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AMENDMENT TO STUDY REPORT

SYSTEMS TOXICOLOGICAL STUDY REPORT SYSTEMS TOXICOLOGICAL EVALUATION OF THS2.2 90 DAY INHALATION STUDY OECD 413 – OECD PLUS PHASE (STUDY NUMBER 150082/150083)

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	31, 32 and 33

Page 31: 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 31: 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 32: 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 33: 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 31: sign in formula changed

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

Page 31: 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 32: 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 33: SDP deleted

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

Reason for Change

Page 31: minus sign in formula is wrong and must be plus sign
Page 31: reference Martin 2012 does not describe the methodology Biological Impact Factor (BIF)
Page 32: for the NPA criteria Martin 2014 should have been cited.
Page 33: SDP (Selventa Development Platform) does not belong to that context.

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Approval	Name	Date and Signature
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