



## SCIENTIFIC COMMITTEE

### MINUTES OF THE 4<sup>th</sup> MEETING OF THE CROSS-CUTTING WORKING GROUP ON BENCHMARK DOSE

**Held on 14 December 2020 via web conference**

**(Agreed on 31 December 2021)**

#### Participants

■ Working Group Members:

Marc Aerts  
Diane Benford  
Lutz Edler  
Thorhallur Halldorsson  
Wim Mennes  
Salomon Sand  
Josef Schlatter (Chair)

■ EFSA:

SCER Unit: Bernard Bottex  
AMU Unit: Jose Cortiñas Abrahantes  
CONTAM Unit: Marco Binaglia

#### 1. Welcome and apologies for absence

The Chair welcomed the participants and informed them about the resignation of Dr. Wout Slob from the working group because of retirement.

#### 2. Adoption of agenda

The agenda was adopted without changes.



### 3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence<sup>1</sup> and the Decision of the Executive Director on Competing Interest Management<sup>2</sup>, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

### 4. Scientific topic(s) for discussion

#### 4.1. Update of the SC guidance on the use of the benchmark dose approach in risk assessment<sup>3</sup>.

##### 4.1.1. Update on the situation

Participants were informed about developments that took place since the last working group meeting (19&20 May 2020). The update of the guidance and the implementation of Bayesian model averaging in the EFSA Platform for BMD analysis have been put on hold because of a disagreement between EFSA and RIVM on two main issues:

- EFSA's request to consider both normal and log-normal distribution assumptions without prior constraints on the model parameters as default, while RIVM wants to use only the log-normal distribution assumption
- EFSA wants to use a model framework with as many models as possible for the purpose of model averaging, while RIVM wants a model framework with only analogous models.

A meeting was organised on 18 November 2020 between EFSA, RIVM, Hasselt University, the US EPA and the main Rapporteur of the updated Chapter 5 of WHO-IPCS Environmental Health Criteria 240 (EH.C240) to try and find a solution but turned out unsuccessful. Following this meeting, EFSA and RIVM decided to stop their collaboration for the implementation of Bayesian model averaging.

The working group was finally informed that the update of the guidance on the use of BMD in risk assessment is now 6-months behind schedule.

##### 4.1.1. Update of the guidance

Participants were reminded that the mandate given to the working group is to update rapidly the 2017 guidance document in order to align it with the updated chapter 5 of EHC 240.

The working group went through the various sections of the document, identified those to be updated and distributed the tasks among the working group members.

<sup>1</sup> [http://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/policy\\_independence.pdf](http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf)

<sup>2</sup> [http://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/competing\\_interest\\_management\\_17.pdf](http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf)

<sup>3</sup> <http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2020-00137>



## 5. Next meeting(s)

- 24 February 2021, from 10.00 to 13.00 and from 14.00 to 17.00; webconference
- 26 May 2021, from 10.00 to 13.00 and from 14.00 to 17.00; webconference

Two physical meetings (1.5 days, Parma) will be organised in the second part of the year, one around September, the other one around November. A Doodle poll will be sent by the Secretariat to identify availability.



## SCIENTIFIC COMMITTEE

### MINUTES OF THE 3<sup>rd</sup> MEETING OF THE CROSS-CUTTING WORKING GROUP ON BENCHMARK DOSE

**Held on 19 and 20 March 2020 via web conference**

**(Agreed on 3 June 2020)**

This meeting, originally scheduled as a physical meeting, was converted into a teleconference to avoid traveling to EFSA in line with the measures established to reduce the risk of coronavirus infection.

#### Participants

■ Working Group Members:

Marc Aerts  
Diane Benford  
Lutz Edler  
Thorhallur Halldorsson  
Wim Mennes  
Salomon Sand  
Josef Schlatter (Chair)  
Wout Slob

■ EFSA:

SCER Unit: Bernard Bottex  
AMU Unit: Jose Cortiñas Abrahantes  
CONTAM Unit: Marco Binaglia

#### 1. Welcome and apologies for absence

The Secretariat welcomed the participants. It was reminded that the mandate of this working group is to align the SC guidance on the use of the benchmark dose approach in risk assessment with the updated chapter 5 of WHO IPCS EHC 240 and to harmonise as far as possible the EFSA approach for BMD analysis with the approach(es) used by EFSA Partners. This includes:

- Introduction of the assumption that data can be normally distributed

- Further guidance on biologically-based BMR selection
- Harmonisation of the models to be fitted to the data
- Bayesian model averaging as the preferred approach
- Further guidance on how to deal with “difficult” datasets not providing a suitable BMDL BMD confidence interval.

## 2. Adoption of agenda

The agenda was adopted without changes.

## 3. Declarations of Interest of Working Groups members

In accordance with EFSA’s Policy on Independence<sup>1</sup> and the Decision of the Executive Director on Competing Interest Management<sup>2</sup>, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

## 4. Scientific topic(s) for discussion

### 4.1. Update of the SC guidance on the use of the benchmark dose approach in risk assessment<sup>3</sup>.

In order to harmonise with Chapter 5 of WHO IPCS EHC240 and with the guidance of the US EPA, possibility will be given to assume a normal distribution, in addition to the log-normal distribution recommended in the current guidance document for continuous endpoints, although there was no full consensus in the WG on the desirability of that option. Under the assumption of a log-normal distribution of the endpoint, the dose-response model  $DRM(x)$  will be defined as  $DRM(x) = e^{\mu(x)}$ , while under the assumption of a normal distribution of the endpoint, the dose-response model will be defined as  $DRM(x) = \mu(x)$ . The consequences of introducing the normal-distribution assumption, e.g. on the way the parameters of the models can be interpreted from a toxicological point of view, are still to be clarified and agreed by the working group.

The working group also agreed on the BMR being defined as a percent change “ $q$ ”, which could be derived for a fixed response threshold or in relation to the maximum response expected for that endpoint.

The working group also reviewed the progress re. the definition and testing of a unified set of models that can be used indifferently whether the data are continuous or quantal.

## 5. Next steps and timeframe

The working group identified the following issues to be clarified / sections to be updated in the guidance document:

<sup>1</sup> [http://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/policy\\_independence.pdf](http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf)

<sup>2</sup> [http://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/competing\\_interest\\_management\\_17.pdf](http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf)

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- **Use of the BMD approach for epidemiological data:** The SC guidance on BMD will clearly state that the principles outlined in this document are applicable to epidemiological data but the document's scope is the modelling of experimental animal data. Important considerations for epi data will be addressed later.
- **NOAEL vs. BMD:** The possibility to shorten the current section in the main text will be explored and discussed at the next working group meeting. The usefulness of the current text for training purpose was acknowledged.
- **Exposed controls:** Following the specific question received from the CONTAM Panel in relation to the assessment of PFAS (see minutes 1<sup>st</sup> meeting of the cross-cutting working group on BMD), the working group identified the need to clarify better in the guidance how to deal with datasets with no zero exposure (background response estimated by extrapolation).
- **Excluding datapoints from the BMD analysis:** the guidance will describe and explain clearly if/when data points can be excluded from a dataset when doing a BMD analysis.
- **Risk characterisation / BMD confidence interval:** further guidance will be provided on how to deal with datasets leading to BMDLs and/or BMD confidence intervals not suitable for Risk Manager's needs (i.e. BMDL too low or BMD confidence interval too large).
- **Potency comparison:** the current section will be further expanded, including discussion on differences in sensitivity
- **Ordinal data:** The current guidance is focussing on continuous and quantal data. Further details will be added regarding the BMD analysis of ordinal data.
- **Specification of BMR:** The section will be redrafted, following the decision tree of the updated chapter 5 of WHO IPCS EHC 240, i.e. start with Tier 1 (use of internationally agreed BMRs (percent change), which should be biologically based), then Tier 2 (expert decision on the BMR to be used). The statistics-based tools available to suggest possible values for q (1 SD, hybrid approach, ES-theory, etc.) will be briefly introduced.
- **Model formulation:** Easy-to-read sections describing the unified set of models and introducing Bayesian model averaging as the preferred approach for BMD analysis will be drafted.

## 6. Next meeting(s)

- 1 & 2 September 2020, starting at 10.00 on the 1<sup>st</sup> and finishing at 12.30 on the 2<sup>nd</sup>; webconference
- 17 & 18 November 2020, starting at 10.00 on the 17<sup>th</sup> and finishing at 12.30 on the 18<sup>th</sup>; webconference



## SCIENTIFIC COMMITTEE

### MINUTES OF THE 2<sup>nd</sup> MEETING OF THE CROSS-CUTTING WORKING GROUP ON BENCHMARK DOSE

**Held on 12<sup>th</sup> March 2020 via web conference**

**(Agreed on 25 March 2020)**

#### Participants

■ Working Group Members:

Marc Aerts  
Lutz Edler  
Thorhallur Halldorsson  
Wim Mennes  
Salomon Sand  
Josef Schlatter  
Wout Slob

■ EFSA:

SCER Unit: Bernard Bottex  
AMU Unit: Jose Cortiñas Abrahantes

#### 1. Welcome and apologies for absence

The Secretariat welcomed the participants. Apologies were received from Diane Benford.

#### 2. Adoption of agenda

The agenda was adopted without changes.

#### 3. Declarations of Interest of Working Groups members



In accordance with EFSA's Policy on Independence<sup>1</sup> and the Decision of the Executive Director on Competing Interest Management<sup>2</sup>, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

## 4. Scientific topic(s) for discussion

### 4.1. Update of the SC guidance on the use of the benchmark dose approach in risk assessment<sup>3</sup>.

The working group was updated on the developments re. dose response assessment methods since the publication of the last version of the SC guidance on BMD (January 2017). In this respect, a summary of the ongoing update of the chapter 5 of WHO/IPCS Environmental Health Criteria 240 was given. This chapter was drafted by an international group of experts with the aim to reach consensus on how to perform dose response assessment and benchmark dose modelling.

The Scientific Committee was requested to update its guidance on the use of the benchmark dose in risk assessment, so that the approach recommended to EFSA Panels and Units is in line with the WHO document.

The working group distributed the various sections of the SC Guidance among its members, with the task to start updating them for the next meeting.

## 5. Next meeting(s)

A Doodle poll will be circulated to fix the meeting dates for 2020.

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<sup>3</sup> <http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2020-00137>



# Minutes of the 1st meeting of the EFSA Cross-Cutting Working Group on Benchmark Dose

**Held on 5 and 6 September 2019 in Parma  
(Agreed on 23 September 2019)**

## **Participants**

### **Working Group Members:**

- Marc Aerts
- Diane Benford<sup>1</sup>
- Lutz Edler
- Thorhallur Halldorsson
- Wim Mennes
- Salomon Sand<sup>2</sup>
- Josef Schlatter
- Wout Slob<sup>2</sup>

## **EFSA**

- Marco Binaglia
- Bernard Bottex (Chair)
- Jose Cortiñas Abrahantes

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<sup>1</sup> Attended via webconference both days

<sup>2</sup> Attended via webconference on day 1

## **1. Welcome and apologies for absence**

The Chair welcomed the participants.

## **2. Adoption of agenda**

The agenda was adopted without changes.

## **3. Declarations of Interest of Working Groups members**

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes<sup>3</sup> and the Decision of the Executive Director on Declarations of Interest<sup>4</sup>, EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

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<sup>3</sup> <http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf>

<sup>4</sup> <http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf>

## **4. Scientific topic(s) for discussion**

The EFSA Cross-Cutting Working Group on Benchmark Dose has received a request for assistance from the Chair of the CONTAM Panel in relation to the ongoing assessment of polyfluoroalkyl substances (PFAs) in food. The cross-cutting working group is more specifically requested to provide advice on the following issues:

- Adequacy of using 102 points (groups of four children) instead of deciles for the modelling
- How to perform dose-response modelling in absence of control group with zero exposure. Proposal has been made by the CONTAM Panel to use dose scaling (subtracting the lowest concentration from each observation).

Three datasets have been provided: the Grandjean et al. (2012) study, looking at the association between serum concentrations of perfluorooctanesulfonic acid (PFOS) in children and reduced antibody response following vaccination; and two animal studies, Peden-Adams et al. (2008) and Dong et al. (2009), both studies showing a dose-related suppression of humoral immunity in mice exposed to PFOS.

### **4.1 Use of 102 groups of 4 children as 102 individual data points**

The working group confirmed the added value of using the 102 points instead of deciles, as the more points are available for fitting mathematical models, the less model uncertainty one will get.

Considering the fact that these 102 points are actually groups of 4 children showing similar exposure levels to PFOS, a member of the cross-cutting working group performed a small simulation (see annex) looking at the impact of ignoring the information on standard deviation within each group for linear models considering the responses to be normally distributed with constant variance. The working group indeed anticipated that the loss of information because modelling less data (102 instead of 440, i.e. broader intervals) is compensated by the grouping of 4 points in one (variability is shrunk given that the means per group is used). The simulation confirmed that, under the setting of the simulation, ignoring the information on standard deviations within each group does not substantially change the estimation of the dose-response parameters (intercept and slopes). Of course, having individual data is to be preferred in any case, as particular model assumptions (e.g. normality assumptions) cannot be checked on grouped data.

### **4.2 Modelling datasets with no zero exposure**

In order to evaluate dose-response data (e.g. by dose-response modelling as described in the SC guidance on the use of the benchmark dose

approach in risk assessment), the datasets should preferably be composed of a control group (effect measured at zero exposure) and a number of tested doses, such that the resulting Reference Point (or Point of Departure) falls within the observed dose range or is close to the applied non-zero doses.

For the three datasets provided by CONTAM, the lowest observed PFOS serum concentration levels are always greater than zero. The absence of controls with zero PFOS in serum implies that the background response is estimated by extrapolation. In most datasets, this model-dependent estimate is highly uncertain, and hence the estimated BMD is highly uncertain as well.

#### **4.2.1 Use of dose scaling**

The working group disagreed with the approach taken by the Panel, consisting in subtracting the lowest concentration from each observation. The lowest PFOS observation is study-dependent, and will be different should the same study be repeated in exactly the same conditions. As a consequence, the Reference Point and resulting Health-Based Guidance Value (HBGV) derived from this dataset will also be study-dependent.

#### **4.2.2 Proposed solution**

The working group underlined from the beginning the importance of providing a solution on the methodology to be applied, instead of a dataset-specific solution, so that the same approach can be applied consistently by the EFSA Panels and Units, should the same issue occur in the future.

Considering point 4.2.1 of these minutes, as well as the two decision trees on how to perform dose-response modelling presented in the EFSA guidance on benchmark dose and currently being developed by WHO for its updated chapter 5 on dose response assessment of WHO/IPCS EHC 240, the working group suggests the following stepwise approach for datasets without zero exposure:

- Ahead of any consideration of the data available, is it possible to identify a dose of reference (Dref), in this particular case, a level of exposure to PFOS that is not associated with any particular adverse effect? This Dref is based on prior knowledge. If such a Dref is available, it will be used as "zero dose" for the modelling. The value of the Dref for a specific endpoint is fixed until new information has been generated that justify modifying this value. As a reminder, the identification of the BMR (e.g., for the Grandjean et al. study, a percent reduction of serum antibody concentration against diphtheria and tetanus challenge considered adverse compared to the serum antibody concentration of reference) should be biology-

based and decided also before considering the dataset to be modelled.

- In the absence of a Dref for the endpoint considered, dose-response modelling using model averaging and the default set of models to be fitted to the data will be performed, considering dose zero as not observed and parameter  $a$  from the models will be estimated from information on the observed doses, without rescaling. The model uncertainty when estimating parameter  $a$  will be limited in case of datasets where the effect goes flat at the lower exposure levels, but may be considered as unacceptable if the curve has not stabilised around the lowest doses.
- In case the BMDL-BMDU confidence interval resulting from the dose response modelling using model averaging is not suitable for the assessment, one may try to get additional information on the background response (parameter  $a$ ), using prior information, historical data and/or expert knowledge elicitation in order to constrain this parameter. If the outcome of this modelling exercise (i.e. using the Bayesian framework) does not result in a useful Reference Point, the suitability of this dataset to derive a HBGV should be reconsidered.

This approach is considered the most appropriate for both human and animal data in the absence of zero exposure (control) groups; it will be reconsidered once EFSA Panels and Units have accumulated further experience.

#### **4.2.3 Additional considerations related to the Peden-Adams et al. (2008) study**

Table 2 in this paper is providing PFOS serum concentration levels for male and female mice resulting from various administered dose of PFOS. For some dose groups, the PFOS serum concentration level is missing. Question was raised whether males and female data can be modelled together or should be considered separately.

The Working Group suggests modelling the internal dose vs. the external dose in order to replace the missing internal dose values, then to perform a covariate analysis to check the assumption that the shape of the dose response for males is identical or sufficiently similar to the one for females, and that males and females PFOS serum concentrations can in that case be combined.

### **5. Next steps**

These minutes will be communicated to the CONTAM Panel as soon as agreed by the working group members so that the Panel can proceed further with its assessment of PFAS in food

In order not to lose the outcome of this discussion and make it easily accessible to EFSA Panels and Units, these concepts will be described in a more formal way in the currently under development SC guidance on appraising and integrating evidence from epidemiological studies for use in EFSA's scientific assessments. It was agreed that the section on modelling would be drafted jointly by the Cross-Cutting Working Group on Benchmark Dose and the SC Working Group on Epidemiology.

These concepts should also be inserted in the SC guidance on the use of the benchmark dose approach on risk assessment, which is planned to be updated in 2020.

## **6. Any Other Business**

The working group was informed about the upcoming update of the Chapter 5 on dose response assessment of the WHO/IPCS Environmental Health Criteria 240. A worldwide consensus on how to perform dose-response assessment was achieved, which needs now to be reflected in the SC guidance on BMD. Discussions are ongoing with the US Agencies (EPA, FDA etc.) and Health Canada to do this exercise jointly in order to ensure further harmonisation on how to perform benchmark dose analysis.

## Annex – code used for the simulation reported in section 4.1

```
ve<-0.7
ni<-4
ng<-100
set.seed(123)
g<-sort(runif(ng,0,10))
Nsim<-1000
b0<-0.7
b1<- -0.62
y<-matrix(NA,ncol=Nsim,nrow=ng*ni)
y1<-matrix(NA,ncol=Nsim,nrow=ng)

confwidth<-function(x,y){
  n <- length(y) # Find length of y to use as sample size
  lm.model <- lm(y ~ x) # Fit linear model

  # Extract fitted coefficients from model object
  b0 <- lm.model$coefficients[1]
  b1 <- lm.model$coefficients[2]

  # Find SSE and MSE
  sse <- sum((y - lm.model$fitted.values)^2)
  mse <- sse / (n - 2)

  t.val <- qt(0.975, n - 2) # Calculate critical t-value
  # Fit linear model with extracted coefficients
  x_new <- x
  y.fit <- b1 * x_new + b0

  # Find the standard error of the regression line
  se <- sqrt(sum((y - y.fit)^2) / (n - 2)) * sqrt(1 / n + (x - mean(x))^2 / sum((x - mean(x))^2))

  # width of confidence band
  width<-t.val * range(se)
  return(width)
}
```

```
resFull<-resRed<-matrix(NA,nrow=Nsim,ncol=4)

for (i in 1:Nsim) {
  for (j in 1:ng){
    set.seed(1000*i+j)
    error<-rnorm(ni,0,ve)
    y[(((j-1)*ni+1):(j*ni)),i]<-b0+b1*g[j]+error
    y1[j,i]<-mean(y[(((j-1)*ni+1):(j*ni)),i])
  }
  lmF <- lm(y[,i] ~ rep(g,each=ni))
  b0F <- lmF$coefficients[1]
  b1F <- lmF$coefficients[2]
  lmR <- lm(y1[,i] ~ g)
  b0R <- lmR$coefficients[1]
  b1R <- lmR$coefficients[2]
  resFull[i,]<-c(confwidth(rep(g,each=ni),y[,i]),b0F,b1F)
  resRed[i,]<-c(confwidth(g,y1[,i]),b0R,b1R)
}

quantile(resFull[,1],probs=c(0.05,0.5,0.95))
quantile(resRed[,1],probs=c(0.05,0.5,0.95))
quantile(resFull[,2],probs=c(0.05,0.5,0.95))
quantile(resRed[,2],probs=c(0.05,0.5,0.95))
quantile(resFull[,3],probs=c(0.05,0.5,0.95))
quantile(resRed[,3],probs=c(0.05,0.5,0.95))
quantile(resFull[,4],probs=c(0.05,0.5,0.95))
quantile(resRed[,4],probs=c(0.05,0.5,0.95))

hist(resFull[,1],breaks="FD")
hist(resRed[,1],breaks="FD")
```





## SCIENTIFIC COMMITTEE

### MINUTES OF THE 3<sup>rd</sup> MEETING OF THE CROSS-CUTTING WORKING GROUP ON BENCHMARK DOSE

**Held on 19 and 20 May 2020 via web conference**

**(Agreed on 3 June 2020)**

This meeting, originally scheduled as a physical meeting, was converted into a teleconference to avoid traveling to EFSA in line with the measures established to reduce the risk of coronavirus infection.

#### Participants

■ Working Group Members:

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Diane Benford  
Lutz Edler  
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Josef Schlatter (Chair)  
Wout Slob

■ EFSA:

SCER Unit: Bernard Bottex  
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- Introduction of the assumption that data can be normally distributed

- Further guidance on biologically-based BMR selection
- Harmonisation of the models to be fitted to the data
- Bayesian model averaging as the preferred approach
- Further guidance on how to deal with “difficult” datasets not providing a suitable BMDL BMD confidence interval.

## 2. Adoption of agenda

The agenda was adopted without changes.

## 3. Declarations of Interest of Working Groups members

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The working group also agreed on the BMR being defined as a percent change “ $q$ ”, which could be derived for a fixed response threshold or in relation to the maximum response expected for that endpoint.

The working group also reviewed the progress re. the definition and testing of a unified set of models that can be used indifferently whether the data are continuous or quantal.

## 5. Next steps and timeframe

The working group identified the following issues to be clarified / sections to be updated in the guidance document:

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- **Use of the BMD approach for epidemiological data:** The SC guidance on BMD will clearly state that the principles outlined in this document are applicable to epidemiological data but the document's scope is the modelling of experimental animal data. Important considerations for epi data will be addressed later.
- **NOAEL vs. BMD:** The possibility to shorten the current section in the main text will be explored and discussed at the next working group meeting. The usefulness of the current text for training purpose was acknowledged.
- **Exposed controls:** Following the specific question received from the CONTAM Panel in relation to the assessment of PFAS (see minutes 1<sup>st</sup> meeting of the cross-cutting working group on BMD), the working group identified the need to clarify better in the guidance how to deal with datasets with no zero exposure (background response estimated by extrapolation).
- **Excluding datapoints from the BMD analysis:** the guidance will describe and explain clearly if/when data points can be excluded from a dataset when doing a BMD analysis.
- **Risk characterisation / BMD confidence interval:** further guidance will be provided on how to deal with datasets leading to BMDLs and/or BMD confidence intervals not suitable for Risk Manager's needs (i.e. BMDL too low or BMD confidence interval too large).
- **Potency comparison:** the current section will be further expanded, including discussion on differences in sensitivity
- **Ordinal data:** The current guidance is focussing on continuous and quantal data. Further details will be added regarding the BMD analysis of ordinal data.
- **Specification of BMR:** The section will be redrafted, following the decision tree of the updated chapter 5 of WHO IPCS EHC 240, i.e. start with Tier 1 (use of internationally agreed BMRs (percent change), which should be biologically based), then Tier 2 (expert decision on the BMR to be used). The statistics-based tools available to suggest possible values for q (1 SD, hybrid approach, ES-theory, etc.) will be briefly introduced.
- **Model formulation:** Easy-to-read sections describing the unified set of models and introducing Bayesian model averaging as the preferred approach for BMD analysis will be drafted.

## 6. Next meeting(s)

- 1 & 2 September 2020, starting at 10.00 on the 1<sup>st</sup> and finishing at 12.30 on the 2<sup>nd</sup>; webconference
- 17 & 18 November 2020, starting at 10.00 on the 17<sup>th</sup> and finishing at 12.30 on the 18<sup>th</sup>; webconference



## SCIENTIFIC COMMITTEE

### MINUTES OF THE 2<sup>nd</sup> MEETING OF THE CROSS-CUTTING WORKING GROUP ON BENCHMARK DOSE

**Held on 12<sup>th</sup> March 2020 via web conference**

**(Agreed on 25 March 2020)**

#### Participants

■ Working Group Members:

Marc Aerts  
Lutz Edler  
Thorhallur Halldorsson  
Wim Mennes  
Salomon Sand  
Josef Schlatter  
Wout Slob

■ EFSA:

SCER Unit: Bernard Bottex  
AMU Unit: Jose Cortiñas Abrahantes

#### 1. Welcome and apologies for absence

The Secretariat welcomed the participants. Apologies were received from Diane Benford.

#### 2. Adoption of agenda

The agenda was adopted without changes.

#### 3. Declarations of Interest of Working Groups members



In accordance with EFSA's Policy on Independence<sup>1</sup> and the Decision of the Executive Director on Competing Interest Management<sup>2</sup>, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

## 4. Scientific topic(s) for discussion

### 4.1. Update of the SC guidance on the use of the benchmark dose approach in risk assessment<sup>3</sup>.

The working group was updated on the developments re. dose response assessment methods since the publication of the last version of the SC guidance on BMD (January 2017). In this respect, a summary of the ongoing update of the chapter 5 of WHO/IPCS Environmental Health Criteria 240 was given. This chapter was drafted by an international group of experts with the aim to reach consensus on how to perform dose response assessment and benchmark dose modelling.

The Scientific Committee was requested to update its guidance on the use of the benchmark dose in risk assessment, so that the approach recommended to EFSA Panels and Units is in line with the WHO document.

The working group distributed the various sections of the SC Guidance among its members, with the task to start updating them for the next meeting.

## 5. Next meeting(s)

A Doodle poll will be circulated to fix the meeting dates for 2020.

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<sup>2</sup> [http://www.efsa.europa.eu/sites/default/files/corporate\\_publications/files/competing\\_interest\\_management\\_17.pdf](http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf)

<sup>3</sup> <http://registerofquestions.efsa.europa.eu/roqFrontend/questionLoader?question=EFSA-Q-2020-00137>

# Minutes of the 1st meeting of the EFSA Cross-Cutting Working Group on Benchmark Dose

**Held on 5 and 6 September 2019 in Parma  
(Agreed on 23 September 2019)**

## **Participants**

### **Working Group Members:**

- Marc Aerts
- Diane Benford<sup>1</sup>
- Lutz Edler
- Thorhallur Halldorsson
- Wim Mennes
- Salomon Sand<sup>2</sup>
- Josef Schlatter
- Wout Slob<sup>2</sup>

## **EFSA**

- Marco Binaglia
- Bernard Bottex (Chair)
- Jose Cortiñas Abrahantes

---

<sup>1</sup> Attended via webconference both days

<sup>2</sup> Attended via webconference on day 1

## **1. Welcome and apologies for absence**

The Chair welcomed the participants.

## **2. Adoption of agenda**

The agenda was adopted without changes.

## **3. Declarations of Interest of Working Groups members**

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes<sup>3</sup> and the Decision of the Executive Director on Declarations of Interest<sup>4</sup>, EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

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<sup>4</sup> <http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014.pdf>

## **4. Scientific topic(s) for discussion**

The EFSA Cross-Cutting Working Group on Benchmark Dose has received a request for assistance from the Chair of the CONTAM Panel in relation to the ongoing assessment of polyfluoroalkyl substances (PFAs) in food. The cross-cutting working group is more specifically requested to provide advice on the following issues:

- Adequacy of using 102 points (groups of four children) instead of deciles for the modelling
- How to perform dose-response modelling in absence of control group with zero exposure. Proposal has been made by the CONTAM Panel to use dose scaling (subtracting the lowest concentration from each observation).

Three datasets have been provided: the Grandjean et al. (2012) study, looking at the association between serum concentrations of perfluorooctanesulfonic acid (PFOS) in children and reduced antibody response following vaccination; and two animal studies, Peden-Adams et al. (2008) and Dong et al. (2009), both studies showing a dose-related suppression of humoral immunity in mice exposed to PFOS.

### **4.1 Use of 102 groups of 4 children as 102 individual data points**

The working group confirmed the added value of using the 102 points instead of deciles, as the more points are available for fitting mathematical models, the less model uncertainty one will get.

Considering the fact that these 102 points are actually groups of 4 children showing similar exposure levels to PFOS, a member of the cross-cutting working group performed a small simulation (see annex) looking at the impact of ignoring the information on standard deviation within each group for linear models considering the responses to be normally distributed with constant variance. The working group indeed anticipated that the loss of information because modelling less data (102 instead of 440, i.e. broader intervals) is compensated by the grouping of 4 points in one (variability is shrunk given that the means per group is used). The simulation confirmed that, under the setting of the simulation, ignoring the information on standard deviations within each group does not substantially change the estimation of the dose-response parameters (intercept and slopes). Of course, having individual data is to be preferred in any case, as particular model assumptions (e.g. normality assumptions) cannot be checked on grouped data.

### **4.2 Modelling datasets with no zero exposure**

In order to evaluate dose-response data (e.g. by dose-response modelling as described in the SC guidance on the use of the benchmark dose



approach in risk assessment), the datasets should preferably be composed of a control group (effect measured at zero exposure) and a number of tested doses, such that the resulting Reference Point (or Point of Departure) falls within the observed dose range or is close to the applied non-zero doses.

For the three datasets provided by CONTAM, the lowest observed PFOS serum concentration levels are always greater than zero. The absence of controls with zero PFOS in serum implies that the background response is estimated by extrapolation. In most datasets, this model-dependent estimate is highly uncertain, and hence the estimated BMD is highly uncertain as well.

#### **4.2.1 Use of dose scaling**

The working group disagreed with the approach taken by the Panel, consisting in subtracting the lowest concentration from each observation. The lowest PFOS observation is study-dependent, and will be different should the same study be repeated in exactly the same conditions. As a consequence, the Reference Point and resulting Health-Based Guidance Value (HBGV) derived from this dataset will also be study-dependent.

#### **4.2.2 Proposed solution**

The working group underlined from the beginning the importance of providing a solution on the methodology to be applied, instead of a dataset-specific solution, so that the same approach can be applied consistently by the EFSA Panels and Units, should the same issue occur in the future.

Considering point 4.2.1 of these minutes, as well as the two decision trees on how to perform dose-response modelling presented in the EFSA guidance on benchmark dose and currently being developed by WHO for its updated chapter 5 on dose response assessment of WHO/IPCS EHC 240, the working group suggests the following stepwise approach for datasets without zero exposure:

- Ahead of any consideration of the data available, is it possible to identify a dose of reference (Dref), in this particular case, a level of exposure to PFOS that is not associated with any particular adverse effect? This Dref is based on prior knowledge. If such a Dref is available, it will be used as "zero dose" for the modelling. The value of the Dref for a specific endpoint is fixed until new information has been generated that justify modifying this value. As a reminder, the identification of the BMR (e.g., for the Grandjean et al. study, a percent reduction of serum antibody concentration against diphtheria and tetanus challenge considered adverse compared to the serum antibody concentration of reference) should be biology-

based and decided also before considering the dataset to be modelled.

- In the absence of a Dref for the endpoint considered, dose-response modelling using model averaging and the default set of models to be fitted to the data will be performed, considering dose zero as not observed and parameter  $a$  from the models will be estimated from information on the observed doses, without rescaling. The model uncertainty when estimating parameter  $a$  will be limited in case of datasets where the effect goes flat at the lower exposure levels, but may be considered as unacceptable if the curve has not stabilised around the lowest doses.
- In case the BMDL-BMDU confidence interval resulting from the dose response modelling using model averaging is not suitable for the assessment, one may try to get additional information on the background response (parameter  $a$ ), using prior information, historical data and/or expert knowledge elicitation in order to constrain this parameter. If the outcome of this modelling exercise (i.e. using the Bayesian framework) does not result in a useful Reference Point, the suitability of this dataset to derive a HBGV should be reconsidered.

This approach is considered the most appropriate for both human and animal data in the absence of zero exposure (control) groups; it will be reconsidered once EFSA Panels and Units have accumulated further experience.

#### **4.2.3 Additional considerations related to the Peden-Adams et al. (2008) study**

Table 2 in this paper is providing PFOS serum concentration levels for male and female mice resulting from various administered dose of PFOS. For some dose groups, the PFOS serum concentration level is missing. Question was raised whether males and female data can be modelled together or should be considered separately.

The Working Group suggests modelling the internal dose vs. the external dose in order to replace the missing internal dose values, then to perform a covariate analysis to check the assumption that the shape of the dose response for males is identical or sufficiently similar to the one for females, and that males and females PFOS serum concentrations can in that case be combined.

### **5. Next steps**

These minutes will be communicated to the CONTAM Panel as soon as agreed by the working group members so that the Panel can proceed further with its assessment of PFAS in food

In order not to lose the outcome of this discussion and make it easily accessible to EFSA Panels and Units, these concepts will be described in a more formal way in the currently under development SC guidance on appraising and integrating evidence from epidemiological studies for use in EFSA's scientific assessments. It was agreed that the section on modelling would be drafted jointly by the Cross-Cutting Working Group on Benchmark Dose and the SC Working Group on Epidemiology.

These concepts should also be inserted in the SC guidance on the use of the benchmark dose approach on risk assessment, which is planned to be updated in 2020.

## **6. Any Other Business**

The working group was informed about the upcoming update of the Chapter 5 on dose response assessment of the WHO/IPCS Environmental Health Criteria 240. A worldwide consensus on how to perform dose-response assessment was achieved, which needs now to be reflected in the SC guidance on BMD. Discussions are ongoing with the US Agencies (EPA, FDA etc.) and Health Canada to do this exercise jointly in order to ensure further harmonisation on how to perform benchmark dose analysis.

## Annex – code used for the simulation reported in section 4.1

```
ve<-0.7
ni<-4
ng<-100
set.seed(123)
g<-sort(runif(ng,0,10))
Nsim<-1000
b0<-0.7
b1<--0.62
y<-matrix(NA,ncol=Nsim,nrow=ng*ni)
y1<-matrix(NA,ncol=Nsim,nrow=ng)

confwidth<-function(x,y){
  n <- length(y) # Find length of y to use as sample size
  lm.model <- lm(y ~ x) # Fit linear model

  # Extract fitted coefficients from model object
  b0 <- lm.model$coefficients[1]
  b1 <- lm.model$coefficients[2]

  # Find SSE and MSE
  sse <- sum((y - lm.model$fitted.values)^2)
  mse <- sse / (n - 2)

  t.val <- qt(0.975, n - 2) # Calculate critical t-value
  # Fit linear model with extracted coefficients
  x_new <- x
  y.fit <- b1 * x_new + b0

  # Find the standard error of the regression line
  se <- sqrt(sum((y - y.fit)^2) / (n - 2)) * sqrt(1 / n + (x - mean(x))^2 / sum((x - mean(x))^2))

  # width of confidence band
  width<-t.val * range(se)
  return(width)
}
```

```
resFull<-resRed<-matrix(NA,nrow=Nsim,ncol=4)

for (i in 1:Nsim) {
  for (j in 1:ng){
    set.seed(1000*i+j)
    error<-rnorm(ni,0,ve)
    y[(((j-1)*ni+1):(j*ni)),i]<-b0+b1*g[j]+error
    y1[j,i]<-mean(y[(((j-1)*ni+1):(j*ni)),i])
  }
  lmF <- lm(y[,i] ~ rep(g,each=ni))
  b0F <- lmF$coefficients[1]
  b1F <- lmF$coefficients[2]
  lmR <- lm(y1[,i] ~ g)
  b0R <- lmR$coefficients[1]
  b1R <- lmR$coefficients[2]
  resFull[i,]<-c(confwidth(rep(g,each=ni),y[,i]),b0F,b1F)
  resRed[i,]<-c(confwidth(g,y1[,i]),b0R,b1R)
}

quantile(resFull[,1],probs=c(0.05,0.5,0.95))
quantile(resRed[,1],probs=c(0.05,0.5,0.95))
quantile(resFull[,2],probs=c(0.05,0.5,0.95))
quantile(resRed[,2],probs=c(0.05,0.5,0.95))
quantile(resFull[,3],probs=c(0.05,0.5,0.95))
quantile(resRed[,3],probs=c(0.05,0.5,0.95))
quantile(resFull[,4],probs=c(0.05,0.5,0.95))
quantile(resRed[,4],probs=c(0.05,0.5,0.95))

hist(resFull[,1],breaks="FD")
hist(resRed[,1],breaks="FD")
```



SCIENTIFIC COMMITTEE AND EMERGING RISKS UNIT

## SCIENTIFIC COMMITTEE

### MINUTES OF THE 2<sup>nd</sup> MEETING OF THE CROSS-CUTTING WORKING GROUP ON BENCHMARK DOSE

**Held on 12<sup>th</sup> March 2020 via web conference**

**(Agreed on 25 March 2020)**

#### Participants

■ Working Group Members:

Marc Aerts  
Lutz Edler  
Thorhallur Halldorsson  
Wim Mennes  
Salomon Sand  
Josef Schlatter  
Wout Slob

■ EFSA:

SCER Unit: Bernard Bottex  
AMU Unit: Jose Cortiñas Abrahantes

#### 1. Welcome and apologies for absence

The Secretariat welcomed the participants. Apologies were received from Diane Benford.

#### 2. Adoption of agenda

The agenda was adopted without changes.

#### 3. Declarations of Interest of Working Groups members



In accordance with EFSA's Policy on Independence<sup>1</sup> and the Decision of the Executive Director on Competing Interest Management<sup>2</sup>, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

## 4. Scientific topic(s) for discussion

### 4.1. Update of the SC guidance on the use of the benchmark dose approach in risk assessment<sup>3</sup>.

The working group was updated on the developments re. dose response assessment methods since the publication of the last version of the SC guidance on BMD (January 2017). In this respect, a summary of the ongoing update of the chapter 5 of WHO/IPCS Environmental Health Criteria 240 was given. This chapter was drafted by an international group of experts with the aim to reach consensus on how to perform dose response assessment and benchmark dose modelling.

The Scientific Committee was requested to update its guidance on the use of the benchmark dose in risk assessment, so that the approach recommended to EFSA Panels and Units is in line with the WHO document.

The working group distributed the various sections of the SC Guidance among its members, with the task to start updating them for the next meeting.

## 5. Next meeting(s)

A Doodle poll will be circulated to fix the meeting dates for 2020.

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# Minutes of the 1st meeting of the EFSA Cross-Cutting Working Group on Benchmark Dose

**Held on 5 and 6 September 2019 in Parma  
(Agreed on 23 September 2019)**

## **Participants**

### **Working Group Members:**

- Marc Aerts
- Diane Benford<sup>1</sup>
- Lutz Edler
- Thorhallur Halldorsson
- Wim Mennes
- Salomon Sand<sup>2</sup>
- Josef Schlatter
- Wout Slob<sup>2</sup>

## **EFSA**

- Marco Binaglia
- Bernard Bottex (Chair)
- Jose Cortiñas Abrahantes

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<sup>1</sup> Attended via webconference both days

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## **1. Welcome and apologies for absence**

The Chair welcomed the participants.

## **2. Adoption of agenda**

The agenda was adopted without changes.

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In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes<sup>3</sup> and the Decision of the Executive Director on Declarations of Interest<sup>4</sup>, EFSA screened the Annual Declaration of Interest and the Specific Declaration of Interest filled in by the working group members invited for the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process or at the Oral Declaration of Interest at the beginning of this meeting.

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## **4. Scientific topic(s) for discussion**

The EFSA Cross-Cutting Working Group on Benchmark Dose has received a request for assistance from the Chair of the CONTAM Panel in relation to the ongoing assessment of polyfluoroalkyl substances (PFAs) in food. The cross-cutting working group is more specifically requested to provide advice on the following issues:

- Adequacy of using 102 points (groups of four children) instead of deciles for the modelling
- How to perform dose-response modelling in absence of control group with zero exposure. Proposal has been made by the CONTAM Panel to use dose scaling (subtracting the lowest concentration from each observation).

Three datasets have been provided: the Grandjean et al. (2012) study, looking at the association between serum concentrations of perfluorooctanesulfonic acid (PFOS) in children and reduced antibody response following vaccination; and two animal studies, Peden-Adams et al. (2008) and Dong et al. (2009), both studies showing a dose-related suppression of humoral immunity in mice exposed to PFOS.

### **4.1 Use of 102 groups of 4 children as 102 individual data points**

The working group confirmed the added value of using the 102 points instead of deciles, as the more points are available for fitting mathematical models, the less model uncertainty one will get.

Considering the fact that these 102 points are actually groups of 4 children showing similar exposure levels to PFOS, a member of the cross-cutting working group performed a small simulation (see annex) looking at the impact of ignoring the information on standard deviation within each group for linear models considering the responses to be normally distributed with constant variance. The working group indeed anticipated that the loss of information because modelling less data (102 instead of 440, i.e. broader intervals) is compensated by the grouping of 4 points in one (variability is shrunk given that the means per group is used). The simulation confirmed that, under the setting of the simulation, ignoring the information on standard deviations within each group does not substantially change the estimation of the dose-response parameters (intercept and slopes). Of course, having individual data is to be preferred in any case, as particular model assumptions (e.g. normality assumptions) cannot be checked on grouped data.

### **4.2 Modelling datasets with no zero exposure**

In order to evaluate dose-response data (e.g. by dose-response modelling as described in the SC guidance on the use of the benchmark dose

approach in risk assessment), the datasets should preferably be composed of a control group (effect measured at zero exposure) and a number of tested doses, such that the resulting Reference Point (or Point of Departure) falls within the observed dose range or is close to the applied non-zero doses.

For the three datasets provided by CONTAM, the lowest observed PFOS serum concentration levels are always greater than zero. The absence of controls with zero PFOS in serum implies that the background response is estimated by extrapolation. In most datasets, this model-dependent estimate is highly uncertain, and hence the estimated BMD is highly uncertain as well.

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The working group disagreed with the approach taken by the Panel, consisting in subtracting the lowest concentration from each observation. The lowest PFOS observation is study-dependent, and will be different should the same study be repeated in exactly the same conditions. As a consequence, the Reference Point and resulting Health-Based Guidance Value (HBGV) derived from this dataset will also be study-dependent.

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The working group underlined from the beginning the importance of providing a solution on the methodology to be applied, instead of a dataset-specific solution, so that the same approach can be applied consistently by the EFSA Panels and Units, should the same issue occur in the future.

Considering point 4.2.1 of these minutes, as well as the two decision trees on how to perform dose-response modelling presented in the EFSA guidance on benchmark dose and currently being developed by WHO for its updated chapter 5 on dose response assessment of WHO/IPCS EHC 240, the working group suggests the following stepwise approach for datasets without zero exposure:

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This approach is considered the most appropriate for both human and animal data in the absence of zero exposure (control) groups; it will be reconsidered once EFSA Panels and Units have accumulated further experience.

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The Working Group suggests modelling the internal dose vs. the external dose in order to replace the missing internal dose values, then to perform a covariate analysis to check the assumption that the shape of the dose response for males is identical or sufficiently similar to the one for females, and that males and females PFOS serum concentrations can in that case be combined.

### **5. Next steps**

These minutes will be communicated to the CONTAM Panel as soon as agreed by the working group members so that the Panel can proceed further with its assessment of PFAS in food

In order not to lose the outcome of this discussion and make it easily accessible to EFSA Panels and Units, these concepts will be described in a more formal way in the currently under development SC guidance on appraising and integrating evidence from epidemiological studies for use in EFSA's scientific assessments. It was agreed that the section on modelling would be drafted jointly by the Cross-Cutting Working Group on Benchmark Dose and the SC Working Group on Epidemiology.

These concepts should also be inserted in the SC guidance on the use of the benchmark dose approach on risk assessment, which is planned to be updated in 2020.

## **6. Any Other Business**

The working group was informed about the upcoming update of the Chapter 5 on dose response assessment of the WHO/IPCS Environmental Health Criteria 240. A worldwide consensus on how to perform dose-response assessment was achieved, which needs now to be reflected in the SC guidance on BMD. Discussions are ongoing with the US Agencies (EPA, FDA etc.) and Health Canada to do this exercise jointly in order to ensure further harmonisation on how to perform benchmark dose analysis.

## Annex – code used for the simulation reported in section 4.1

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g<-sort(runif(ng,0,10))
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confwidth<-function(x,y){
  n <- length(y) # Find length of y to use as sample size
  lm.model <- lm(y ~ x) # Fit linear model

  # Extract fitted coefficients from model object
  b0 <- lm.model$coefficients[1]
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  # Find SSE and MSE
  sse <- sum((y - lm.model$fitted.values)^2)
  mse <- sse / (n - 2)

  t.val <- qt(0.975, n - 2) # Calculate critical t-value
  # Fit linear model with extracted coefficients
  x_new <- x
  y.fit <- b1 * x_new + b0

  # Find the standard error of the regression line
  se <- sqrt(sum((y - y.fit)^2) / (n - 2)) * sqrt(1 / n + (x - mean(x))^2 / sum((x - mean(x))^2))

  # width of confidence band
  width<-t.val * range(se)
  return(width)
}
```

```
resFull<-resRed<-matrix(NA,nrow=Nsim,ncol=4)

for (i in 1:Nsim) {
  for (j in 1:ng){
    set.seed(1000*i+j)
    error<-rnorm(ni,0,ve)
    y[(((j-1)*ni+1):(j*ni)),i]<-b0+b1*g[j]+error
    y1[j,i]<-mean(y[(((j-1)*ni+1):(j*ni)),i])
  }
  lmF <- lm(y[,i] ~ rep(g,each=ni))
  b0F <- lmF$coefficients[1]
  b1F <- lmF$coefficients[2]
  lmR <- lm(y1[,i] ~ g)
  b0R <- lmR$coefficients[1]
  b1R <- lmR$coefficients[2]
  resFull[i,]<-c(confwidth(rep(g,each=ni),y[,i]),b0F,b1F)
  resRed[i,]<-c(confwidth(g,y1[,i]),b0R,b1R)
}

quantile(resFull[,1],probs=c(0.05,0.5,0.95))
quantile(resRed[,1],probs=c(0.05,0.5,0.95))
quantile(resFull[,2],probs=c(0.05,0.5,0.95))
quantile(resRed[,2],probs=c(0.05,0.5,0.95))
quantile(resFull[,3],probs=c(0.05,0.5,0.95))
quantile(resRed[,3],probs=c(0.05,0.5,0.95))
quantile(resFull[,4],probs=c(0.05,0.5,0.95))
quantile(resRed[,4],probs=c(0.05,0.5,0.95))

hist(resFull[,1],breaks="FD")
hist(resRed[,1],breaks="FD")
```