Study Number	176500	Report Amendment Number	1

AMENDMENT TO STUDY REPORT

SYSTEMS TOXICOLOGICAL EVALUATION OF THS2.2 MENTHOL 90 DAY INHALATION STUDY OECD 413 – OECD PLUS PHASE (STUDY NUMBER 176500)

Study Director	Ulrike Kogel
Completion Date	19 April 2016

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Current Text Version			
Concerning	**8.2.2 Network Perturbation Amplitude** and **8.2.3 Biological Impact Factor**	Page	45, 46 and 47

Page 45: sign in formula

$$NPA = \frac{1}{|E|} \sum_{e\ in\ E} (f(e_0) - \sigma(e) f(e_1))^2$$

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Page 46: reference Martin 2012 The methodology Biological Impact Factor (BIF) (Martin 2014, Martin 2012) provides a unified and coherent framework for investigating mechanistic effects at each level of granularity of the biological processes represented in the network models.

Page 47: reference Hoeng 2014

Using the notation above, a "perfect" network response (differential node values) is both maximizing the $f_T Q f$ with $||f||_2 = 1$ and minimizing the $f_T L_3 f$ (the NPA criteria (Hoeng 2014)).

Page 47: SDP in formular

$$\frac{\frac{1}{|\mathcal{F}|} \sum_{\mathcal{N}_i^* \in \mathcal{F}} \frac{1}{NPA_{max}(\mathcal{N}_i)} \sum_{e \in E(\mathcal{N}_i)} \frac{1}{o(e)} (f(e_0) + \sigma(e) f(e_1))^2}{BIF_{SDP}}$$

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New Text Version

Page 45: sign in formula changed

$$NPA = \frac{1}{|E|}\sum_{e \in E}(f(e_0) + \sigma(e)f(e_1))^2$$

Page 46: reference Martin 2012 changed to Hoeng 2014

The methodology Biological Impact Factor (BIF) (**Hoeng 2014**, Martin 2014) provides a unified and coherent framework for investigating mechanistic effects at each level of granularity of the biological processes represented in the network models.

Page 47: reference Hoeng 2014 replaced by Martin 2014

Using the notation above, a "perfect" network response (differential node values) is both maximizing the f^TQf with $||f||_2 = 1$ and minimizing the f^TL_3f (the NPA criteria (**Martin 2014**)).

Page 47: SDP deleted

$$\frac{\frac{1}{|F|}\sum_{N_i \in F}\frac{1}{NPA_{max}(N_i)}\sum_{e \in E(N_i)}\frac{1}{\sigma(e)}(f(e_0) + \sigma(e)f(e_1))^2}{BIF}$$

Reason for Change

Page 45: minus sign in formula is wrong and must be plus sign
Page 46: reference Martin 2012 does not describe the methodology Biological Impact Factor (BIF)
Page 47: for the NPA criteria Martin 2014 should have been cited.
Page 47: SDP (Selventa Development Platform) does not belong to that context.

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Approval	Name	Date and Signature
Study Director	Ulrike Kogel	06. July 2016 U. Kogel
Program Management	Julia Hoeng	06 July 2016 Julia Hoeng
Management of Test Site	Nikolai Ivanov	07-Jul-2016
Supervision Tissue Research	Keyur Trivedi	14th JULY 2016 K.A. Trivedi
Supervision Gene expression	Emmanuel Guedj	12 JUL 2016 Emmanuel Guedj
Supervision Proteomics	Ashraf Elamin	14 Jul 2016 Ashf