK was blocked by two very different interventions (pharmacological blockade and genetic adenovirus). The Defendant therefore contends that the combined data clearly indicates that BDNF, through the activation of AMPK, increases fat burning in muscle cells.

As part of the consultation on the draft ruling of 25 June 2013, the Defendant asserted that the shortcomings of the original methodology section were merely the result of an error during the proofreading process, which meant that the description of the main study in the article was omitted from the methodology section, and that this does not constitute a serious breach of good scientific practice. With reference to this point, the Defendant also pointed out that the final version of the manuscript erroneously indicates biopsy times in the secondary study that correspond to the main study. In support of this point, the Defendant states that this was just a mistake, which the journal agreed to correct by publishing an erratum. The Defendant contends that the error in the methodology section is a matter of the quality of the research, which in the Defendant’s opinion means that the question falls outside the remit of the Committee.



As part of the consultation on the draft ruling of 25 June 2013, the Defendant further contended that the Defendant was not the last author of the article, and that the Committee's argumentation relating to "leading senior author" is therefore unsubstantiated.

#### **5.14 The parties' claims and contentions related to the reopening of the case**

The comments made by the parties to the DCSD letter of 3 February 2014 concerning the reopening of the case, i.e. prior to the consultation on the draft ruling of 9 May 2014 on the reopened case, are reproduced below to the extent that they contain significant new information (sections 5.14.1 and 5.14.2). The points of view submitted by the parties during the consultation on the draft ruling of 9 May 2014 on the reopened case follow in sections 5.14.3 and 5.14.4.

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It must be borne in mind from the outset that the two co-authors of articles 6, 7 and 10 wrote the following in their letter to DCSD of 9 February 2014:

*"Comments on DCSD's representation of facts concerning the biopsy material in the three articles mentioned in the letter sent by e-mail on 3 February 2014 from DCSD..."*

#### ***DCSD's representation written in italics.***

*This is correct.*

#### ***DCSD's questions relating to the biopsy material in article 10 following the initial review.***

*When taking the muscle biopsies, an attempt was made to divide the biopsies into three parts, depending on type of analysis intended: immunohistochemistry labelled 'Histo', real-time PCR labelled 'PCR' and lysate for protein determination labelled 'Protein'. This classification applies only to the test tube in which the biopsy pieces are stored. The sections of muscle for immunohistochemistry are embedded and frozen according to a separate procedure, whereas the sections for 'PCR' and 'Protein' are frozen in liquid nitrogen and according to the same procedure. In other words, if the muscle biopsy was large enough, it was divided into three test tubes labelled 'Histo', 'PCR' and 'Protein'. If the biopsy was small, it was divided into two parts. The 'Histo' part was embedded separately, and the rest of the biopsy frozen in liquid nitrogen in test tubes labelled 'PCR' or 'Protein'. This procedure is designed to allow you to form an overview of the material once all of the biopsies have been taken. However, you cannot conclude on the basis of the labelling on the test tubes which analyses were subsequently carried out.*

*This explains why there is no check mark beside the following:*

- Subject 3 for vastus and soleus in the 'Protein' field.*
- Subject 5 for triceps in the 'Protein' field.*
- Subject 14 for triceps in the 'Protein' field.*

*'Minus' is written beside the soleus biopsy for subject 5, as no biopsy was successfully taken from the muscle, so it never existed, as noted by the [Complainant] in article 7.*



*For subject 9, neither ‘Histo’, ‘PCR’ nor ‘Protein’ has been marked for the soleus. The fields have not been filled in but a biopsy was taken from subject 9’s soleus and analysed for both PCR and Protein in article 10.”*

#### **5.14.1 The Complainant’s claims and contentions before the consultation on the draft ruling of 9 May 2014 on the reopened case**

The Complainant states that all of the patient records<sup>15</sup> bear the title “TNF, IL-18 and fibre types”. The Complainant asserts that this is not consistent with article 10, which is about IL-15. According to the Complainant, this could reflect the fact that the guidelines for Good Laboratory Practice were not followed or that the subjects actually included in article 10 were not included in the material.

The Complainant also asserts that the patient records show that subjects 3 and 5 cannot have contributed to the cytokine measurements for the three muscles studied in article 6, as there is no protein to determine this. On this point, the Complainant asserts that subject 5 cannot have contributed to the determination of mRNA and histochemistry of the soleus muscle in articles 6 and 7, as the patient records show that PCR and histochemistry analyses necessary for this were not performed.

The Complainant alleges that the inclusion of n=14 in article 10 does not match the information in the patient records because of the missing information mentioned above for subjects 3 and 5, and because the records show that there were no PCR or protein measurements of the soleus muscle for subject no. 9, nor were protein measurements taken of the triceps muscle of subject 14.

The Complainant also asserts that the reader of article 10 must assume that the biopsy material was obtained within a shorter period of time with the specific purpose of conducting the tests described, but in reality, the material was obtained in two stages with an interval of over a year and with quite different purposes. According to the Complainant, this means that the reader is denied the opportunity to consider the implications of this for the article’s findings, including that the material – according to the Complainant – has probably been thawed during the writing of articles 6 and 7 and then frozen again.

#### **5.14.2 The Defendant’s responses and contentions before the consultation on the draft ruling of 9 May 2014 on the reopened case**

The Defendant states that DCSD’s representation of facts in the letter of 3 February 2014 (see section 4) is correct. The Defendant contends that articles 6 and 7 refer to seven subjects, and that these seven subjects were supplemented by another seven subjects in article 10, i.e. that article 10 refers to a total of 14 subjects.

The Defendant refers to the two co-authors’ correspondence and materials submitted to DCSD. The Defendant contends that the muscle biopsy was either divided up between three test tubes labelled “Histo”, “PCR” and “Protein” if it was big enough,

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<sup>15</sup> Concerning the articles covered by this ruling, the Danish term “patientjournaler” (patient records) is used to describe the way in which the subjects were registered.





or into two parts if it was small, after which the “Histo” section was embedded separately and the rest of the biopsy frozen in liquid nitrogen, either in the test tube labelled “PCR” or in “Protein”. Regarding this, the Defendant contends that it cannot therefore be inferred that the analysis was not conducted because there is no tick beside “Protein” or “PCR” in the patient records, which is the case with subjects 3, 5 and 14.

The Defendant states that the biopsy from the soleus of subject 5 was not a success. The Committee took this into account in its ruling of 18 December 2013 and found that it did not constitute a serious breach of good scientific practice. The Defendant also states that subject no. 9 had a biopsy taken and analysed from the soleus, even though this is not included in the patient record.

Concerning the biopsies in articles 6, 7 and 10, the Defendant states that samples from all 14 subjects (three biopsies from each, except one subject from whom there was no soleus biopsy) were analysed with PCR and for protein. To this, the Defendant contends that immunohistochemistry for IL-15 was only performed on the first seven subjects, as indicated in Figure 2 in the article.

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In the light of this, the Defendant contends that no selection was made of the subjects in articles 6, 7 and 10.

The Defendant claims that the Committee’s ruling of 18 December 2013 draws the wrong conclusion about selection in article 4. The Defendant contends that some of the analyses were only performed on 11 out of a total of 18 subjects in the article, as the biological material from the 18 persons did not extend to being able to conduct all of the analyses on all of the subjects.

Regarding this, the Defendant contends that the research concerned relates to integrative physiology, and according to the Defendant, human integrative physiology cannot be interpreted according to the standards that apply to, for example, epidemiological and clinical research. Within integrative physiology, it is – according to the Defendant – the rule rather than the exception that it is not possible to perform all analyses on all samples. With reference to this point, the Defendant contends that the subjects are selected according to criteria designed to establish a particularly homogeneous group, which means that a reduced n-value does not lead to significantly divergent characteristics, which is the reason why a separate description of the reduced group of subjects is – in the Defendant’s opinion – not necessary. The Defendant cites a series of articles that, according to the Defendant, indicates that current practice in the Defendant’s field of research was followed in article 4.

In relation to the section on the recycling of biopsy material in the ruling of 18 December 2013, the Defendant argues that there is considerable disagreement in research circles about when cross-referencing is necessary. In this respect, the Defendant refers to a series of articles that, according to the Defendant, show that omission of cross-referencing is common practice. In this context, the Defendant argues that it is very strange that in the ruling of 18 December 2013 the Committee decided to denounce this as “intentionally dishonest” given that the Defendant has stated that the practice is common and adopted deliberately.



Concerning the evaluation of the erroneous description of a group of subjects in article 12 in the ruling of 18 December 2013, the Defendant further acknowledges that it should have been highlighted in the proofreading of article 12 that some subjects had spent two hours exercising on a bike and others three hours, but asserts that this difference in the design of the experiment is a mere detail and insignificant in relation to the article's conclusion.

#### ***5.14.3 The Complainant's claims and contentions after the consultation on the draft ruling of 9 May 2014 on the reopened case***

The Complainant challenges the validity of the conclusion that the Committee only finds evidence of scientific dishonesty in four articles in this latest draft ruling.

The Complainant asserts that the Defendant should also be criticised for the image manipulation in articles 1 and 3; that the Committee has excessively narrowed the criteria for condemnation of recycling of subjects and tissue samples; that the Defendant also acted with intent by including previously used subjects in article 12; and that the Committee has changed the dishonesty criteria in relation to conflicting information about the plasma concentrations of IL-8 and false information about the inter-assay variability in article 9 on a false basis by accepting the Defendant's changing and untenable explanations for this.

The Complainant also states that the Committee should have conducted a more detailed examination of the allegations that were rejected in the draft ruling because they related to the quality of research or the credibility of scientific theories. According to the Complainant, seen in isolation, these facts may be considered to reflect poor-quality research, but when taken as a whole they raise suspicions of scientific dishonesty.

Finally, the Complainant states that it is incorrect in the draft ruling when the Committee writes that the Complainant complained about an ethical aspect of article 5 and that the Complainant cited an incorrect biopsy time. The Complainant requests that the Committee correct these errors, as the Complainant had also done in previous consultation responses.

#### ***5.14.4 The Defendant's responses and contentions after the consultation on the draft ruling of 9 May 2014 on the reopened case***

The Defendant continues to contend that the Defendant is innocent of the charge of scientific dishonesty.

The Defendant contends once again that the Committee should apply the criteria for scientific dishonesty that applied at the time each article was written. As such, articles 3, 4 and 5 should be assessed in accordance with executive order no. 933 of 15 December 1998 on intentional or grossly negligent falsification or distortion of the scientific point. In this regard, the Defendant refers to a memorandum on gross carelessness (appendix to the Defendant's consultation response), arguing that gross carelessness is not synonymous with gross negligence. In this connection, the Defendant argues that, pursuant to the DCSD Order section 9 (4), it is the chairperson who should decide which term will be applied and should assess the extent to which the Defendant meets the subjective criteria for scientific dishonesty.

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The Defendant also contends that the Committee overrides the transparency requirement applicable to findings of dishonesty, for example because the Committee's arguments concerning the recycling of material have changed since the draft ruling of 25 June 2013. Regarding this, the Defendant states that the Committee's finding of good scientific practice must be demonstrated as being applicable in research circles and by reference to recognised rules, and that the two petitions that the Defendant has submitted show that there is no empirical basis for the Committee's requirement on information about recycling material. Further, the Defendant refers to a table (appendix to the Defendant's consultation response) that – according to the Defendant – contains five articles that use results from previous articles to introduce, underpin or put into perspective new results without always mentioning that the same group of subjects was used. The Defendant also states that the same applies to some of the articles that the Defendant referred to in the Defendant's response of 15 August 2013 and when the case was reopened.

The Defendant challenges the validity of the Committee's arguments about the importance of information about the recycling of previously used subjects and refers in this regard to the opinion of a statistician (appendix to the Defendant's response to the consultation). Regarding this, the Defendant contends that there is no mutual interdependence between the results of the articles concerned. The Defendant therefore states that article 5 puts article 1 into perspective rather than relies on it, and that the reference in article 5 to the [ET AL ARTICLE] is a mention of the article, not a comparison of results.

The Defendant also challenges the idea that there was dishonest selection in articles 3 and 5, and in this connection refers to a reduced n-value in article 4 as the result of insufficient material, which is not considered scientific dishonesty by the Committee. In relation to article 5, the Defendant states that selection means selecting within a defined group, so it cannot be considered selection that not all of the groups from the [ET AL ARTICLE] are included in article 5.

The Defendant rejects the idea that there is or has been a special responsibility for the last or senior author. In this respect, the Defendant refers to the copies of the contribution made by a professor and submitted by the Defendant on 22 April 2014 and 7 May 2014 about the ICMJE's understanding of author responsibility. The Defendant contends therefore that the Defendant cannot be held liable for the image manipulation in article 4, as the Defendant did not participate directly in the transmission of false or distorted research.

The Defendant also contends that the error concerning two as opposed to three hours of exercise in article 12 is not serious enough to justify the term dishonesty. In this connection, the Defendant points out that – according to the Defendant – the journal considers an erratum to the already published erratum to the article superfluous (appendix to the Defendant's response to the consultation). The Defendant also points out that in another case concerning the methodology section of article 12 (the ruling in the case concerned was also announced on 18 December 2013), the Committee found that the Defendant had not acted in a scientifically dishonest manner in connection with deficiencies in the description of the methodology.



## 6 Rules and regulations

This case has been processed under the Danish act on research consulting, etc., cf. consolidation act no. 365 of 10 April 2014 and the related executive order no. 306 of 20 April 2009 on the Committees on Scientific Dishonesty, as amended by executive order no. 144 of 20 February 2012 (the DCSD Order).

Scientific dishonesty is defined in section 2, no. 3 of the act and in section 2 of the DCSD Order:

**“Section 2.** *Scientific dishonesty is defined as: falsification, fabrication, plagiarism and other serious violations of good scientific practice committed intentionally or due to gross negligence during the planning, implementation or reporting of research results.*

*Included hereunder are:*

- 1) Undisclosed fabrication and construction of data or substitution with fictitious data.*
- 2) Undisclosed selective or surreptitious discarding of a person's own undesired results.*
- 3) Undisclosed unusual and misleading use of statistical methods.*
- 4) Undisclosed biased or distorted interpretation of a person's own results and conclusions.*
- 5) Plagiarisation of other persons results or publications.*
- 6) A false credit given to the author or authors, misrepresentation of title or workplace.*
- 7) Submission of incorrect information about scientific qualifications.”*

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DCSD's remit is described in the DCSD Order, sections 3 and 6:

**“Section 3.** *The Committees shall not be entitled to consider cases involving the validity or truth of scientific theories or cases involving the research quality of a scientific product.*

[...]

**Section 6.** *The Committees on Scientific Dishonesty may consider cases involving complaints about a written scientific product after the defendant's voluntary handing over thereof, cf. section 1(4).*

**(2)** *The Committees may also consider cases involving complaints about an application filed with a view to applying for a grant from public research funds.”*

The DCSD is empowered to reopen a closed case, pursuant to the DCSD Order, section 14:

**“Section 14.** *The Committees on Scientific Dishonesty may, at the request of a party, resume a case that has been closed if new information is received which, if it had been available during the consideration of the case, might probably have led to a different outcome.”*



## 7 Assessment

Based on the new information that the Committee received in January/February 2014 concerning the biopsy material in articles 6, 7 and 10, the case was reopened and reconsidered. The Committee notes that the Defendant also urged the Committee to reopen the case in a letter dated 10 February 2014.

The Committee requested that the parties submit comments on DCSD's letter of 3 February 2014 (see section 4). As a result of the new information and the parties' comments on the letter of 3 February 2014, the Committee has reassessed section 7.7 (Article 4) and section 7.16 (Use of biopsies in multiple scientific works).

The Committee's reconsideration of the assessment in section 7.16 consisted of an overall review of a series of articles cited by the Defendant to imply that the Defendant followed common practice in relation to the use of biopsy material in multiple scientific works (see section 5.14.2.). Members of the Committee, or individuals close to members of the Committee, were co-authors of certain of the articles to which the Defendant refers. As a result, the Committee conducted an evaluation of whether or not the members concerned were eligible to take part in review of the articles. The Committee found no basis for declaring them ineligible, because the articles do not form part of the complaint filed. As such, the Committee did not process the articles as part of the complaint, but conducted an overall review of them as examples of practice. In reaching this decision, the Committee's main consideration was that it would render the work of the Committee impossible if members were to be declared ineligible because a party to a case submits articles co-authored by them for information.

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Following the reopening of the case, a draft ruling of 9 May 2014 was sent to the parties for consultation. The Committee finds that the parties' responses to the consultation do not contain new information or anything else that gives the Committee cause to change the conclusions in its draft ruling of 9 May 2014. The points of view put forward by the parties in their responses to the consultation are reproduced in section 5.14, and any comments on these by the Committee, are reproduced in the relevant subsections below.

In this context, the Committee notes that the Complainant has not submitted information that gives the Committee cause to change or conduct a further re-evaluation of its ruling regarding the matters dismissed below as falling outside the remit of the Committee as they relate to the quality of research or the credibility of scientific theories.

During the case, the Defendant has repeatedly – most recently, during the consultation on the draft ruling of 9 May 2014 on the reopened case – asserted that a number of aspects of the ruling should be determined solely by the chairperson of the DCSD, pursuant to the DCSD Order section 9 (4). The Committee notes that the DCSD Order, section 9 (4) does not preclude the inclusion of decisions on legal issues in its rulings, although the chairperson always has the final word on such legal issues. This is the Committees' standard practice.



## 7.1 The composition of the committee

As part of the consultation on the draft ruling of 25 June 2013, the Defendant challenged the composition of the Committee, and asserted that Ulla Feldt-Rasmussen, Palle Holmstrup, Kirsten Ohm Kyvik and Jens Overgaard were ineligible to participate in the proceedings, including with regard to making the ruling, as there was no legal basis for extending their membership (in Jens Overgaard's case, that of his alternate membership) until a number of cases before the Committee were completed.

On 3 and 16 September 2013, the Minister responded by letter to the Defendant's objection to the composition of the Committee. In these letters, the Minister maintains that the extension of the period of office of both the members and the alternate was legal.

In this light, the Committee saw no reason why Ulla Feldt-Rasmussen, Palle Holmstrup, Kirsten Ohm Kyvik and Jens Overgaard should not be eligible to participate in the proceedings. These members and the alternate concerned were, therefore, involved in making the ruling of 18 December 2013.

As part of the reopened case, the Defendant submitted a letter on 24 March 2014, again contending that, according to the Act on research consulting, etc. section 31 (5), the question of the composition of the committee should be determined exclusively by the chairperson. The Defendant contends that it is not enough to refer to the fact that the Minister maintains that the extensions of the terms of the three members and one alternate were legal. In a letter of 24 March 2014, the Defendant therefore requests that the chairperson reconsider the question of the extensions. The Defendant refers to the points made in the letter of 24 March 2014 in the Defendant's response to the consultation on the draft ruling of 9 May 2014 on the reopened case.

The Committee notes that the Act on research consulting, etc., one of the functions of which is to regulate the activities of the DCSD, was amended by Act no. 310 of 29 March 2014, which came into force on 1 April 2014. A new provision, section 40 of the Act, expressly endows the Minister with the authority to grant extensions of the membership of chairpersons, members and alternates over and beyond the periods set out in the Act in exceptional cases. The comments regarding specific provisions in the bill (Bill L 109, parliament 2013–14) included the following about this provision:

*“This provision is proposed to clarify the current administrative practice under which the Minister may, in exceptional cases, extend the appointment period for members and alternates of the bodies covered by the Act for a limited period beyond the normal term of appointment.*

[...]

*The express purpose of the proposal is that members and alternates who have been closely involved in processing major, resource-intensive cases that are considered close to completion, are able to see the case to the end regardless of the expiry date for the normal term of appointment. In such situations, replacing*





*members late in the proceedings could result in an excessive and inappropriate burden on resources. This would be relevant to the Committees on Scientific Dishonesty, for example, where cases can extend over prolonged periods, and the proceedings can involve very wide-ranging and technically complicated material. In this context, extensions would allow the members to see cases to an end, particularly cases in which the Committee is considering its ruling following the standard consultation process. In such circumstances, new members and alternates would not be involved in the completion of cases.*

*[...]*

The Committee notes that the current Act on research consulting, etc. expressly provides for the extension of terms of membership and that the legislature adopted the amendment simply to clarify the regulatory framework, in the sense that, even before the amendment, the necessary authority was granted by section 33 of the Act, under which the Minister is permitted to specify rules for the work of the DCSD. The Committee sees no reason why Ulla Feldt-Rasmussen, Palle Holmstrup, Kirsten Ohm Kyvik and Jens Overgaard should not be eligible to participate in the proceedings.

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## **7.2 The concept of scientific dishonesty**

As part of the consultation on the draft ruling of June 2013, the Defendant pointed out that the wording of the definition of scientific dishonesty had changed, and that the definition used at the time the articles were produced differs from the one used now. In this regard, the Defendant contends that the Committee should use the definition as expressed at the time the articles were written.

During the period 1992–1998, the definition of scientific dishonesty rested solely on a set of rules for DCSD approved on 18 December 1992 by the Danish Health and Medical Research Council (Statens Sundhedsvidenskabelige Forskningsråd (SSVF)). The definition was as follows:

*“Section 2.*

*[...]*

*(2) Scientific dishonesty includes all deliberately fraudulent actions in the course of the application-research-publication process, as well as cases of neglect so severe that they can be considered to have an equivalent impact on the scientific credibility. This corresponds to the presence of intent or gross negligence.*

*(3) The area of scientific dishonesty covered by DCSD’s remit are characterised by falsifying or distorting scientific messages or falsely highlighting the input of particular researchers. As such, it covers:*

- construction of data*
- selective and surreptitious discarding of unwanted results*
- substitution with fictitious data*
- deliberate misuse of statistical methods with the aim to draw other conclusions than the data provides a basis for*
- distorted interpretation of results and distortion of conclusions*





- *plagiarism of another person's results or entire articles*
- *distorted presentation of the results of others*
- *improper indication of authorship*
- *misleading applications*

In 1998, a definition of scientific dishonesty was inserted in the order of the DCSD, see executive order No. 933 of 15 December 1998, entered into force on 1 January 1999. Section 3 of the order reads:

**“Section 3.** *Academic dishonesty covers acts or omissions that cause research to be falsified, the scientific message to be distorted or gross misrepresentation of an individual's involvement in the research. This includes the following:*

- 1) *Construction of data*
- 2) *Selective and surreptitious discarding of unwanted results*
- 3) *Substitution with fictitious data*
- 4) *Deliberate misleading use of statistical methods*
- 5) *Deliberate distorted interpretation of results and distortion of conclusions*
- 6) *Plagiarism of another person's results or publications*
- 7) *Deliberate distorted reproduction of the results of others*
- 8) *Improper indication of author*
- 9) *Applications with incorrect information.*

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*(2) In order to label conduct scientific dishonesty, it must be possible to document that the individual concerned acted with intent or in a grossly negligent manner.”*

In 2005, the definition of scientific dishonesty was amended by a new DCSD Order, see executive order no. 668 of 28 June 2005, which came into force on 1 August 2005. Section 2 of the order reads:

**‘Section 2.** *Scientific dishonesty is defined as intentional or grossly negligent conduct in the form of falsification, plagiarism, concealment or similar, which involves improper misrepresentation of one's own scientific work and/or research results. This includes the following:*

- 1) *Undisclosed construction of data or substitution with fictitious data*
- 2) *Undisclosed selective or surreptitious discarding of own undesired results*
- 3) *Undisclosed unusual and misleading use of statistical methods*
- 4) *Undisclosed biased or distorted interpretation of own results and conclusions*
- 5) *Plagiarism of another person's results or publications*
- 6) *Improper statements concerning authorship, title or workplace*
- 7) *Submission of incorrect information about scientific qualifications. ”*

Act no. 552 of 16 June 2008 introduced a definition of scientific dishonesty into the act on research consulting, etc. This provision came into force on 1 December 2008 (see executive order no. 1130 of 24 November 2008).

The preparatory memoranda for the amendment reveal that the intention was to clarify the provision.



The definition, which is preserved in section 2 no. 3 of the current act on research consulting, reads:

*“Scientific dishonesty is defined as: falsification, fabrication, plagiarism and other serious violations of good scientific practice committed intentionally or due to gross negligence during the planning, implementation or reporting of research results”.*

As a result of the amendment, the DCSD Order was also amended to reflect the definition in the act. The definition below was inserted by order no. 1122 of 25 November 2008, and the wording has been preserved in the current order from 2009:

**“Section 2.** *Scientific dishonesty is defined as: falsification, fabrication, plagiarism and other serious violations of good scientific practice committed intentionally or due to gross negligence during the planning, implementation or reporting of research results. Included hereunder are:*

- 1) Undisclosed fabrication and construction of data or substitution with fictitious data*
- 2) Undisclosed selective or surreptitious discarding of a person’s own undesired results*
- 3) Undisclosed unusual and misleading use of statistical methods*
- 4) Undisclosed biased or distorted interpretation of a person’s own results and conclusions*
- 5) Plagiarisation of other person’s results or publications*
- 6) A false credit given to the author or authors, misrepresentation of title or workplace*
- 7) Submission of incorrect information about scientific qualifications.”*

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The Committee is of the opinion that, even though changes have been made to the wording of the definition of scientific dishonesty, no substantive changes have been made to the content, i.e. the substance of the definition remains the same, despite changes to the wording. This perception is underpinned by statements in past DCSD annual reports. Following the 2005 amendment, the DCSD chairperson stated that the change was not considered to represent any real difference to the definition of dishonesty. After the 2008 amendment, the chairperson noted that the change consisted of a clarification of the previous definition. Comparing the wording of the various iterations of examples shows that the definition has remained almost identical from 1992 until the present.

The Committee notes that the requirement for ‘improper misrepresentation’ in the 2005 definition was not repeated verbatim in 2008. It adds that the word ‘improper’ was chosen to indicate the requirement for a certain degree of gravity, a requirement that the 2008 definition covers by stating that only a ‘serious’ breach of good scientific practice is tantamount to dishonesty. In assessing whether a serious breach of good scientific practice has been committed, it is implicit that the breach is likely to mislead the reader of the scientific product concerned. In practice, a criterion about misleading will, therefore, be part of DCSD’s assessment of whether a given action can be characterised as scientific dishonesty.



Since 1992, the subjective requirements in the definition have been intent or gross negligence. The use of “grov forsømmelighed” in the 1998 definition does not alter this, since this wording has in practice been interpreted as corresponding to gross negligence.

In this light, the Committee finds that the definition of scientific dishonesty, as currently worded, has in reality remained unchanged since 1992. The Committee has also assessed the individual charges based on the definitions of scientific dishonesty as expressed at the time that the scientific products emerged, and found no reason to arrive at a different conclusion to the one that results from the application of the current definition. In the presentation of its ruling below, the Committee will therefore only use the definition of scientific dishonesty as it appears in the current act on research consulting, etc. and in the DCSD Order.

The Committee further notes that – in ruling on whether the events to which the charges refer constitute a serious breach of good scientific practice – the Committee has based its conclusions on what was considered good scientific practice at the time at which the events took place. In other words, the Committee has assessed whether a serious breach of good scientific practice was committed under the standards for good scientific practice in force at the time these scientific works (the articles) were produced.

In the submission dated 24 March 2014, the Defendant contends that it is only since the 2008 amendment to the Act that scientific dishonesty has related to scientific practice, and that before 2008 there was a precise and narrow definition in actual legal regulations that clearly and directly defined dishonesty. The Committee does not share this view. The pre-2008 definitions involved a substantial element of discretion, as witnessed, for example, by the general and far from exhaustive examples of scientific dishonesty outlined in the executive orders regulating the DCSD. Even a concept like plagiarism was/is not defined in either the previous or new rules, and anyone who has ever had to judge a case of plagiarism knows how difficult it can be to determine whether a particular case is in fact an example of plagiarism.

These assessments involve academic discretion, which the committee is expected to exercise. In questions of discretion, good scientific practice has always been a crucial parameter, even – or perhaps precisely – in cases where no authoritative definitions are enshrined in binding legal regulations. The Committee’s rulings are therefore based on general science theory for empirical research methodology, including statistical methods, health science theories and generally recognised good scientific practice.

The Committee finds that no new information has arisen during the consultation on the draft ruling of 9 May 2014 on the reopened case that would give rise to the Committee changing its assessment concerning the Committee’s use of the concept of scientific dishonesty. The Committee notes that the memorandum on ‘grov forsømmelighed’ submitted by the Defendant does not change this.

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### 7.3 Author responsibility

The Committee is of the opinion that all authors of a scientific article share responsibility for its content, including responsibility for reading the final manuscript prior to submission to the journal. This follows from good scientific practice and is also set out in DCSD's own guidelines on good scientific practice from 1998, i.e. from before the articles in this case were submitted for publication.

The 1998 DCSD guidelines include the following:

*"Within the bounds of the possible and the reasonable, all authors of an article share responsibility for ensuring that it is based on honest research."*

This practice, i.e. that all authors share responsibility for the content of the article, has been laid down in numerous scientific guides since then, including DCSD's own guide to good scientific practice in 2009<sup>16</sup>, the European Code of Conduct for Research Integrity<sup>17</sup> and the so-called Vancouver Rules<sup>18</sup>, all of which set non-statutory standards for good scientific practice in the publishing of health-science articles.

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The 2009 DCSD guidelines state:

*"All authors of an article also have – within the realms of possibility and reason – a responsibility for ensuring that it is based on honest research, so that the risk of fraud is minimised. If irregularities or dishonesty are demonstrated in the research, it will be difficult for the co-authors of the work to disclaim responsibility."*

The 2011 European Code of Conduct states:

*"All authors, unless otherwise specified, should be fully responsible for the content of publication."*

The Vancouver Rules, last updated in 2013, state:

*"Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4."*

The Committee is therefore of the opinion that authors of scientific articles, at least from 1998 onwards, share responsibility for ensuring that an article is based on honest research.

Co-responsibility for scientific dishonesty requires that the co-responsible person is covered by the terms of the DCSD Order. This means that a serious breach of good scientific practice (by deed or omission), must have been committed intentionally or gross negligently by the person in question, pursuant to the DCSD Order, section 2.

<sup>16</sup> <http://fivu.dk/publikationer/2009/vejledninger-i-god-videnskabelig-praksis-med-saerlig-fokus-paa-sundhedsvidenskab-naturvidenskab-og-teknisk-videnskab>, p. 31 ff.

<sup>17</sup> <http://www.esf.org/publications/member-organisation-fora.html>, p.7.

<sup>18</sup> Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, Updated December 2013, pt. II.A.1, p. 3.



It is the view of the Committee that it is generally accepted practice for a scientific article to have one (or more) lead author(s), often referred to as the senior author(s) or last author(s). A lead author has a particular responsibility for all of the article's content, including reading the final manuscript carefully before submitting it to a journal. This is standard practice, and takes into account the role that a lead author plays in connection with the publication of an article. This is underlined, for example, by the fact that final-author status (as indicated in his or her list of publications) is considered important when evaluating researchers, including in connection with applications for professorships and research funding. The Committee notes that the standard practice for articles of the type addressed in this ruling is for the last author to be the lead author.

In ruling on the Defendant's co-responsibility for scientific dishonesty, the Committee will base its ruling on the Defendant's qualifications and special circumstances so that the ruling relates to the Defendant's actual role and contribution to the scientific articles.

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The Committee finds that no new information has arisen during the consultation on the draft ruling of 9 May 2014 on the reopened case that would give rise to the Committee changing its observations about author responsibility. The Committee notes that this is not changed by the letters submitted by the Defendant, in which a professor refers to the ICMJE's opinion of author responsibility.

#### 7.4 Article 1

In the article "[ARTICLE 1]" the authors demonstrate that muscle fibres could express IL-6 during muscle activity.

The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the quality of research, which are outside the Committees' remit, pursuant to the DCSD Order, section 3 (1):

- The Complainant's allegation of inadequacies in relation to the methodology for the IHC procedure for detecting IL-6 and the results of this (refers to the quality of the scientific work)
- The Complainant's allegation of a discrepancy between IL-6-mRNA and IL-6 protein (refers to the credibility of scientific theories)
- The Complainant's allegation that the research group published conflicting results regarding IL-6 protein (refers to the credibility of scientific theories)
- The Complainant's allegation that the IL-6 mRNA change during exercise could not be evaluated on the basis of the available data (refers to the quality of the scientific work)
- The Complainant's allegation that the results do not justify the conclusion (refers to the quality of the scientific work)
- The Complainant's allegations about the statistical analyses (refers to the quality of the scientific work).



The Committee therefore finds that all assertions and allegations relating to this article (with the exception of allegations concerning the reuse of biopsy material and image manipulation, see below) refer to the credibility of scientific theories and/or the quality of research and therefore fall outside the remit of the DCSD.

The question of repeated use of the human biopsy material in multiple scientific works will be addressed in a separate section below.

The question of the Defendant's responsibility for the reuse and/or manipulation of images will be addressed in a separate section below.

## 7.5 Article 2

In the article "[ARTICLE 2]", the authors study how the oral delivery of vitamin C and E influences the release of IL-6 in working skeletal muscles.

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The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the quality of research, which are outside the Committees' remit, pursuant to the DCSD Order, section 3 (1):

- The Complainant's allegation about the accumulation of IL-6 in muscle cells versus venous blood during exercise and in the control group (refers to the quality of the scientific work)
- The Complainant's allegation about the accumulation of IL-6 in muscle cells in people receiving and not receiving vitamin treatment (refers to the quality of the scientific work)
- The Complainant's allegation about a three-hour period after exercise with a fall in intracellular IL-6 in muscle cells (refers to the quality of the scientific work)
- The Complainant's allegation that it is not possible to reconcile the different results within the frameworks of the overall conclusion (refers to the credibility of scientific theories)
- The Complainant's allegation about the lack of relation to muscle-fibre type in comparisons between adjacent sections stained for ATPase and IL-6 (refers to the quality of the scientific work)
- The Complainant's assertion that personal characteristics in the two groups should not differ (refers to the quality of the scientific work)

The Defendant has informed the Committee that the BMI unit is wrongly specified, because a minus sign is missing in the printed version of the manuscript.

In the light of the information furnished by the Defendant, the Committee finds that a mistake/typo was made in the printed version of the article.

The Committee finds that such a mistake/typo is below the level for actions that warrant suspicion of scientific dishonesty.

With reference to the Complainant's assertion that it is difficult to assess the actual amounts of IL-6 mRNA in the tissue, because the data is not presented as absolute values only as relative values compared to "0", the Defendant states that the  $\delta$ - $\delta$ -Ct method of calculating mRNA expression was the standard method of presenting data of the type found in this article.



The Committee finds that, when an article presents relative values, the original data and the variation ought also to be presented so that the reader can assess the actual biological variation. The Committee is of the opinion that citing the original data and the variation helps avoid any obscuration of the actual data.

The Committee finds that the authors did provide a sufficient account of the conditions for the calculations of the mRNA results in the methodology section of the article, and that Figure 3 shows variation for all observation times. It is the Committee's opinion, therefore, that the article's readers were able to evaluate the validity and biological relevance of the presented data.

The Committee therefore finds that this does not constitute a breach of good scientific practice.

### 7.6 Article 3

In the article "[ARTICLE 3]" the authors demonstrate that muscles produce the cytokine interleukin-8 (IL-8) in connection with exercise.

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The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the quality of research, which are outside the Committees' remit, pursuant to the DCSD Order, section 3 (1):

- The Complainant's allegation of inadequacies in relation to the methodology for the IHC procedure for detecting IL-8 and the results of this (refers to the quality of the scientific work)
- The Complainant's allegation about the lack of any basis for expressing an opinion on IL-8 mRNA in muscle fibres (refers to the credibility of scientific theories)
- The Complainant's allegation of a discrepancy between IL-8 mRNA and IL-8 protein (refers to the credibility of scientific theories)
- The Complainant's allegation about the calculation of IL-8 release from the leg (refers to the quality of the scientific work)

With reference to the Complainant's assertion that it is difficult to assess the actual amounts of IL-8 mRNA in the tissue because the data is not presented as absolute values, only as relative values compared to pre-exercise values, the Defendant states that it is standard practice to normalise data to 1, as the authors have done in this article.

The Committee finds that, when an article presents relative values, the original data and the variation ought also to be presented so that the reader can assess the actual biological variation. The Committee is of the opinion that citing the original data and the variation helps avoid any obscuration of the actual data.

The Committee finds that, in the methodology section of the article, the authors have accounted in detail for the calculations of the mRNA data presented in Figure 1. The Committee also finds that Figure 1 does not specify variation for the data in relation to the time point "0", but that the variation is set for data from the other observation times. The Committee also notes that the IL-8 expression is low at time point "0".





The Committee finds that, despite the lack of variation for data at time point “o”, the reader is able to assess the validity and biological relevance of the data presented.

The Committee therefore finds that this does not constitute a breach of good scientific practice.

With reference to the Complainant’s assertion that it is difficult to identify the actual size of the study populations in the work concerned, the Committee finds that there are no grounds to conclude that the results from one of the subjects have been omitted on the basis of the number of subjects alone.

However, with reference to the number of subjects, the Committee finds that the description of the material included is unclear and that the information in the article is conflicting, as there are differences in the information provided on the number of subjects in study 1.

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In the abstract, the exercise group is described as consisting of six individuals (n=6), whereas the resting group is described as consisting of five (n=5). The total number of subjects in study 1 is described in the methodology section as 11.

The results section contains the following description of the subjects:

*“The IL-8 protein was not expressed in muscle tissue before exercise (n=12, Fig. 2A), and repetitive muscle samples at rest did not show induction of IL-8 expression (n=6, data not shown).”*

In addition, only one group is stated in Figures 1 and 3 in the article, comprising six individuals (n=6). As part of the consultation on the draft ruling of 25 June 2013, the Defendant stated that the inclusion of n=12 in the results section was due exclusively to a writing error, and that the inclusion of n=6 in Figures 1 and 3 refers to the “exercise” group. With reference to this point, the Defendant contends that it would have been more correct to write n=6 “exercise” and n= 5 “resting” in Figures 1 and 3, but that a reading of the article makes it clear that the inclusion of n=6 in Figures 1 and 3 refers to the “exercise” group.

In the light of the information provided by the Defendant during the proceedings, the Committee finds that the unclear description of the subjects referred to in article 3 only reflects a regrettable mistake, which cannot be classified as a serious breach of good scientific practice.

The question of repeated use of the human biopsy material in multiple scientific works will be addressed in a separate section below.

The question of the Defendant’s responsibility for the reused and/or manipulated images will also be addressed in a separate section below.

## 7.7 Article 4

In the article “[ARTICLE 4]”, the authors demonstrate that exercise leads to the expression of metallothionein in human muscles.



The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the quality of research, which are outside the Committees' remit, pursuant to the DCSD Order, section 3 (1):

- The Complainant's allegation of inadequacies in relation to the methodology for the IHC procedure for detecting metallothionein and the results of this (refers to the quality of the scientific work)
- The Complainant's allegation that information on Ct values is necessary to comment on mRNA levels in muscle fibres at rest (refers to the quality of the scientific work)
- The Complainant's allegation that the reported expression of metallothionein mRNA in type-1 and type-2 muscle fibres after exercise was not justified by the results (refers to the quality of the scientific work)

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Regarding the Complainant's assertion that it is difficult to identify the actual size of the study population, the Committee finds that the description of the material is unclear and that the article contains conflicting information, because there are differences in the information on the number of subjects.

In the article's methodology section, the total number of subjects is described as 18, of whom 12 are in the exercise group ( $n=12$ ), while six are in the resting group ( $n=6$ ). In Figure 1 in the results section, the exercise group is shown to consist of six subjects ( $n=6$ ) and the resting group of five ( $n=5$ ), i.e. the total number of subjects in Figure 1, as per the description, is 11.

With reference to the number of subjects/biopsies included, the Defendant has stated that the authors informed the readers that mRNA measurements were only performed on a sub-group, due to "lack of material".

As part of the consultation on the draft ruling of 25 June 2013, the Defendant stated that the information in Figure 1 that the number of subjects was 11 was due to the fact that the measurements of MTmRNA expressions that appear in these figures were only conducted on this part of the overall study population because material for mRNA was not prioritised from the start.

In the Defendant's response to the Committee's letter of 3 February 2014 concerning the reopening of the case, the Defendant states that, when presenting findings in the article, including the mRNA measurements on a subgroup of subjects, the Defendant followed standard practice in integrative physiology, which is the Defendant's field of research. In this context, the Defendant refers to a series of articles within the same field of research in which the same procedures were followed, i.e. where measurements on subgroups are only indicated by the value  $n$ , without any description of the criteria for selecting the subset.

The Committee notes at the outset that it is only in the description of Figure 1 in the article, in the form of  $n=11$ , that the reader is provided with information that MTmRNA measurements were performed on a selected part (11 subjects) of the overall study population (18 subjects). It is not clear from the article why the measurements were performed on a selected subset of the overall population. It was not until the Defendant submitted material during the case proceedings that it was



stated that the MTmRNA measurements on a subset of the total population were due, according to the Defendant, to lack of material.

The Committee notes that one of the main requirements for a scientific product is that the reader is given the opportunity to evaluate the results of the article, its data and the material used to achieve the results on an informed basis. In this regard, the Committee is of the opinion that it is essential for the reader's assessment of the article that it provides information about any selection in relation to the material used, including the study population, and that the criteria for selection ought also to be described in the article. This is reflected, for example, in the textbook for medical research, which states:

*“When citing material, it should be clear to the reader which patients, if any, the authors have omitted from the primary material, and which, for one reason or another, did not complete the studies, so that the secondary material, for this and that reason, was of this and that size.”<sup>19</sup>*

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In this light, the Committee finds that, in accordance with good scientific practice, the article should have contained a brief description of why MTmRNA measurements were taken from 11 subjects out of a total study population of 18. This would have ensured transparency in the dissemination of the research results. However, the Committee finds that the absence of a description of the background to the selection cannot with a sufficient degree of certainty be considered to constitute a serious breach of good scientific practice, as the reader is informed by the article's description of Figure 1 that the results presented therein stem only from 11 subjects (n=11). In reaching this conclusion, the Committee has taken into account the articles to which the Defendant refers in the Defendant's comments to the Committee's letter of 3 February 2014 concerning the reopening of the case. On this basis, the Committee can confirm that the practice chosen by the Defendant has also been used in a number of comparable scientific works in the same field of research.

In relation to the Complainant's allegation about the presentation of data as fold changes, the Committee finds that an article that presents relative values should also include both the original data and the variation so that the reader can assess the actual biological variation. The Committee is of the opinion that citing the original data and the variation helps avoid any obscuration of the actual data.

The Committee finds that the Defendant did account for the calculation of the mRNA results in the methodology section. The Committee also finds that Figure 1 does not specify variation for data at the time point “o”, but that the variation is stated for data at the other observation times.

The Committee finds that, despite the lack of variation for data at “o”, the reader is able to assess the validity and biological relevance of the data presented.

The Committee therefore finds that this does not constitute a breach of good scientific practice.

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<sup>19</sup> Riis P “Skriftlig præsentation” (Written Presentation) in: Pedersen J & Havsteen B (ed.), “Lægevidenskabelig Forskning – en introduktion” (Medical Research - an introduction), 2nd edition, FADL Publishing, Copenhagen, 1972 and subsequent editions.



The question of the repeated use of the human biopsy material in multiple scientific works will be addressed in a separate section below.

The question of the Defendant's responsibility for the reused and/or manipulated images will also be addressed in a separate section below.

## 7.8 Article 5

The article "[ARTICLE 5]" included two human studies and one of mice. The authors studied the interaction between the cytokine IL-6 and its receptor in muscle tissue during exercise.

The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the quality of research, which are outside the Committees' remit, pursuant to the DCSD Order, section 3 (1):

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- The Complainant's allegation of inadequacies in relation to the methodology for the IHC procedure for detecting the presence of the IL-6 receptor and the results of this (refers to the quality of the scientific work)
- The Complainant's allegation about the need to underpin the histochemical findings using Western Blot (refers to the quality of the scientific work)
- The Complainant's allegation about lack of documentation about the identical expression of IL-6-receptor in type 1 and type 2 muscle fibres in the discussion section (refers to the quality of the scientific work)
- The Complainant's allegation that information about Ct values is necessary in order to comment on mRNA levels in muscle fibres at rest (refers to the quality of the scientific work)

With reference to the Complainant's allegation concerning Plasma IL-6 data from exercise experiments, as mentioned in the article's discussion section, the authors referred, according to the Defendant, to the work from which this data was obtained.

The Committee finds that, in the part of the discussion section about plasma IL-6 data from exercise experiments, a reference to the experiments from which the data stems is not specified. The Committee therefore finds that this part of the discussion is based on unclear foundations.

The Committee considers that the lack of reference to the article from which the plasma IL-6 data stems is not in accordance with good scientific practice, but that this fact does not constitute a serious breach of good scientific practice, as reference is made to this plasma IL-6 data in the introduction and elsewhere in the article.

Regarding the Complainant's allegation concerning the ethical aspect of the injection of recombinant human IL-6 in the femoral artery, the article states that permission was obtained for the project from the Research Ethics Committee. The Committee notes in this respect that such ethical issues generally fall outside its remit. The Committee also notes that during the consultation on the draft ruling, the Complainant stated that the Complainant did not wish to complain about the ethical aspect of Article 5.



Regarding the description of the mouse experiment, the Committee notes that meeting the requirements for the extent of such descriptions always involves a judgement call that must take into account the journal's space requirements and any possible interpretations of the results obtained.

In this particular case, the Committee finds that the omission of details does not represent such a serious shortcoming as to provide a basis upon which to characterise the description as so flawed that it constitutes a breach of good scientific practice.

With reference to the Complainant's assertion that it is difficult to assess the actual amounts of IL-6R mRNA in the tissue because the data is not presented as absolute values, only as relative values compared to basic values, the Defendant states that it is standard practice to normalise data to 1.

The Committee finds that, when an article presents relative values, the original data and the variation ought also to be presented so that the reader is able to assess the actual biological variation. The Committee is of the opinion that citing the original data and the variation helps avoid any obscuration of the actual data.

The Committee finds that the Defendant did account for the calculation of the mRNA results in the methodology section in article 5. The Committee also finds that Figure 1 does not specify variation for data at the time point "o", but that the variation is stated for data at the other observation times.

The Committee finds that, despite the lack of variation for data at "o", the reader is able to assess the validity and biological relevance of the data presented.

The Committee therefore finds that this does not constitute a breach of good scientific practice.

The question of the repeated use of the human biopsy material in multiple scientific works will be addressed in a separate section below.

The question of the Defendant's responsibility for the reused and/or manipulated images will also be addressed in a separate section below.

## 7.9 Article 6

In the article "[Article 6]", the authors study the cytokine profile of different types of skeletal muscle fibres.

The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the quality of research, which are outside the Committee's remit, pursuant to the DCSD Order, section 3 (1):

- The Complainant's allegation of significant differences between the findings in the present and a previous study (refers to the quality of the scientific work)



- The Complainant's allegation of specificity of cytokine expression in different muscle fibres (refers to the credibility of scientific theories)
- The Complainant's allegation that "in situ hybridisation" should have taken place (refers to the quality of the scientific work)
- The Complainant's allegation about the cytokine-mRNA and MHC1-mRNA levels in different muscle-fibre types (refers to the credibility of scientific theories)

The Committee therefore finds that all assertions and allegations relating to this article (with the exception of the allegation concerning reuse of biopsy material – see below) refer to the credibility of scientific theories and/or the quality of research and therefore fall outside the remit of the DCSD.

The question of the repeated use of the human biopsy material in multiple scientific works will be addressed in a separate section below.

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### 7.10 Article 7

In the article "[Article 7]", the authors study whether there is any link between muscle-fibre types in terms of isoforms of myosin heavy chain (MHC) and the mRNA profile of metabolic genes and functions.

The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the quality of research, which are outside the Committees' remit, pursuant to the DCSD Order, section 3 (1):

- The Complainant's allegation that the article's conclusion about correlations between the mRNA expression of certain metabolic genes is not supported by the results (refers to the credibility of scientific theories)
- The Complainant's allegation that the wrong approach was adopted to the statistical analysis (refers to the credibility of scientific theories)

The Complainant asserts that data from one of the muscles was not included, and that this was not accounted for. The Defendant has not commented on this point.<sup>20</sup>

The Committee finds that the article should have informed readers that data from one of the muscles was not included.

In this particular case, the Committee finds that the omission of this information does not represent such a serious shortcoming that it provides a basis on which to characterise the description as so flawed that it constitutes a serious breach of good scientific practice.

The question of the repeated use of the human biopsy material in multiple scientific works will be addressed in a separate section below.

### 7.11 Article 8

In the article "[ARTICLE 8]", the authors study whether muscle-derived IL-8 stimulates angiogenesis during muscle work.

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<sup>20</sup> The Committee notes that the Defendant has commented on this fact in connection with the reopening of the case.



The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the quality of research, which are outside the Committees' remit, pursuant to the DCSD Order, section 3 (1):

- The Complainant's allegation that staining of the TGF- $\beta$ -receptor is not described, and that these stains are not reported in the results section (refers to the quality of the scientific work)
- The Complainant's allegation that the results of a two-layer immunofluorescence staining of the two receptors were presented, even though neither the fluorescence marking nor the fluorescence-microscopy method had previously been described (refers to the quality of the scientific work)
- The Complainant's allegation that the results section does not match the methodology section (refers to the quality of the scientific work)
- The Complainant's allegation that the choice of muscle sections is not described, including whether they are from the same subject and how they were examined (refers to the quality of the scientific work)
- The Complainant's allegation that Western Blot ought to have been used on the receptor protein, particularly because of the apparent inconsistency between the absence of IHC detectable IL-8-receptor protein when IL-8-receptor-mRNA expression occurs at rest (refers to the quality of the scientific work)
- The Complainant's allegation that the authors conclude in the article that the IL-8 receptor is located primarily in activated microvascular endothelium (refers to the credibility of scientific theories)
- The Complainant's allegation that Figure 2 contradicts the conclusion that 21<sup>21</sup> hours after exercise, the expression of the receptor protein had fallen to the same level as before exercise (refers to the credibility of scientific theories)
- The Complainant's allegation that the statement in the article that the IL-8 receptor was low or absent in the muscle before exercise and during the first 1½ hours after exercise, is inconsistent with protein being expressed in muscle fibres and the sarcolemma at all times (refers to the credibility of scientific theories)
- The Complainant's allegation that the cellular source of the observed increase in receptor-mRNA is not known because "in situ hybridisation" did not take place (refers to the quality of the scientific work)
- The Complainant's allegation that it is not mentioned in the article that the release of IL-8 was only seen in the middle part of the three-hour exercise session, whereas an increase in IL-8-receptor expression in muscle was only seen after exercise (refers to the quality of the scientific work)
- The Complainant's allegation that data was wrongly presented as geometric mean value  $\pm$  SEM (refers to the quality of the scientific work)

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<sup>21</sup> The Committee bases its ruling on the fact that the section cited by the Complainant must be the 24-hour section, as no biopsies were conducted at 21 hours. During the consultation about the draft ruling, the Complainant has stated that since the "exercise" period was three hours, it is possible, as the Complainant did, also to describe it as taken 21 hours after (the end of) the exercise.





Regarding the Complainant's assertion that the interpretation of the increased protein expression was not discussed, the Committee finds that the low CXCR2-mRNA level was not necessarily obvious to the reader because the basic CXCR2/GAPDH-mRNA ratios in Figure 1 were close to 1.

The Committee finds that this approach shows ratios between measurements in absolute terms (CXCR2-RNA/GAPDH), and that the form of normalisation procedure used is described in detail for the reader in the section on materials and methods.

The Committee therefore finds that there was no breach of good scientific practice, as the reader is given a sufficient basis for evaluating the results in the article.

The question of the repeated use of the human biopsy material in multiple scientific works will be addressed in a separate section below.

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## 7.12 Article 9

In the article "[ARTICLE 9]", the authors show that the protein interleukin-18 (IL-18) can play a role in the processes that lead to muscle loss in patients with chronic obstructive pulmonary disease.

The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the quality of research, which are outside the Committees' remit, pursuant to the DCSD Order, section 3 (1):

- The Complainant's allegation that a genuine matching between control groups and subjects was not made and the allegation that the control groups were not randomly selected (refers to the quality of the scientific work)
- The Complainant's allegation that the appropriateness of including smokers in the control group was questionable and, in this context, the assertion that the effect of smoking was not discussed (refers to the quality of the scientific work)
- The Complainant's allegation that data from four excluded steroid patients was not published (refers to the quality of the scientific work)
- The Complainant's allegation that ATPase staining is described in two different sections of the published article (refers to the quality of the scientific work)
- The Complainant's allegation that the article describes muscle tissue being immune-stained for IL-8 but that this data is not reported (refers to the quality of the scientific work)
- The Complainant's allegation that there is no correlation between IL-1- $\beta$  and IL-18 expression (refers to the credibility of scientific theories)
- The Complainant's allegation of a discrepancy between IL-18-mRNA levels and IL-18 protein in selected groups (refers to the credibility of scientific theories)
- The Complainant's allegation of a discrepancy between TNF- $\alpha$  mRNA and TNF- $\alpha$  protein (refers to the credibility of scientific theories)



- The Complainant's allegation of a discrepancy between IL-6 mRNA and IL-6 protein (refers to the credibility of scientific theories)
- The Complainant's allegation that the conclusion is untenable (refers to the credibility of scientific theories)

Regarding the Complainant's allegation that the information regarding IL-18 levels in plasma in the abstract is not consistent with the data in Figure 1, the Committee notes that it is true that the values for the IL-18 data in the abstract are higher than those shown in Figure 1. The Committee also finds that the unit span in the abstract ("range") (pg/pl) does not harmonise with the given IL-18 levels in the two groups studied (pg/ml) in Figure 1.

As part of the consultation on the draft ruling of 25 June 2013, the Defendant stated that the discrepancy concerning IL-18 levels in the article was due to the fact that the levels stated in Figure 1 stem from an analysis that suffered from technical problems and should not have been included in the article. According to the Defendant, this also explains why the levels in Figure 1 are not consistent with the interassay variation.

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In this light, the Committee finds that the discrepancy between IL-18 levels in the article only represents an error that cannot be characterised as a serious breach of good scientific practice.

Regarding the Complainant's allegation of a lack of p-values in relation to the results in Table 1, the Committee notes that it is true that p-values are not specified in Table 1, but that several p-values are included in the text in the results section ("Patient Characteristics").

The Committee also notes that p-values are not specified for indicators of lung function (FEV, FEV<sub>1</sub>/FVC, RV, TLC, diffusion capacity, PaCO<sub>2</sub>, Pao<sub>2</sub>, saturation and leukocyte count).

The Committee finds that the omission of p-values in this article does not represent a serious breach of good scientific practice because the relevant data is available in the article (mean  $\pm$  SD and number of people in each group).

The Committee finds that no new information has arisen during the consultation on the draft ruling of 9 May 2014 on the reopened case that would give rise to the Committee changing the above ruling concerning the plasma concentration and the inter-assay variation in article 9.

### 7.13 Article 10

In the article "[ARTICLE 10]", the authors show that the cytokine interleukin-15 (IL-15) is present in type-2 muscle cells, and that the volume is increased further by resistance-based physical activity.

The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the quality of research, which are outside the Committee's remit, pursuant to the DCSD Order, section 3 (1):



- The Complainant's allegation that although MHC-mRNA-2a is not measured in the article, a negative correlation between this variable and the incidence of type-1 fibres is reported in the results section (refers to the quality of the scientific work)
- The Complainant's allegation that the illustration of histochemical findings is flawed (Figure 2) (refers to the quality of the scientific work)
- The Complainant's allegation that a section stained for IL-15 was shown for each of the three muscles, but that the selection of these sections was not described (refers to the quality of the scientific work)
- The Complainant's allegation that adjacent sections stained for fibre type and identical fibres stained for IL-15 and fibre type were allegedly marked with an asteriks, which is not consistent with the fact that the two sections from the vastus lateralis muscle (c and d) and the fibres reproduced for these are apparently not identical (refers to the quality of the scientific work)
- The Complainant's allegation that Figure 2 makes a comparison of sections stained for IL-15 and negative control sections, and that these sections should have been adjacent but clearly were not (refers to the quality of the scientific work)
- The Complainant's allegation that the description of the evaluation of sections was inadequate (refers to the quality of the scientific work)
- The Complainant's allegation of a discrepancy between IL-15 mRNA and IL-15 protein in Study 1 (refers to the credibility of scientific theories)
- The Complainant's allegation of lack of correlation between IL-15 mRNA and IL-15 protein in Study 2 (refers to the credibility of scientific theories)
- The Complainant's allegation that it was not discussed in detail that the mRNA increase happened relatively late in relation to the exercise stimulus (refers to the credibility of scientific theories)
- The Complainant's allegation that the lack of parallelity between mRNA and protein findings in the two experiments was attributed to the existence of transcription without translation (refers to the credibility of scientific theories)

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The Committee therefore finds that all assertions and allegations relating to this article (with the exception of the allegation concerning reuse of biopsy material – see below) refer to the credibility of scientific theories and/or the quality of research and therefore fall outside the remit of the DCSD.

The question of the repeated use of the human biopsy material in multiple scientific works will be addressed in a separate section below.

#### **7.14 Article 11**

In the article “[Article 11]”, the authors demonstrate that there is a correlation between plasma-TNF- $\alpha$  and insulin resistance, but there is no connection between the content of TNF- $\alpha$  in adipose- and muscle tissue and the degree of insulin resistance.

The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the



quality of research, which are outside the Committees' remit, pursuant to the DCSD Order, section 3 (1):

- The Complainant's allegation that the article's results are contrary to previous findings from the group and that this is not mentioned in the article (refers to the credibility of scientific theories)
- The Complainant's allegation of lack of any correlation between TNF- $\alpha$  staining and TNF- $\alpha$  Western Blot of muscle fibres from the diabetics and control subjects (Figure 3) (refers to the credibility of scientific theories)
- The Complainant's allegation that the description of the evaluation of histochemical data was inadequate (refers to the quality of the scientific work)
- The Complainant's allegation that negative control sections were incubated without goat serum (refers to the quality of the scientific work)
- The Complainant's allegation that there is a discrepancy between Figures 2B and C (the text and the blots shown) in terms of the amounts of membrane-bound proTNF- $\alpha$  and a cleaved form of TNF- $\alpha$  (refers to the quality of the scientific work)
- The Complainant's allegation that the discrepancy between TNF- $\alpha$ -mRNA and protein levels is attributed to post-transcript regulation of the protein content, whereas a similar discrepancy in article 10 was attributed to negative feedback inhibition of mRNA (refers to the credibility of scientific theories)
- The Complainant's allegation that VO<sub>2</sub>max and fat mass values were reported, but the methods of analysis of these variables were not (refers to the quality of the scientific work)
- The Complainant's allegation that the conclusion that plasma TNF- $\alpha$  is associated with insulin resistance, and possibly plays a role in the pathogenesis of chronic insulin resistance, seems daring in the light of the results for the control group and diabetics (refers to the quality of the scientific work)
- The Complainant's allegation that the spread between the estimate of several variables was very small (refers to the quality of the scientific work)

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The Committee notes that, according to the article's statistical section, two-way ANOVA was used to analyse the difference in mean/average ratios between pro-TNF- $\alpha$  and  $\beta$ -actin and cleaved TNF- $\alpha$  and  $\beta$ -actin, while the caption (Fig. 2) shows that one-way ANOVA was used.

Based on the fact that an average of several patient groups was used, rather than repeated measurements in the same groups, the Committee finds that the use of one-way ANOVA is the correct scientific approach, and that there is therefore an error in the methodology section.

The Committee finds that the error does not constitute a serious breach of good scientific practice. In reaching this conclusion, the Committee emphasises that the most important aspect must be that the data is analysed correctly and that this is clear from the article. The Committee therefore finds that it is sufficiently clear from the article how the data was analysed and, furthermore, that the data in the article was analysed correctly.



Regarding the authors' choice of the "case-control" design, the Committee notes that "case-control" studies can be analysed with both matched and unmatched statistical tests.

In this particular case, the authors have chosen to analyse with unmatched tests, even though the introduction to the article points out that the authors had decided to match cases and control individuals. On the other hand, the final material also includes an odd number of cases and control individuals, so non-matched tests provide a better opportunity to take advantage of all of the data.

The Committee considers that the rationale for the choice of the "case-control" design could have been explained more clearly in the article, but does not find that the lack of explanation represents a serious breach of good scientific practice because it is sufficiently clear from the article how the data was analysed.

### 7.15 Article 12

In the article "[ARTICLE 12]", the authors demonstrate that BDNF is induced in skeletal muscle during contraction and increases lipid oxidation via activation of AMPK.

The Committee finds that several of the Complainant's assertions and allegations regarding the above article relate to the credibility of scientific theories and/or the quality of research, which are outside the Committees' remit, pursuant to the DCSD Order, section 3 (1):

- The Complainant's allegation about the choice of points in time for the collection of specimens for measurement of BDNF protein (refers to the quality of the scientific work and the credibility of scientific theories)
- The Complainant's allegation of a lack of correlation between BDNF mRNA and BDNF protein determined by Western Blot (refers to the credibility of scientific theories)
- The Complainant's allegation of lack of discussion of divergent findings in BDNF-mRNA expression in C2C12-"myotubes" versus human muscle (refers to the credibility of scientific theories)
- The Complainant's allegation of inadequate description of the methodology for the IHC and poor correlation between BDNF-protein detected by IHC versus Western Blot (refers to the quality of the scientific work and the credibility of scientific theories)
- The Complainant's allegation of lack of correlation between BDNF mRNA and BDNF protein determined by IHC (refers to the credibility of scientific theories)
- The Complainant's allegation regarding the placement of the o-point on the Y axis in the presentation of BDNF-induced palmitate oxidation (Figure 4) and the narrow spread of data (refers to the quality of the scientific work)
- The Complainant's allegation that the wrong conclusions are drawn concerning the intracellular signalling pathways for the observed BDNF-induced increase of palmitate oxidation (refers to the quality of the scientific work).



Regarding the Complainant's assertion that it is difficult to evaluate the actual amounts of BDNF mRNA in the tissue because the data is not presented as absolute values, but only as relative values compared to "0"/pre-exercise values, via a normalisation procedure that is not described, the Defendant refers to her general comments on common practice concerning the presentation of mRNA-expression.

The Committee finds that, when an article presents relative values, the original data and the variation ought also to be presented so that the reader is able to assess the actual biological variation. The Committee is of the opinion that citing the original data and the variation helps avoid any obscuration of the actual data.

The Committee finds that the Defendant did not account for the calculation of the mRNA data presented in the article in the methodology section. The Committee notes that the article cites reference #34 (Chan et al 2004), an article that also omits a description of its calculations, and contains a further reference.

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The Committee also notes that Figure 1A presents the variation of data in all of the observations (0, 2, 3, 5, 8, 24, 48 and 72 hours).

The Committee finds that due to the lack of a description of how the data underlying Figure 1A was arrived at, readers of article 12 are unable to fully assess the validity of the data presented.

The Committee therefore finds that the approach adopted in the article is not in accordance with good scientific practice, but cannot be characterised as a serious breach of good scientific practice and therefore scientific dishonesty, as the reader can infer that normalisation of the data has taken place.

Regarding the Complainant's assertion of inadequate description of the calculation of the AUC, the Committee notes that, in this case, a passage of time is evaluated and that the pattern turns out to be the same for the whole group. With this in mind, the Committee considers the use of an AUC calculation to be acceptable.

It is correct that the assumptions on which the AUC is calculated are not specified, and thus the reader of the article is not aware of the mean value and spread for AUC for the two groups.

The Committee is of the view that the assumptions for the AUC calculations ought to have been specified. However, it does not consider that this omission constitutes a serious breach of good scientific practice because it is not critical to the reader's assessment of the article's content and findings.

Regarding the Complainant's allegation of a discrepancy in the description of the subjects involved, the Committee notes that the authors have issued an erratum to the article, which was published online on 10 January 2012.

The Committee is of the opinion that the criticisms arose partly because the original article contained an incomplete description of the test subjects. The full description has now been added to the published erratum.



In a separate ruling concerning this point of criticism, the Committee stated the following about the original methodology description in the article (see ruling of 18 December 2013):

*“The Committee notes that a full description of the test subjects has been added to the methodology section in the erratum. It has now been made clear that the control group and the active group consist of different people and it is therefore correct to use an un-paired analysis instead of a paired one.*

*In the case at hand, the Committee is of the opinion that the time sequence and the pattern are the same for the whole group. In this light, the Committee considers the use of an AUC calculation to be acceptable.*

*It is correct that the assumptions on which the AUC is calculated are not specified, and thus the reader of the article is not aware of the mean value and spread for AUC for the two groups.*

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*The Committee is of the view that it would have been preferable to have specified the assumptions for the AUC calculations. However, it does not consider that this omission constitutes a serious breach of good scientific practice because it is not critical to the reader’s assessment of the article’s content and findings.*

*The Committee notes that the choice of statistical method was wrong in relation to the original description of the test subjects in the article, as this was inadequate.*

*In addition, the Committee finds that the information in the article concerning the number of persons/control population (n-values) is unclear. The original methodology section indicates  $n=8$ . Figure 1 also stipulates  $n=8$ , but the Committee does not think it is entirely clear whether there are four people in each group ( $2 \times 4 = 8$ ) or eight people in each group. No control group is specified in the original methodology, and it appears therefore as if all eight test subjects were involved in the cycling experiment. Figure 2 specifies  $n=10$ , but the Committee finds that it is not clear whether this means ten people ( $2 \times 5 = 10$ ) or 20 people ( $2 \times 10 = 20$ ).*

*The Committee finds, therefore, that the article does not make clear that the material refers to two different test groups, nor does it inform the reader how many subjects there are or how big the control population in the groups actually is.*

*The Committee, therefore, finds it impossible to assess the relevance of the effect shown in Figures 1B and 1C, because the original article does not mention that the two figures contain data pertaining to different test subjects, and that these subjects participated in the experiment at different times. It was not until the erratum was published that it became clear that two different groups were referred to in these two figures.*

*One of the most important requirements on scientific work of the type concerned is transparency in the choice of methodology and the description of the methodology, because this facilitates reproduction and relevant interpretations of the results presented, as well as assessments of their credibility.*





*The Committee finds that the omission of significant information about the test subjects from the original methodology description constitutes a serious breach of good scientific practice on a par with “undisclosed construction of data”, pursuant to the DCSD Order 2, no. 1. As described above, the inadequate description of the subjects in the methodology section has consequences for the interpretation of results contained in the article.*

*The Committee finds that the erratum containing a revised description of the methodology does not justify any change to its findings, as the complaint concerned the article in its original form and the erratum was published after the complaint had been submitted. The Committee also finds that the fact that the journal accepted an erratum cannot be accorded any prominence in its ruling.*

*Defendant 1 [Defendant 1 in the case concerned is the same individual as the Defendant in this case] has stated that the shortcomings of the original methodology section were merely the result of an error during the editing process, which meant that the description of the main study in the article was omitted from the methodology section, and that this does not constitute a serious breach of good scientific practice. Defendant 1 also pointed out that the final version of the manuscript erroneously indicates points in time for biopsies in the secondary study that correspond to the main study. According to Defendant 1, this happened during an extensive editing process involving the 16 co-authors. In this light, Defendant 1 is of the view that the erroneous description of the methodology cannot be blamed on her.*

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*The Committee notes that Defendant 1 is listed as “co-director” of the article, which in this case is equivalent to the final author (see section 7.4). Information supplied by Defendant 1 during the case also shows that Defendant 1 was involved in the selection of test subjects for the article, including the description of them in the methodology section. This is also reflected by the fact that the article incorporated material (because of lack of material) that had previously been used in a publication for which Defendant 1 was the final author, and that Defendant 1 had significant insight into the study that formed the basis for the article concerned.*

*In the light of the information provided by Defendant 1, the Committee concludes that a test group was mistakenly omitted from the original methodology section during the editing process, and that incorrect biopsy times were stated. The Committee also notes that, according to Defendant 1, it was Co-author 1 who prepared the final draft of the article and was responsible for all correspondence with the journal.*

*Due to the role played by Defendant 1 in writing the article, the Committee is of the opinion that Defendant 1 should have discovered and responded to the lack of information. However, the Committee recognises that an editing process involving multiple co-authors from different countries inherently entails a certain risk of error. It is therefore the opinion of the Committee that Defendant 1’s conduct cannot be characterised as gross negligence. In reaching this conclusion, the Committee has taken into account that the error occurred in the course of an editing process involving multiple writers from different countries.*



*In this light, the Committee finds that Defendant 1 did not act in a scientifically dishonest manner.”*

In its ruling on this point, the Committee found that the Defendant did not act in a scientifically dishonest manner, and the Committee therefore refers to this ruling. In the light of this, the Committee will not take any further action in relation to this allegation in the present case.

The question of repeated use of the scientific biopsy material in multiple scientific works will be addressed in a separate section below.

### **7.16 Use of the same scientific biopsy material in multiple scientific works**

The Complainant asserts that, in a number of the scientific works about which complaints have been submitted, material was reused without this being stated in the articles concerned. The Complainant states as follows:

- that articles 1, 3 and 4 represent the same material, i.e. the same subjects and thus the same tissue samples, and furthermore, there is an overlap of the material between the three articles and the material referred to in article 5 (the exercise study),
- that the subjects in article 5 (the infusion study) are the same as those found in a previous article<sup>22</sup> (hereinafter [THE ET AL ARTICLE]) for which the Defendant was the last author,
- that the subjects, experimental protocols and materials in articles 6, 7 and 10 are the same, and
- that articles 8 and 12 use the same group of subjects and therefore biopsy material.

As part of the consultation on the draft ruling of 25 June 2013, the Defendant stated that the same subjects appear in articles 1, 3, 4 and 5 (the exercise study) and articles 6, 7 and 10. In a response to the consultation dated 12 August 2011, the Defendant states that it is correct that the authors included a previous study in article 5, and that the previous use is not mentioned in the methodology section, but that reference is made to the article in the discussion section of article 5 (ref. 38).<sup>23</sup>

The Defendant states that, because of the intrusive nature of the sampling, it would be unethical not to make optimal use of the material, and that it is therefore permissible to use previously collected material if new scientific questions emerge in the wake of earlier publications.

Regarding this point, the Defendant states that it is standard practice to make a reference to this in the methodology section or to provide an in-depth description of the design and procedures in each article. With this in mind, the Defendant contends that it is not common practice in an article to refer explicitly to the previous use of the same biopsy material if the respective articles study different scientific questions.

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<sup>22</sup> [THE ET-AL ARTICLE].

<sup>23</sup> The Committee notes that this reference is to [THE ET-AL ARTICLE].



The Defendant states that the authors of the articles that form the subject matter for the complaints have, in some cases, failed to provide a proper reference in the methodology section, but that they usually provided a reference in the results and discussion section.

With regard to articles 6, 7 and 10, the Defendant contends that it is clear that the same subjects were used in the three articles, and that the authors made no attempt to conceal this.

As part of the consultation on the draft ruling of 25 June 2013, the Defendant stated that biopsies were taken as part of the research project, and then divided into several pieces of tissue so that experiments could be conducted on each piece. According to the Defendant, the pieces of tissue were taken at the same time, but had not previously been used. They were then made the subject of new research, with new data based on new samples obtained from the original biopsies. However, it is the Committee's opinion that the unit of study in the studies concerned is the subject(s), not the individual parts of subdivided biopsy material from the same individual.

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As part of the consultation on the draft ruling of 25 June 2013, the Defendant also rejects the idea that the Vancouver rules contain a stipulation that information about previously applied test subjects must be disclosed, since the concept of "subjects" must be understood to mean the topics rather than the test subjects.

As part of the consultation on the draft ruling of 25 June, the Defendant cited a letter from 70 Danish researchers (attached to the Defendant's response to the draft ruling of 25 June 2013). The letter includes the following:

*"It would be completely unethical not to take full advantage of material that, in cases like this, is often obtained at the expense of substantial discomfort to the subject.*

*To the extent that the scientific studies conducted on these materials relate to separate questions, the practice represents separate and independent scientific utilisation of material.*

*It is important that the material is presented in the scientific publications in which the research results are published in such a way that the reader is able to evaluate the nature of the material, but it is of no scientific interest whatsoever whether the same material has been used or will be used in other scientific studies."*

In response to the Committee's letter of 3 February 2014 concerning the reopening of the case, the Defendant also contends that there is considerable disagreement in research circles about when cross-referencing is necessary. In this respect, the Defendant refers to a series of articles that, according to the Defendant, show that omission of cross-referencing is common practice.

The Committee notes at the outset that the basis for disclosing that the same material has been used in multiple empirical studies of biological material is that the findings and conclusions of the individual studies are based on samples. Based on



these samples, the purpose of the studies is to describe general correlations, i.e. valid for all individuals with the characteristics included in the studies. As individual differences in patterns of reaction are common in biological material, the value and generalisability of studies depends largely on results from other samples that produce similar or supportive findings. If readers are not informed that the study findings are based on the same samples, they are misled into thinking that they are from different samples. This means that conclusions based on the same biological sample material are accorded greater weight than they are entitled to, and erroneous conclusions are likely to be drawn.

The Committee also notes that material from experiments conducted on people can, of course, be used in multiple studies and scientific articles. The Committee is of the opinion that there may be very good reasons to make optimal use of material collected at the expense of substantial discomfort to the subject(s). Responsible research practice entails always providing the readers with all information necessary to assess the results in the article on an adequately informed basis. In many cases, this will involve explicitly informing readers about the origin of the test material and possible previous use of the same material. This can take the form of 1–2 relevant references or a reference to a familiar name of a project, biobank, etc.

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On the basis of the Complainant and the Defendant's contentions, including the Defendant's reference to a letter from 70 Danish researchers and a number of scientific works in which the same subjects are used in multiple articles, the Committee notes the absence of a sufficiently clear practice for generally disclosing information about test materials, including previous use in articles based on the same subjects. The Committee has conducted an overall review of the articles to which the Defendant refers (see section 7).

However, as stated above, the Committee finds that it follows from good scientific practice that the specific circumstances of a given scientific work can lead to it being necessary explicitly to disclose information about the origin of the material used in the article, e.g. in the following cases:

- i. When the results from two or more articles based on the same subjects are compared and used to support conclusions from individual articles. If information about the origin of the test material is not provided in cases like this, knowledge is withheld from the reader about the correlation between the findings in the various articles and the mutual interdependence of the conclusions. In a worst-case scenario, this can lead to results from the same study being used to support the conclusions in different publications, without the reader being aware that the same experiment and subjects are being referred to. In this way, a single study can be used to underpin a wide range of conclusions via follow-up articles because the conclusions appear to be unrelated.
- ii. When the selection of subjects is concealed from the reader due to lack of information about the origin of the test material. This means that the reader is unable to evaluate the article's findings on an adequately informed basis.



The Committee finds therefore that the review of the scientific works referred to by the Defendant cannot change the Committee's view that it is good scientific practice, at least in the two situations mentioned above, explicitly to provide information in the article concerned about the origin of the test material.

The Committee finds that no new information has arisen during the consultation on the draft ruling of 9 May 2014 on the reopened case that would give rise to the Committee changing the above ruling regarding the use of the same biopsy material in multiple articles.

The Committee has the following additional comments about this point:

- Based on the consultation responses and information submitted by the parties during the proceedings, the Committee has made changes to its ruling compared to the first draft ruling of 25 June 2013, e.g. in section 7.16 regarding the use of the same biopsy material in multiple articles. This is partly due to information provided by the parties during consultations about the draft decision, including information that expands upon the sparse and occasionally incomplete information in the material- and methodology sections of the articles concerned. The Committee has also strived to make its findings clearer.
- The Committee's ascertainment of good scientific practice reflects that which is generally accepted in research circles, as it is impossible to codify, as a legal standard, every facet of good scientific practice in a set of rules or similar document.
- The Committee finds no basis for giving further consideration to the petition submitted to the Committee by the Defendant on 2 April 2014, as the basis of the statement is that it is at the discretion of the researchers whether an article should contain information about previous use of the same test material. In the opinion of the Committee, such discretion must therefore take good scientific practice into account. One key element of this is that the reader is given a sufficient basis on which to assess the article's conclusions.
- The Committee has previously conducted a review of the articles to which the Defendant refers in the Defendant's response to consultation on 15 August 2013 and in the Defendant's observations following the reopening of the case, in which the Committee found that, in its view, this review does not alter the Committee's understanding of good scientific practice in relation to information about the origin of the material.
- The Committee finds that the five articles submitted by the Defendant as an appendix to the Defendant's response to consultation do not change the Committee's view on when authors should explicitly inform readers about the origins of test material, because the material- and methodology sections of these five articles (with the exception of the first one produced) contain descriptions of the test material that make explicit reference to the original article in which the subjects were included.
- The Committee finds that the statement by a statistician submitted by the Defendant does not alter the Committee's observations concerning samples (see the Committee's view above). This is because samples from the same individual are to be considered mutually dependent due to the common genetic profile of the cells and tissues in the individual subjects, which dif-

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ferentiates them from other individuals. This means that apparently different conditions are mutually related, for example to the individual's genetic profile, and therefore do not necessarily reflect findings of a general nature. It is particularly essential to respect this in studies with very limited sample material (e.g. n=6).

In sections 7.16.1–7.16.4 below, the Committee considers the use of the same biopsy material in the articles where complaints have been lodged about the use of the same subjects, and assesses whether the various instances reflect serious breaches of good scientific practice. In section 7.16.5, the Committee summarises the assessments in sections 7.16.1–7.16.4, and assesses whether any serious breach has been committed intentionally or with gross negligence.

#### **7.16.1 Concerning the use of the same biopsy material in articles 1, 3, 4 and 5**

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The Committee finds that the same biopsy material is used in articles 1, 3, 4 and 5 (the exercise study). Article 1 was the first of the four articles in question to be published. For this reason, the Committee's assessment of whether explicit information ought to have been provided about the origin of the material in the individual articles is only made in relation to articles 3, 4 and 5.

The Committee notes that articles 3, 4 and 5 do not contain information indicating that the biopsy material has been used in previous articles.

The Committee notes that article 4 contains the following paragraph, which refers to article 1:

*"...and IL-6 immunohistochemical staining is significantly increased in human skeletal muscle cells after exercise (Penkowa et al. 2003b<sup>24</sup>). As IL-6 is a major inducer of MT-I+II (Hernandez et al. 1997; Carrasco et al. 1998; Penkowa et al. 2000), the increased IL-6 expression in muscle tissue in response to exercise might explain the increases in MT-I+II."*

The Committee also notes that article 5 contains a reference to article 1 in the introduction and the following two sections, where reference is made to article 1:

*"Increased expression of the IL-6 receptor in muscle fibers after an exercise bout suggests that the muscle is sensitized by IL-6. The peak in IL-6 receptor production occurs several hours after the end of the exercise bout, at the time when IL-6 plasma levels are decreasing (4<sup>25</sup>). Expression of the IL-6 receptor may therefore be a mechanism whereby muscle is sensitized to the effects of IL-6 when IL-6 levels are sparse."*

[...]

*"We have previously shown that IL-6 is produced in both type I and type II skeletal myofibers, when subjects perform 3 h of intense ergometer bicycle exercise (4), whereas another study by Hiscock et al. reported specificity to fiber type II in response to 2 h of ergometer exercise (36). The studies (4, 36) indicate that the mode and intensity of exercise determines to which degree either fiber type ex-*

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<sup>24</sup> This is a reference to article 1.

<sup>25</sup> Note 4 is a reference to article 1.





*presses IL-6. In the present study, we studied 3 h of ergometer bicycle exercise and saw uniform expression of the IL-6 receptor in both type I and type II fibers, suggesting that both fiber types are rendered responsive to IL-6.*

*The kinetics of IL-6 and IL-6 receptor expression suggest that the pathways regulating IL-6 and the IL-6 receptor are linked, thus factors initiating IL-6 transcription may be inhibiting IL-6 receptor transcription.”*

In this light, the Committee finds that the results in articles 4 and 5 are compared with the results from article 1, and that results from article 1 are used to support the results in articles 4 and 5, without the reader being informed that the same study, biopsy material and, therefore, subjects formed the basis for the articles.

The Committee therefore finds that the lack of information in articles 4 and 5 about the fact that the biopsy material has been used in a previous article (article 1) constitutes a serious breach of good scientific practice, as the reader of the article is misled into believing that these are different studies with different biopsy material from which results are being compared with and incorporated into the scientific discussion in articles 4 and 5. Important information about the mutual interdependence of the results in the various articles is, therefore, withheld from the readers. With reference to this point, the Committee notes that the wording above – “We have previously shown...” and “In the present study...” – gives reason to believe that two separate studies are being referred to.

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The Committee finds that the results in article 3 are not compared in the same way with the results in the other articles with the same biopsy material (articles 1, 4 and 5). Previous results are not, therefore, used to support the conclusions in article 3 in the same way as in articles 4 and 5 (see above). In this light, the Committee finds that in this instance there was no serious breach of good scientific practice in article 3.

The Committee notes, however, that 18 subjects are listed in articles 1 and 4, and 11 subjects are listed in articles 3 and 5 (the exercise study), in which – as confirmed by the Defendant – the same biological material is used. In the light of this, the Committee finds that articles 3 and 5 only include 11 subjects out of an initial study population of 18 people, without this being stated in the articles.

The Committee finds that one of the main requirements for a scientific product is that the reader is given the opportunity to assess the results of the article, its data and the material used to achieve the results on an informed basis. In this regard, the Committee is of the opinion that it is essential for the reader’s evaluation that the article provides information about any selection of the material, including the study population, and that the criteria for such selection are stated in the article.

The Committee finds, therefore, that the lack of information in articles 3 and 5, about the fact that the biopsy material stems from a previous study with at least 18 subjects, constitutes a serious breach of good scientific practice, because information is withheld from the reader that a selection of subjects was made in articles 3 and 5.

The Committee finds that no new information has arisen during the consultation on the draft ruling of 9 May 2014 on the reopened case that would give rise to the Committee changing the findings above about the use of the same biopsy material in articles 1, 3, 4 and 5.





The Committee has the following additional comments about this point:

- In the opinion of the Committee, the Defendant's argument, that the Committee had found that the reduced n-value in article 4 did not reflect a serious breach of good scientific practice, cannot be applied to articles 3 and 5. By reading article 4, the reader can see a reduction of n-value in relation to certain measurements. This is not the case for articles 3 and 5, in which the readers are not informed about the reduction in n-value nor that the material has been previously used.

#### **7.16.2 Concerning the use of the same biopsy material in article 5 (the infusion study) and [THE ET AL ARTICLE]**

The Committee finds that the same biopsy material has been used in article 5 (the infusion study) and [THE ET AL ARTICLE].

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The Committee notes that article 5, which is the most recent of the two articles, does not contain information about the origin of the material, including the fact that the biopsy material has been used in the previous article.

The Committee notes that article 5 contains the following sentence, which refers to [THE ET AL ARTICLE]:

*"A role for IL-6 in metabolism is suggested, as rhIL-6 infusion to humans increases lipolysis and fat oxidation (38<sup>26</sup>)..."*

In this light, the Committee finds that the results in article 5 are compared with the results from [THE ET AL ARTICLE], and that the results from [THE ET AL ARTICLE] are partially used to support the discussion and conclusion in article 5, without the reader being informed that the same study and biopsy material form the basis for both articles.

The Committee therefore finds that the lack of information in article 5, about the fact that the biopsy material stems from a previous study and has been used in another article [THE ET AL ARTICLE], constitutes a serious breach of good scientific practice, as the reader of the article is misled into believing that these are different studies with different biopsy material from which results are being compared with and incorporated into the scientific discussion in article 5. Important information about the mutual interdependence of the results in the various articles is, therefore, withheld from the readers.

The Committee also notes that 18 subjects are listed in [THE ET AL ARTICLE] (n=6 with "low rhIL-6 infusion", n=6 with "high rhIL-6 infusion" and n=6 with "saline infusion") and 12 subjects are listed in article 5 (the infusion study) (n=6 with "rhIL-6 infusion" and n=6 with "saline infusion"), in which – as confirmed by the Defendant – the same biopsy material was used. In the light of this, the Committee finds that article 5 only includes 12 subjects out of an initial study population of 18 people, without this being stated in the article. On the basis of the methodology sections in the two articles, including the subdivision into groups of six, the

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<sup>26</sup> This is a reference to [THE ET-AL ARTICLE].



Committee finds that the authors seem to have chosen only to include one IL-6 infusion group from [THE ET AL ARTICLE] in article 5, without informing the reader of this in the latter.

The Committee finds that one of the main requirements for a scientific product is that the reader is given the opportunity to evaluate the results of the article, its data and the material used to achieve the results on an informed basis. In this regard, the Committee is of the opinion that it is essential for the reader's evaluation that the article provides information about any selection of the material, including the study population, and that the criteria for such selection are stated in the article.

The Committee finds, therefore, that the lack of information in article 5, about the fact that the biopsy material stems from a previous study with at least 18 subjects, constitutes a serious breach of good scientific practice because information is withheld from the reader that a selection of human subjects was made in article 5.

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The Committee finds that no new information has arisen during the consultation on the draft ruling of 9 May 2014 on the reopened case that would give rise to the Committee changing the findings above about the use of the same biopsy material in article 5 and [THE ET AL ARTICLE].

The Committee has the following additional comments about this point:

- The Committee notes that, as stated by the Defendant, there can be cases where subjects from a previous study are used, and where a group of these subjects is omitted in the new article based on objective criteria for non-selection. The Committee is of the opinion that information about the fact that any such form of selection has taken place and about the criteria used for it is important for the reader's perception of the article in question, and that it is good scientific practice to inform the readers of the selection. However, failure to provide information about selection cannot be characterised as a serious breach of good scientific practice in all cases, e.g. in cases where those omitted are completely irrelevant to and have no relationship to the subjects who are included and to the study in the article. The Defendant contends that it is the group from [THE ET AL ARTICLE] that was administered a high dose of rhIL-6, which is not included in article 5, and that the material from this group of subjects was irrelevant to the study in article 5. The Committee notes in this regard that the methodology section of article 5 states that, in this article, blood samples were taken at the intervals 0, 3, 6 and 24 hours from the group from [THE ET AL ARTICLE], which received a low dose of rhIL-6. Figure 2 of [THE ET AL ARTICLE] shows that the two IL-6 groups (high and low dose) only have a statistically significant difference in IL-6 level during the infusion period (0–3 hours) and not, for example, at six hours. The Committee notes that [THE ET AL ARTICLE] does not contain a measurement for 24 hours, as [THE ET AL ARTICLE] states that blood samples were taken at 0, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7 and 8 hours, whereas in article 5, which uses two of the three test groups from [THE ET AL ARTICLE], blood samples are reported to have been taken at 0, 3, 6 and 24 hours. Figure 2 in [THE ET AL ARTICLE] also shows that after 4 hours (240 minutes) there is probably no statistically significant difference in arterial IL-6 (pg/ml) between the high- and low-



dose IL-6 groups. In light of this, the Committee finds no basis for concluding that the test group with high dose rhIL-6 from [THE ET AL ARTICLE] can be considered completely irrelevant to and unrelated to article 5. It is the Committee's view that essential information about the material has been withheld from readers of article 5, thereby depriving them of the opportunity to properly consider the weaknesses and strengths of the protocol used. This also makes it more difficult for readers to evaluate the credibility of the findings presented in article 5. It therefore remains the view of the Committee that essential information about the material was withheld from readers of article 5, as they would presumably have evaluated article 5's description of the subject group with low-dose rhIL-6 differently had they been informed that there was also a group with a high dose of rhIL-6 that showed similar results at some of the same test times. The Committee also notes that the same experimental protocol is applied to the three subject groups (control, low- and high-dose IL-6) in [THE ET AL ARTICLE]. The protocol, which is described for the control group and the low-dose IL-6 group in article 5, not only omits the high-dose IL-6 group but also omits other important information about the protocol to which the subjects were subjected.

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### **7.16.3 Concerning the use of the same biopsy material in articles 6, 7 and 10**

The Committee finds that the same biopsy material has been used in articles 6, 7 and 10. Article 6 was the first of the three articles in question to be published. For this reason, the Committee's assessment of whether explicit information ought to have been provided about the origin of the material in the individual articles – due to this material being used to support the results – is only made in relation to articles 7 and 10.

The Committee notes that articles 7 and 10 do not contain information about the origin of the material, including the fact that the biopsy material has been used in a previous article.

The Committee finds that the results in articles 7 and 10 are not compared with each other or with the findings of the previous article using the same biopsy material (article 6). Previous results are not, therefore, used to support the conclusions in articles 7 and 10 in the same way as in articles 4 and 5 (see above). In this light, the Committee finds that in this instance there was no serious breach of good scientific practice in articles 7 and 10.

The Committee notes that the Defendant stated the following in a response to the complaint of 19 July 2011, dated 12 August 2011:

*“As described in the methods section, we included muscle biopsies from 14 individuals. Seven of these individuals were also included in paper 6 ([ARTICLE 6]). We do not give a reference to the latter study in the methods description, because the n-values were twice as high in the present study and thereby the anthropometric measures differed. The main results were on IL-15 mRNA and IL-15 protein, which was carried out on the total study population. We clearly indicate that*



*supportive data regarding fibre type distribution and IHC were related to analyses carried out on n=7.”*

The Committee also notes that article 10 does not state that the 14 subjects in the article are composed of two groups, each consisting of seven subjects and studied a year apart.

In light of this, the Committee came to the following conclusion in its ruling of 18 December 2013:

*“The Committee notes, however, that 14 subjects are listed in article 10, while seven subjects are listed in articles 6 and 7, in which the same biopsy material is used. In the light of this, the Committee finds that articles 6 and 7 only involve seven subjects out of an initial study population of 14, without this being stated in the article.*

*The Committee finds that one of the main requirements for a scientific product is that the reader is given the opportunity to evaluate the results of the article, its data and the material used to achieve the results on an informed basis. In this regard, the Committee is of the opinion that it is essential for the reader’s evaluation that the article provides information about any selection of the material, including the study population, and that the criteria for such selection are stated in the article.*

*The Committee finds, therefore, that the lack of information in articles 6 and 7, about the fact that the biopsy material stems from a previous study with at least 14 subjects, constitutes a serious breach of good scientific practice because information is withheld from the reader that a selection of subjects was made in articles 6 and 7.”*

On 20 December 2016, the Committee received an e-mail from two co-authors of articles 6, 7 and 10 (hereinafter referred to as “the two co-authors”), in which the two co-authors stated that the Committee had made a mistake in the part of its ruling of 18 December 2013 that referred to the selection of subjects in articles 6, 7 and 10.

In January 2014, the Committee received additional information regarding the biopsy material in articles 6, 7 and 10 from the Defendant and the two co-authors, including patient records for the subjects in the articles.

In the light of this information, on 3 February 2014 the Committee contacted the Defendant and the two co-authors and asked them to confirm the following understanding of the facts:

*“Articles 6 and 7 feature seven subjects (who are the same people in both articles). The biopsies from these subjects were taken on 20 and 21 January 2005, as per the copies of the patient records received by DCSD from [the two co-authors] (the record for subject 7 says 20-10-05 on the front page). This appears to be a typographical error because the blood samples on page 2 are dated 21/01-05. The Committee therefore assumes that the biopsies for subject no. 7 were also taken on*

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21/01-05). Material from only seven subjects was therefore used in the preparation of articles 6 and 7.

*Fourteen subjects feature in article 10. These 14 subjects are made up of the seven from articles 6 and 7 plus another seven who had biopsies taken on 17 February, 20 February and 3 March 2006, as shown by the patient records, copies of which were sent to DCSD by [the two co-authors].”*

The Defendant and the two co-authors confirmed this understanding in letters dated 9 and 10 February 2014.

In this light, the Committee finds that there was no selection of subjects in articles 6 and 7, and so there was no serious breach of good scientific practice as a result of the lack of information on the origin of the biopsy material.

On this point, the Committee finds that, in accordance with good scientific practice, it should have been stated in article 10 that the 14 subjects in the article consist of two groups of subjects, each consisting of seven individuals, and also that there was an interval of more than a year between the experiments concerned. It is the view of the Committee that relevant information about the composition of the study population was withheld from the readers in article 10. However, the Committee does not find that this fact is of sufficient importance to the article’s findings that it can be characterised as a serious breach of good scientific practice.

In a letter dated 3 February 2014, the Committee also requested that the Defendant and the two co-authors submit any comments they might have about the apparent inconsistency between the material used in the analyses presented in article 10 and the information contained in the patient records. The wording of the letter of 3 February 2014 from the Committee was as follows:

*“After an initial review of the patient records, it would also appear that not all of the biopsies from the 14 subjects in article 10 were studied by histochemistry and PCR and for protein:*

- *For subject no. 3, the field for protein in the vastus and soleus has not been filled in*
- *For subject no. 5, a minus sign has been entered in the field for protein in the triceps and in the fields for histochemistry, PCR and protein in the soleus.*
- *For subject no. 9, the fields for histochemistry, PCR and protein in the soleus have not been filled in*
- *For subject no. 14, ‘OK’ in the field for protein in the triceps has been scored out and ‘No’ inserted instead.”*

The Defendant and the two co-authors replied that it cannot be inferred which analyses were carried out on the basis of the terms “Histo”, “PCR” and “Protein” regarding the individual muscles in the patient records. The Defendant and the two co-authors state that small biopsies were frozen in liquid nitrogen, either in the test tube labelled “PCR” or “Protein”, and then ticked off in the appropriate box in the patient record. This explains the lack of crosses, minuses or “No” in the protein field in the patient records for subjects 3, 5 and 14.



The Defendant and the two co-authors also assert that a biopsy of the soleus muscle was taken from subject 9 and analysed, and that the only biopsy not included is the one from the soleus muscle of subject 5.

The Committee notes that in section 7.10 (on article 7), the Committee has responded to the omission of data concerning the biopsy from the soleus muscle of subject 5 and finds that this omission does not constitute a serious breach of good scientific practice.

The Committee finds no basis for rejecting the above information from the Defendant and the two co-authors that (apart from the biopsy of the soleus muscle from subject 5) the biopsies/analyses are consistent with the material in article 10. As a result, the Committee does not intend to pursue this matter any further because the Committee, as mentioned previously, has already ruled on the omission of data concerning the biopsy from the soleus muscle of subject 5.

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Regarding the Complainant's assertion that the subjects in the patient records may not be the subjects used in article 10, the Committee finds no basis in the submissions received on which to conclude that the subjects in article 10 are not the same as those in the patient records.

#### **7.16.4 Concerning the use of the same biopsy material in articles 8 and 12**

The Committee finds that the same subjects recur, with identical descriptions, in articles 8 and 12.

In Article 8, there are 15 subjects with the following average values for age, height, weight and BMI (body mass index):

*Age  $24.9 \pm 4$  years, height  $180.9 \pm 1$  cm, weight  $82.0 \pm 8$  kg, BMI  $24.9 \pm 2$  kg m<sup>-2</sup>*

The 15 subjects in article 8 are divided into two groups – eight people exercising and seven resting – and the article states that there is no difference between the two groups with respect to age, weight, height and BMI.

In article 12, there are 8 subjects with the following average values for age, height, weight and BMI (body mass index):

*Age  $25 \pm 4$  years, weight  $82.0 \pm 8$  kg, height  $181 \pm 1$  cm, BMI  $25 \pm 2$  kg m<sup>-2</sup>*

The eight individuals referred to in article 12 are all exercising.

In the light of the above, and of the Defendant's information that the authors included a previous experiment in the article due to lack of material, the Committee finds that the eight individuals in article 12 are the eight exercising individuals from article 8, because the descriptions of the groups in the two articles are identical, except that the values for age, height and BMI in article 12 appear to be rounded values of those occurring in article 8, and because the number of exercising subjects is the same in the two articles.





The Committee notes that article 12 does not contain information about the origin of the material, including the fact that the biopsy material has been used in a previous article.

The Committee notes that the eight exercising subjects in article 8 were subject to a research protocol in which they cycled for three hours and then rested for six hours.

The Committee further notes that the original methodology description (i.e. before the erratum was published) in article 12 stated that the eight exercising subjects in the article were subject to a research protocol in which they cycled for two hours (120 minutes), followed by six hours of rest. The erratum does not stipulate directly which protocol the eight exercising subjects followed, because they are listed as being included due to a lack of material. However, nowhere in the article or erratum is it stated that these eight people were subject to a different protocol than the one described in the erratum for the ten exercising subjects, which is the same protocol as the one mentioned in the original methodology description. Against this background, the reader of the article would think that the eight exercising subjects followed the same protocol as the ten subjects.

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In light of this, the Committee finds that essential information regarding the subjects has been withheld from the readers of article 12, by omitting from the article the fact that the eight exercising subjects stem from material in a previously published article, and that it is therefore not clear from the article that these eight individuals were subject to a different protocol than the one described in the article's methodology section. The Committee finds that its assessment is not altered by the Defendant's comment that it had no impact on the article's findings whether the subjects cycled for two hours or three, partly because other articles show the importance of training duration for protein expression. What matters is that the readers were not informed that there were differences in the experimental protocols for the two groups of subjects, and therefore did not have the opportunity to evaluate the significance of this in relation to the article's findings. On this point, the Committee notes that it is highly important for scientific work that the conditions under which experiments are conducted are described correctly and accurately. In this light, the Committee finds that it constitutes a serious breach of good scientific practice, as the reader of the article is misled into thinking that the eight people in the article followed the same protocol as the other exercising subjects referred to in the article.

The Committee finds that no new information has arisen during the consultation on the draft ruling of 9 May 2014 on the reopened case that would give rise to the Committee changing the findings above about the use of the same biopsy material in articles 8 and 12.

The Committee has the following additional comments about this point:

- The Committee believes that the serious breach of good scientific practice consists of the failure to inform the readers about the origin of the biopsy material in article 12, which leads to the fact that information is withheld from them that there was a difference in the experimental protocol for the two groups of subjects in the article. The Committee finds no reason to al-





ter its view on the basis of the information submitted by the Defendant about a potential erratum to the one already published.

#### **7.16.5 Overall assessment on the use of the same biopsy material in multiple articles**

In summary, the Committee finds that the lack of information about the origin of the test material in articles 3, 4, 5 and 12 reflects serious breaches of good scientific practice (see sections 7.16.1, 7.16.2 and 7.16.4).

The Defendant contends that it is not standard practice to refer to previous studies that use the same biopsy material in the type of instances covered by this case. With reference to this point, the Defendant states that the authors of each article have provided a detailed description of the design and methodology, which, in the Defendant's view, was sufficient.

In this light, the Committee has based its ruling on the fact that in articles 3, 4 and 5, the Defendant has deliberately failed to disclose the origin of the test material, including the fact that the biopsy material stems from previous studies and has been used in other publications. The Committee therefore finds that the Defendant acted with intent in this instance. The Committee notes that in comments to the DCSD letter of 3 February 2014 concerning the reopening of the case, the Defendant states that the practice adopted in the articles was chosen deliberately.

The Committee notes that the Defendant is listed as co-director of article 12. Information supplied by the Defendant during the case also shows that the Defendant was involved in the selection of biopsy material for article 12. This is also reflected in the fact that, due to a lack of material, the article incorporated material that had previously been used in a publication for which the Defendant was the last author (article 8), and that the Defendant had significant insight into the study that formed the basis for the article concerned.

In light of this, the Committee finds that the Defendant had a responsibility to ensure that article 12 gave a fair description of the subjects involved, including information that the individuals used due to a lack of material were not subject to the research protocol described in article 12.

The Committee therefore finds that the Defendant did act in a grossly negligent manner, as the Defendant on reading article 12 should have reacted to the lack of information if the Defendant had exercised due diligence in the preparation and editing of the article, which is only to be expected given the role the Defendant played in the production of the article.

In this light, the Committee finds that the Defendant acted in a scientifically dishonest manner in the preparation and reporting of articles 3, 4, 5 and 12.

Pursuant to the DCSD Order, section 15 (2), the Committee's ruling must include an opinion on the degree of scientific dishonesty ascertained and its importance to the scientific message in the product concerned. The Committee finds that the instance of scientific dishonesty in articles 3, 4, 5 and 12 is of a serious nature and had a significant impact on the articles' message, because the lack of information



about the origins of the material means that the readers were not given the necessary information with which to assess the articles' conclusions.

The Committee finds that no new information has arisen from the parties' comments on the draft ruling of 9 May 2014 on the reopened case that would give rise to the Committee changing the above ruling regarding the use of the same biopsy material in multiple articles.

The Committee has the following additional comments about this point:

- Regarding article 12, the Committee finds that it cannot be considered intentional but only grossly negligent that the Defendant did not react to the lack of information in the article, and in doing so withheld significant information from the readers.
- The Defendant refers to a previous ruling by the Committee (18 December 2013), in which the Committee found that the Defendant had not acted in a scientifically dishonest manner despite omitting information from the description of the methodology in article 12. In the case concerned, the Committee found that the Defendant had not acted grossly negligent, referring to the Defendant's explanation that the lack of information was due to a mistake made during the editing process. The Committee notes that the Complainant in the case concerned had not complained about the reuse of test material. In this case, however, the Committee is of the opinion that it must be considered grossly negligent that the Defendant did not react to the fact that the lack of any reference to the origin of the biopsy material means that the reader is not informed that different protocols were applied to the two groups of subjects. In this context, the Committee placed particular emphasis on the Defendant's knowledge of both groups of subjects, which means that the omission cannot have been due to a similar mistake in the editing process.

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### **7.17 Reused and/or manipulated images**

The Complainant asserts that the same figures are used as illustrations for different things in articles 1, 3, 4 and 5 – i.e. Figure 1H in article 1, Figures 2A and 2G in article 3, Figures 3D and 3F in article 4 and Figure 3D in article 5.

In a separate ruling concerning this criticism (see Ruling of 18 December 2013), the Committee found that figures are reused in articles 1, 3, 4 and 5 such that the same figure is used to illustrate different things in them, and that attempts have been made to conceal the reuse by manipulating images, which corresponds to “undisclosed construction of data or substitution with fictitious data”, pursuant to the DCSD Order, section 2 (1).

With reference to this separate ruling, the Committee finds that the reuse of figures in articles 1, 3, 4 and 5 constitutes a serious breach of good scientific practice.

The Defendant contends that Co-author 1 conducted the IHC study associated with the figures in articles 1, 3, 4 and 5, and that the Defendant submitted these articles to the DCSD because the Defendant was aware that something might be wrong with them.



The Committee notes that the Defendant is listed as the last author of articles 1, 3, 4 and 5. With reference to section 7.3, the Committee finds that, as the leading author of articles 1, 3, 4 and 5, the Defendant had a particular responsibility for the entire content of each article, including reading the final manuscript carefully prior to submission to a journal.

Against this background, the Committee finds that the Defendant has a particular responsibility for the overall content of the articles.

The Committee finds that the close reading expected of a lead author would not have made it immediately clear to the Defendant that the images in articles 1, 3, 4 and 5 had been used in a previous article. In reaching this conclusion, the Committee emphasised that the images have been manipulated (rotated, colours and contrast changed, etc.).

The Committee finds, however, that a separate evaluation must be conducted of the individual image material in each article in order to determine whether the Defendant should have been able to notice the manipulation on reading the individual articles.

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#### **7.17.1 The images in article 1**

The Committee notes that Figure 1 in the article shows eight sections from biopsies of striated muscle, supposedly stained for IL-6 by IHC (see the reproduction of the figure from the article below).

Figure 1 from article 1:

Figure 1 from [ARTICLE 1]

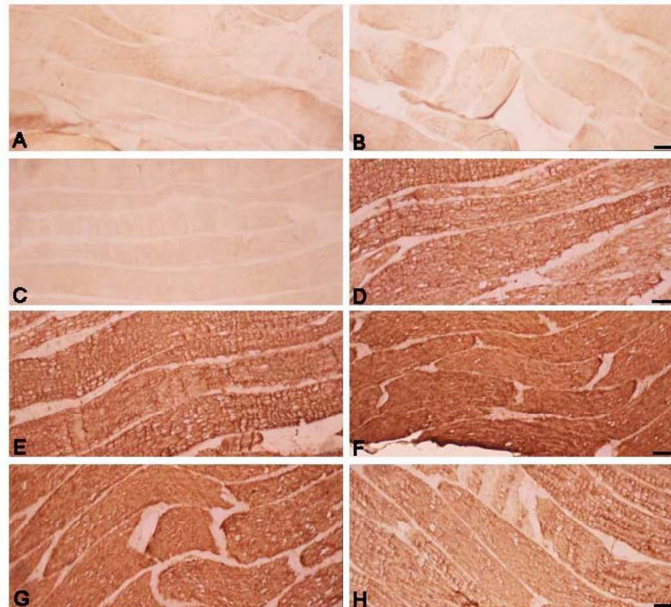
## IL-6 immunostainings of human muscle biopsies

A+B: Resting  
subjects

C-H:

Time points  
0; 3h, 4.5h;  
6h; 9h and 24h

3 h of bicycling  
(0-3h)



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With the caption

**“Figure 1.** IL-6 expression in skeletal muscle tissue of resting subjects (A–C) and exercising subjects (D–H). A, B) Resting subjects at 1/2 h (A) and 6 h (B) show no significant IL-6 immunostaining. C) Before exercise began, IL-6 expression was generally absent in the muscle tissue. D) By 3 h, when the exercise had just ended, the muscle tissue showed significantly increased IL-6 immunoreactivity. E–G) By 4.5 (E), 6 (F), and 9 h (G), the IL-6 expression was still significantly increased relative to that of resting muscle tissue. H) By 24 h, the IL-6 levels had decreased but was still clearly higher than those of resting muscle tissue. Scale bars: A–H) 50 µm.”

The Committee notes that the staining of the sections essentially appears to consist of structural representations, without the characteristics that normally form the basis for specific staining of a given antigen. The Committee also finds that the staining of the figure in sections A–C appears weaker than in D–H, where it is uniformly darker.

The Committee notes that section A is said to show IL-6 expression in resting subjects after half an hour, while section B shows IL-6 expression in resting individuals after six hours.

After a detailed analysis of the structure of the sections, the Committee finds that sections A and B represent two halves of a picture in which one half has been rotated 180 degrees in relation to the other. In this light, the Committee finds that the sections cannot, as specified, stem from biopsies corresponding to different points in time.



The Committee notes that sections C–H allegedly show sections of biopsies corresponding to different points in time.

After closer analysis of the structures in the individual sections, the Committee finds that sections E and D must stem from the same section, as the structures in the upper edge of section E are a continuation of the structures in the upper edge of D (section E is rotated 180 degrees relative to sample D). Similarly, the Committee also finds that sections G and F must stem from the same section, as the structures in the upper edge of sample G are a continuation of the structures in the upper edge of section F (section G is rotated 180 degrees relative to section F). The Committee finds that this means that the sections cannot, as specified, stem from biopsies corresponding to different points in time.

The Committee is of the view that identifying the structural convergence of the sections would require a certain degree of attention. The Committee finds that the Defendant, who was lead author of the article and therefore had a particular responsibility for the project, should have noticed the colour reaction and the description of it in the caption, as well as the structural similarities. In the view of the Committee, the Defendant ought, therefore, to have subjected the sections concerned to further examination under the microscope, which would have revealed the true nature of the images.

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However, the Committee finds that the Defendant did not act in a manner that can be considered gross negligence because the manipulated images in the article concerned were rotated 180°, which obscures the manipulation. Although the Defendant, as lead author of the article, should have noticed and responded to the manipulated images, this cannot be characterised as gross negligence because it is not sufficiently obvious that the images have been manipulated.

In the light of the above, the Committee concludes that the Defendant did not act in a scientifically dishonest manner in relation to the image manipulation in this article.

The Committee finds that no new information has arisen during the consultation on the draft ruling of 9 May 2014 on the reopened case that would give rise to the Committee changing the above assessment of article 1.

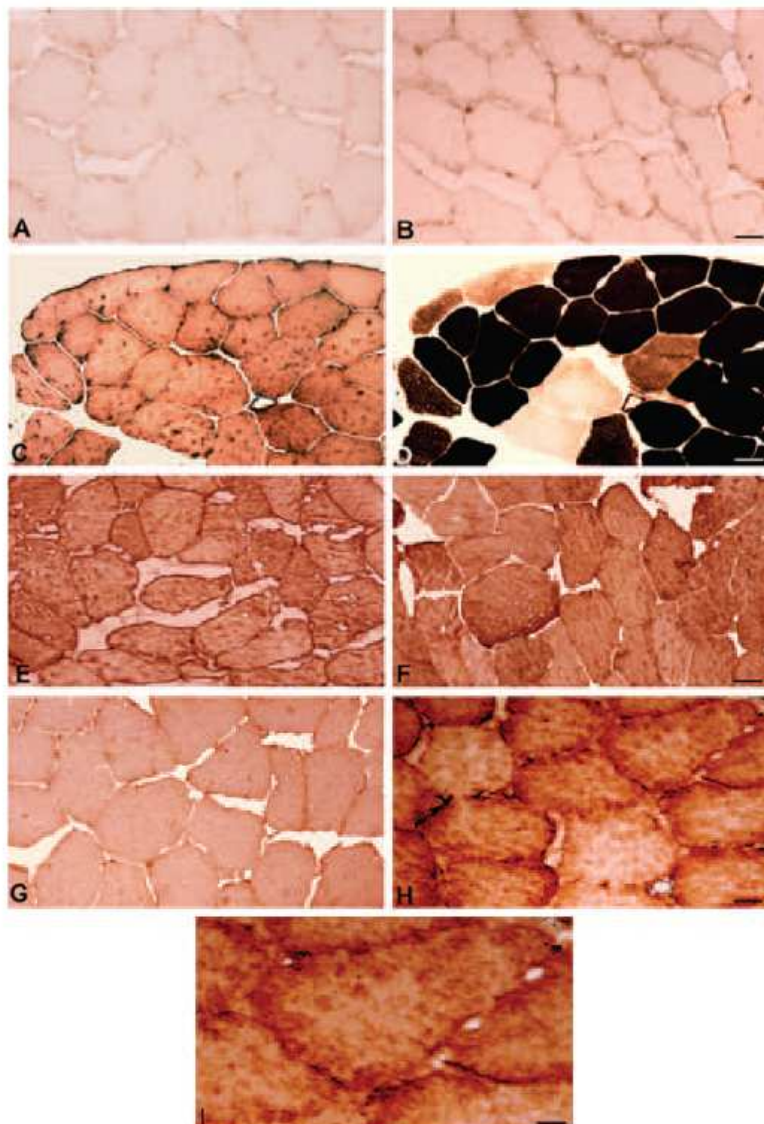
### **7.17.2 The images in article 3**

The Committee notes that Figure 2 in the article shows nine sections from biopsies of striated muscle, allegedly stained for IL-8 by IHC. Sections A, B, C, D, E, F and G supposedly stem from the points in time 0, 3, 4, 5, 6, 9 and 24 hours after exercise (see the reproduction of the figure from the article).

Figure 2 from article 3:

Figure 2 from [ARTICLE 3]





With the caption:

**“Figure 2. IL-8 Immunohistochemical expression in skeletal muscle tissue before and after 3 h of bicycle exercise**

A, before the exercise began IL-8 expression was almost absent in the muscle tissue. B, by 3 h, when the exercise had just ended, the muscle tissue showed a comparable IL-8 expression relative to the level seen before exercise. C, by 4.5 h after exercise, the IL-8 expression was significantly increased in the skeletal muscle tissue, which showed a high level of IL-8 both in general in the cytoplasm and related to the cell membranes, as well as in vessels in the muscle. D, ATPase-stained section. This is the neighbouring section to that seen in C. By comparing C and D it is seen that both muscle fibre types express IL-8 after exercise. E and F, IL-8 expression was still very high, and peaked at 6 (E) and 9 h (F) following the bicycle exercise. G, after 24h, the levels of IL-8 protein had decreased again, and the staining appeared homogeneous and mildly increased in the fibres. H and I, higher magnification of skeletal muscle tissue at 9 h following exercise. As shown,



*IL-8 protein is mainly expressed in the cytoplasm, and it is also expressed in the membranes, including the nuclei. We also detected intermittently vascular IL-8 expression in the vessel endothelium of the muscle tissue. Scale bars; A-G, 50  $\mu$ m; H, 29  $\mu$ m; I, 14  $\mu$ m.”*

After comparing sections A (before exercise) and G (24 hours after exercise), the Committee notes that there is pronounced overlapping of structural elements. In the Committee's view, this implies that the two sections must stem from the same sample. The Committee therefore considers that the sections cannot represent different points in time, as stated in the article.

The Committee is of the view that the structural convergence requires a certain degree of attention in order for it to be identified. The Committee finds, however, that the Defendant, who was lead author of the article and therefore had a particular responsibility for the project, should have noticed the structural similarities. In the view of the Committee, the Defendant ought, therefore, to have subjected the sections concerned to further examination under the microscope, which would have revealed the true nature of the images.

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However, the Committee finds that the Defendant did not act in a manner that can be considered gross negligence because the manipulated images in the article concerned were moved slightly and their colour tones were altered, which obscures the manipulation. Although the Defendant, as lead author of the article, should have noticed and responded to the manipulated images, this cannot be characterised as gross negligence because it is not sufficiently obvious that the images have been manipulated.

In the light of the above, the Committee concludes that the Defendant did not act in a scientifically dishonest manner in relation to the image manipulation in this article.

The Committee finds that no new information has arisen during the consultation on the draft ruling of 9 May 2014 on the reopened case that would give rise to the Committee changing the above assessment of article 3.

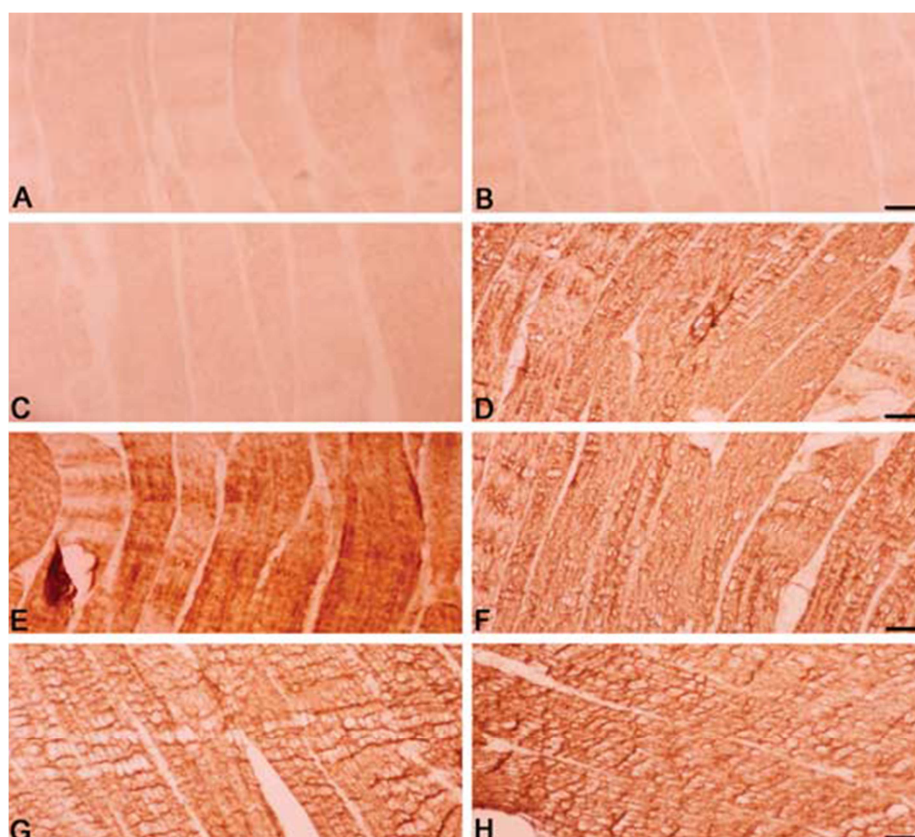
### **7.17.3 The images in article 4**

The Committee notes that Figure 3 shows a sample of striated muscle, allegedly stained by IHC for the oxidative stress marker NITT, corresponding to different points in time after exercise, as shown in the following reproduction.

Figure 3 from article 4:

Figure 3 from [ARTICLE 4]





With the caption:

**“Figure 3. Immunoreactivity for oxidative stress marker NITT in muscle tissue of resting (A and B) and exercising (C–H) subjects**

*A and B, resting subjects at 0 h (A) and 6 h (B) show no signs of oxidative stress as NITT staining is absent. C, before exercise began, NITT immunoreactivity was generally absent in skeletal muscles. D, by 3 h when the exercise had just ended, the muscle tissue showed notably increased NITT immunostaining. E, by 4.5 h the NITT immunoreactivity peaked. F–H, by 6 h (F), 9 h (G), and 24 h (H), NITT levels in skeletal muscle decreased relative to those seen by 4.5 h. However, the NITT staining was still clearly increased when compared with resting muscle. Scale bars, 50  $\mu$ m.”*

Sections D and F represent the muscles three and six hours after exercise. Upon closer inspection of the two sections, the Committee finds that tissue structures on the bottom edge of D continue at the top of F, which suggests that the two sections are from the same tissue and thus cannot represent muscles corresponding to different points in time, as stated in the article. The Committee also finds that sections A, B and C are part of the same image and thus cannot represent muscles corresponding to different points in time, as stated in the article.

The Committee is of the view that the structural convergence requires a certain degree of attention in order for it to be identified. The Committee finds, however, that the Defendant, who was lead author of the article and therefore had particular responsibility for the project, should have noticed the structural similarities. In the view of the Committee, the Defendant ought, therefore, to have subjected the sec-



tions concerned to further examination under the microscope, which would have revealed the true nature of the images.

In light of this, the Committee finds that the Defendant should have noticed and responded to the image manipulation by reviewing the article. On this point, the Committee notes in particular that figures 3D and 3F in article 4 clearly come across as a single section divided in two (taken from article 1), and that figures 3A, B and C in article 4 have exactly the same colour tone and display identical structures. The Committee is of the view that the Defendant did not exercise the due care required of a lead author in terms of reading and editing final manuscripts prior to submission to journals.

The Committee therefore finds that the Defendant acted in a grossly negligent manner. In its deliberations, the Committee emphasises that, as lead author of the article, the Defendant had particular responsibility and that the figure quite clearly appears to be manipulated as described above.

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In the light of the above, the Committee concludes that the Defendant acted in a scientifically dishonest manner during the production and reporting of this article.

Pursuant to the DCSD Order, section 15 (2), the Committee's ruling must include an opinion on the degree of scientific dishonesty ascertained and its importance to the scientific message in the product concerned. The Committee finds that the instance of scientific dishonesty in article 4 is of a serious nature and had a significant impact on the article's message, because the manipulated figure is crucial to the article's results, which are therefore misleading as a result of the manipulation.

The Committee finds that no new information has arisen during the consultation on the draft ruling of 9 May 2014 on the reopened case that would give rise to the Committee changing the above assessment of article 4.

The Committee has the following additional comments about this point:

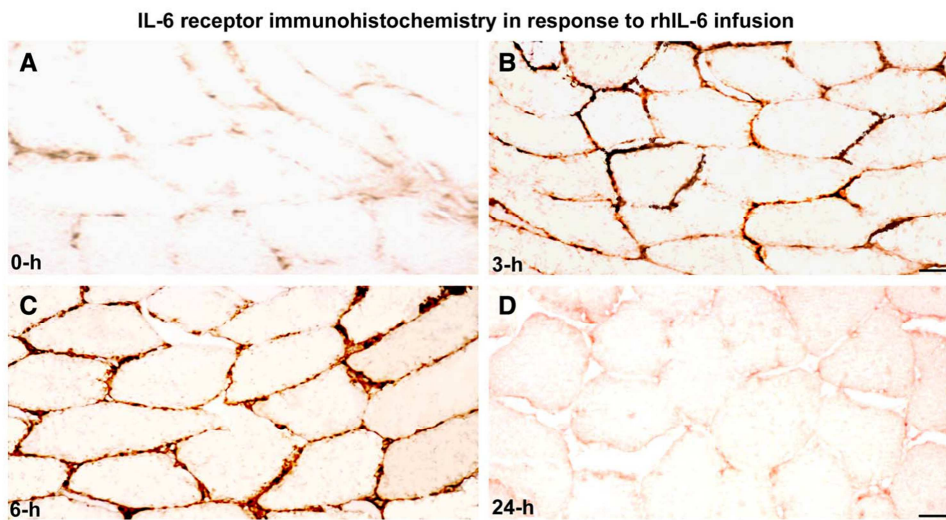
- The Committee finds that the Defendant submitted a scientific product containing a serious breach of good scientific practice in the form of image manipulation and that this serious violation of good scientific practice was committed by gross negligence on the part of the Defendant, who was the lead author on the article concerned.

#### **7.17.4 The images in article 5**

The Committee notes that Figure 3 in the article shows six sections from biopsies of striated muscle, allegedly stained for IL-6- receptor by IHC. Sections A, B, C and D allegedly stem from the points in time 0, 3, 6 and 24 hours after exercise, as shown in the reproduction below.

Figure 3 from article 5:

Figure 3 from [ARTICLE 5]



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With the caption:

**“Figure 3.** *IL-6 receptor protein following rhIL-6 infusion (n=6+6). Protein staining of the IL-6 receptor increases in response to an rhIL-6 infusion with staining being located to the muscle fiber membranes. The staining is most pronounced at 3 and 6 h and has returned to prelevels at the 24-h time-point. A) 0 h; B) 3 h; C) 6 h; and D) 24 h. Scale bars (A–D): 30 μm.*”

The Committee notes that, unlike the figures in articles 1, 3 and 4, this figure appears not to have been manipulated in article 5.

In light of this, the Committee finds that the Defendant, as lead author of the article, could not have been expected to have noticed the manipulation in article 5, as this would require a comparison with Figure 2 in article 3.

The Committee therefore finds that there are no grounds on which to conclude that the Defendant acted in a grossly negligent manner in connection with the reading and editing of this article.

In the light of the above, the Committee concludes that the Defendant did not act in a scientifically dishonest manner in relation to the image manipulation in this article.

## 8 Summary

The Committee finds that the Defendant acted in a scientifically dishonest manner in the following instances:

1. The lack of information in articles 4 and 5 that the biopsy material stems from the same subjects as used in article 1 and another article authored by the Defendant, from which results are compared and incorporated into the scientific



discussion in articles 4 and 5 to support the articles' conclusions. Significant information is thus withheld from the reader about the mutual interrelationships between the results, which represents a serious breach of good scientific practice corresponding to "undisclosed distorted interpretation of own results", pursuant to the DCSD Order, section 2, no. 4. See also sections 7.16.1 and 7.16.2.

2. Lack of information in articles 3 and 5 that the biopsy material stems from previous studies with more subjects than in articles 3 and 5, which means that a selection of subjects in articles 3 and 5 is concealed from the readers. This represents a serious breach of good scientific practice, corresponding to "undisclosed selective or surreptitious discarding of own undesired results" pursuant to the DCSD Order, section 2, no. 2. See also sections 7.16.1 and 7.16.2.
3. Failure to provide information in article 12 about the fact that the eight trained subjects stem from a previous article (article 8), and were subject to a different research protocol than the one described in the article's methodology section, which constitutes a serious breach of good scientific practice, corresponding to "undisclosed construction of data", pursuant to the DCSD Order, section 2, no. 1. See also section 7.16.4.
4. Manipulation of images in article 4. The image manipulation constitutes a serious breach of good scientific practice corresponding to "undisclosed construction of data", pursuant to the DCSD Order, section 2, no. 1. See also section 7.17.3.

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With reference to the failure in connection with point 1 to provide information about the origins of the test material in articles 1 and 4, the Committee finds that the Defendant acted intentionally, as the Defendant has stated that the Defendant is of the view that there is no requirement to explicitly state such information in an article. The Committee therefore bases its ruling on the fact that the Defendant intentionally failed to disclose the origin of the test material. The Committee notes that in comments to the Committee's letter of 3 February 2014 concerning the reopening of the case, the Defendant states that the practice adopted in the articles concerned was chosen deliberately.

With reference to the failure in connection with point 2 to provide information about the origins of the test material in articles 3 and 5, the Committee also finds that the Defendant acted intentionally, as the Defendant has stated that the Defendant is of the view that there is no requirement to explicitly state such information in an article, and the Defendant, in response to the Committee's letter of 3 February 2014 about the reopening of the case, has also stated that the practice was a deliberate choice.

With reference to the lack of information in connection with point 3 about the origin of the eight subjects in article 12, and the fact that they were therefore subject to a different research protocol than the one described in the article's methodology section, the Committee finds that the Defendant acted in a grossly negligent manner, as the Defendant was the co-director of the article and had specific knowledge of the subjects concerned, who were also included in the study referred to in article 8. The defendant ought, therefore, to have read the article and reacted



to the lack of information if the Defendant had exercised due diligence in the preparation and editing of the article, which is to be expected given the role the Defendant played in the production of the article.

With reference to point 4 and the manipulation of images in article 4, the Committee finds that the Defendant acted in a grossly negligent manner, because, as lead author of this article, the Defendant should have noticed and responded to the obvious manipulation.

In summary, the Committee finds that the Defendant acted in a scientifically dishonest manner during participation in the work concerning articles 3, 4, 5 and 12 pursuant to the DCSD Order, section 2.

## **9 Appeals procedure**

This decision cannot be appealed to any other administrative authority, cf. section 34 of act no. 365 of 10 April 2014 on research consulting, etc.

Yours sincerely,

Henrik Gunst Andersen  
Chairperson  
Danish Committees on Scientific Dishonesty:

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Secretariat of the DCSD