European Commission

Combined Draft Renewal Assessment Report prepared according to Regulation (EC) N° 1107/2009
and
Proposal for Harmonised Classification and Labelling (CLH Report) according to Regulation (EC) N° 1272/2008

Glyphosate

Volume 1
ED assessment for humans

Rapporteur Member State: Assessment Group on Glyphosate (AGG) consisting of FR, HU, NL and SE

Version History

When	What
2021/06	Initial RAR

The RMS is the author of the Assessment Report. The Assessment Report is based on the validation by the RMS, and the verification during the EFSA peer-review process, of the information submitted by the Applicant in the dossier, including the Applicant's assessments provided in the summary dossier. As a consequence, data and information including assessments and conclusions, validated and verified by the RMS experts, may be taken from the applicant's (summary) dossier and included as such or adapted/modified by the RMS in the Assessment Report. For reasons of efficiency, the Assessment Report should include the information validated/verified by the RMS, without detailing which elements have been taken or modified from the Applicant's assessment. As the Applicant's summary dossier is published, the experts, interested parties, and the public may compare both documents for getting details on which elements of the Applicant's dossier have been validated/verified and which ones have been modified by the RMS. Nevertheless, the views and conclusions of the RMS should always be clearly and transparently reported; the conclusions from the applicant should be included as an Applicant's statement for every single study reported at study level; and the RMS should justify the final assessment for each endpoint in all cases, indicating in a clear way the Applicant's assessment and the RMS reasons for supporting or not the view of the Applicant.

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2.10 ENDOCRINE DISRUPTING PROPERTIES

2.10.1 Gather all relevant information

Literature search
A comprehensive literature search for toxicology and ecotoxicology was performed. For details on the literature search, please refer to the related Literature Review Report (LRR) in the dossier.

The search was conducted in accordance with provisions of the ECHA/EFSA Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (ECHA/EFSA ED Guidance, 2018), Annex F.

The objective of the literature search was to identify scientific peer-reviewed open literature that could inform an assessment of potential endocrine disrupting properties of glyphosate.

As the previous literature search on potential endocrine disrupting properties (reported in a separate report) only covers the publication period between January 2014 and October 2016, a new literature search has been conducted in order to extend the existing search. This new literature search covers the publication period between November 2016 and July 2019.

The literature search has been conducted accessing 11 bibliographic databases: AGRICOLA, BIOSIS, CABA, CAPLUS, EMBASE, ESBIOBASE, MEDLINE, TOXCENTER, FSTA, PQSCITECH, and SCISEARCH via the service provider STN.

For articles which appeared to be relevant AND reliable and provided data for establishing / refining risk assessment parameters (EFSA GD Point 5.4.1 A for relevance) a summary has been compiled.

For articles relevant regarding the data requirement, but which in opinion of the applicant provided only supplementary information that does not alter existing risk assessment, a justification for such evaluations has been provided (EFSA GD Point 5.4.1 B).

For articles of an unclear relevance, an explanation has been provided why the relevance could not be determined (EFSA GD Point 5.4.1 C).

Detailed reporting of the results of the literature search is to be found in the LRR.

In addition, a non-STN database screening was conducted for glyphosate. The results are compiled in the overview below (Table 1). Glyphosate is included in the following lists:

- EU priority list:

Not listed due to ED concern (listed as glyphosate with CAS 1071-83-6, referring to glyphosin)

- EU Impact assessment screening study:

Unclassified

- EDSP 21 lists:

The initial chemicals to be tested under the USEPA Endocrine Disruptor Screening Program were selected based on four human exposure pathways, which included food consumption, drinking water consumption, residential use exposure and occupational exposure. The highest priority chemicals for inclusion on List 1 were those having potential exposure through all four pathways and included glyphosate. Throughout the selection process, EPA clearly stated that the list should not be construed as a list of known or likely endocrine disruptors.

Conclusion Tier 1: No convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways. This conclusion was made after reviewing the 11 Tier 1 assays that provided an *in vitro* mode of action assessment of estrogenicity, anti-estrogenicity, androgenicity, anti-androgenicity and steroidogenesis and an *in vivo* assessment of the hypothalamus-pituitary-gonadal axis and hypothalamus-pituitary-thyroid axis.

With regard to the EU priority list, it has to be noted that this database is not recent and actually relevant but included for completeness sake.

With regard to the EU Impact assessment screening report, the following should be noted:

The results of the screening do not constitute evaluations of individual substances to be carried out under the respective chemical legislations [in particular, Regulation (EC) No 1107/2009 on plant protection products, Regulation (EU) No 528/2012 on biocidal products, Regulation (EC) No 1907/2006 REACH, Regulation (EC) No 1223/2009 on cosmetic products and the Water Framework Directive (EC) No 2000/60] and in no way prejudge future decisions on active substances to be taken pursuant to these pieces of the EU legislation.

It would thus be erroneous to consider that the substances listed in the results of this study (SANTE/2015/E3/SI2.706218) are considered as endocrine disruptors within the meaning of the EU legislation.

Table 1: Non-STN database screening results for glyphosate

Substance	CAS	Candi-date list of SVHCs	CoRAP list	ECHA ED assess-ment list	Priority list EU	European Commission impact assessment	ED SP 21 lists	C&L Carc/ Repro / STOT RE	PACT
Glyphosate	1071-83-6	N	N	N	Y [1)]	Y: Unclassified	Y [2)]	N[3)]	Y: no ED concern

Y: yes, N: no

1) Priority list EU: not listed due to ED concern (listed as glyphosate with CAS 1071-83-6, referring to glyphosin)
2) EDSP 21 lists: Pesticide Active Ingredient (list 1), EDSP WoE conclusion Tier 1: No convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways (results)
3) Glyphosate is not classified for carcinogenicity, reproduction toxicity and Single Target Organ Toxicity after Repeated Exposure according to the current Annex VI entry of Regulation (EC) No 1272/2008 nor according to the latest RAC Opinion proposing harmonised classification and labelling at EU level of glyphosate (Adopted March 2017).

Note RMS:
An additional literature search was performed by the GRG covering the publication period of January 2020 to June 2020, as requested by the AGG. The same databases, input parameters, search terms and filters were used for this top-up search. See also Vol. 3 B.6.10 for more details on the literature search. It is noted that RMS requested the applicant to provide several studies, including study summaries and an evaluation, which were excluded for evaluation by the applicant.

In silico screening for potential endocrine disrupting properties
Following the recommendations given in Annex D of the ED Guidance, an *in silico* screening for potential endocrine disrupting properties and endocrine activity of glyphosate was performed (for details please refer to the ED QSAR report (report no 110517-1, KCA 5.8.3-11).

(Q)SAR predictions were generated using selected publicly available and commercial models. Five QSAR tools were applied for predictions of potential endocrine activity of Glyphosate: OECD QSAR

Toolbox, Vega, Endocrine Disruptome, Danish QSAR database and ToxCast COMPARA/CERAPP consensus models. The list of investigated receptors include: estrogen receptor (ER), androgen receptor (AR), thyroid receptor (TR), glycocorticoid receptor (GR), mineralocorticoid receptor (MR), liver X receptor (LXR), peroxisome proliferator-activated receptor (PPAR), retinoid X receptor (RXR), aryl hydrocarbon receptor (AhR), pregnane X receptor (PXR), and CYP3A4 activation.

The general outcome of the *in silico* screening for glyphosate is shortly summarised in Table 2.

Table 2: Summary of (Q)SAR screening

Modality	**Summary outcome of *in silico* screening**	**Remarks**
Estrogen	No indication	Estrogenic activity was predicted negative with all five applied models. Due to the high amount of data available on ER activity, the high quality of CERAPP Consensus predictions and glyphosate being part of the training set for ER binding tests, the assessment of ER activity of glyphosate is considered reliable.
Androgen	No indication	Androgenic activity was predicted negative with all five applied models. Due to the quality of COMPARA consensus predictions in combination with other models (predicting no androgenic activity), the assessment of androgenic activity based on the available models is considered reliable. This is further strengthened, as glyphosate is part of the testing battery of the Danish QSAR database and tested negative for antagonistic effect on the human androgen receptor *in vitro*.
Steroid	No indication	There are three results available for steroid receptors: glucocorticoid receptor (GR) and glucocorticoid receptor antagonism and mineralocorticoid receptor (MR). No steroid activity is predicted for all three receptors by the molecular docking method (Endocrine Disruptome).
Thyroid	No indication	TR binding activity is predicted to be low for glyphosate by the molecular docking method (Endocrine Disruptome). Results of the two models available in the Danish QSAR database are either inconclusive or negative. Both predictions are out of applicability domain and thus of low reliability.
Other	No indication	Overall, there is no indication of activity for endocrine activities other than estrogen, androgen, steroid and thyroid (e.g. PPAR, RXR, PXR), however due to the general lack of models for the various receptors, the result should be considered with caution.

Note by RMS:
This study (report no. 110517-1) was evaluated in Volume 3, CA, B.6.8.3.10. RMS concluded that the QSAR analysis did not indicate a potential ED concern.

2.10.2 ED assessment for humans

The assessment follows the strategy as laid down in the ECHA/EFSA ED Guidance (Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009). All available data were evaluated and the relevant and reliable data (i.e. available repeated dose toxicity studies in mammals, *in vivo* and *in vitro* mechanistic data, *in silico* information) on glyphosate were considered for the ED assessment (a list of studies is included in Appendix E Table attached to chapter 2.1.2).

Note by RMS:
RMS has included below the table with the list of studies.

Study ID Matrix	Study type	Species	Study Guideline	Year	Study Reference (Report No.)	KCA No.
1	Repeated dose 90-day oral toxicity study in rodents	Rat	OECD 408 (1981)	1996	CTL/P/1599	KCA 5.3.2/001-002
2	Repeated dose 90-day oral toxicity study in rodents	Rat	JMAFF (1985), similar to OECD 408 (1981)	1996	434/016	KCA 5.3.2/003
3	Repeated dose 90-day oral toxicity study in rodents	Rat	JMAFF (1985), similar to OECD 408 (1981)	1995	IET 94-0138	KCA 5.3.2/004
4	Repeated dose 90-day oral toxicity study in rodents	Mouse	OECD 408 (1981), JMAFF (1985)	1995	IET 94-0136	KCA 5.3.2/017
5	Repeated dose 90-day oral toxicity study in dogs	Dog	OECD 409 (1998), JMAFF (2000)	2007	29646 TCC	KCA 5.3.2/020
6	Repeated dose 90-day oral toxicity study in dogs	Dog	OECD 409 (1981)	1999	1816	KCA 5.3.2/021-024
7	Repeated dose 90-day oral toxicity study in dogs	Dog	OECD 409 (1981), JMAFF (1985), US EPA OPPTS (1984)	1996	IET 94-0158	KCA 5.3.2/027
8	Repeated dose 90-day oral toxicity study in dogs	Dog	OECD 409 (1981), US EPA 82-1	1996	CTL/P/1802	KCA 5.3.2/025-026
9	Repeated dose 1-year oral toxicity study in dogs	Dog	OECD 452 (1981), JMAFF (2000)	2008	29647 TCC	KCA 5.3.2/031
10	Repeated dose 1-year oral toxicity study in dogs	Dog	OECD 409 (1981), JMAFF (1985), US EPA OPPTS (1984)	1997	IET 94-0157	KCA 5.3.2/032
11	Repeated dose 1-year oral toxicity study in dogs	Dog	OECD 452 (1981), EEC Directive 67/548 (1987), US EPA 83-1(b)	1996	CTL/P/5079	KCA 5.3.2/033-034
12	Chronic toxicity 1-year oral toxicity study in rats	Rat	OECD 452 (1981), US EPA 83-1	1996	CTL/P/5143	KCA 5.5-006

13	Chronic toxicity 2-year oral toxicity study in rats	Rat	OECD 453 (1981)	1996	886CCR	KCA 5.5-005
14	Chronic toxicity 2-year oral toxicity study in rats	Rat	OECD 453 (1981), JMAFF (1985), US EPA 83-5 (1984)	1997	IET-94-0150	KCA 5.5-004
15	Chronic toxicity 2-year oral toxicity study in rats	Rat	OECD 453 (1981), EEC Directive 87/302 (1988), US EPA OPPTS 870.4300 (1998)	2001	CTL/PR/1111	KCA 5.5-002
16	Chronic toxicity 2-year oral toxicity study in rats	Rat	US EPA 83-5 (1984)	1993	7867	KCA 5.5-007 KCA 5.5-008 KCA 5.5-009
17	Chronic toxicity 2-year oral toxicity study in rats	Rat	US EPA 83-5 (1984)	1990	MSL-10495	KCA 5.5-010
18	Chronic toxicity 2-year oral toxicity study in rats	Rat	OECD 453, JMAFF (2005), US EPA OPPTS 870.4300 (1996)	2009a	SPL2060-0012	KCA 5.5-001
19	Chronic toxicity 18 months oral toxicity study in mice	Mouse	OECD 451 (1981)	2001	1559.CARCI-M	KCA 5.5-016 KCA 5.5-017
20	Chronic toxicity 18 months oral toxicity study in mice	Mouse	OECD 416 (2001), US EPA OPPTS 870.3800 (1998), JMAFF 12 Nohsan No 8147 (2005)	2009b	SPL 2060-0011	KCA 5.5-012 KCA 5.5-013 KCA 5.5-014 KCA 5.5-015
21	Chronic toxicity 18 months oral toxicity study in mice	Mouse	US EPA 82-1 (1984)	1997	IET 94-0154	KCA 5.5-018 KCA 5.5-019
22	Two-generation oral toxicity study in rats	Rat	OECD 416 (2001), JMAFF 2-1-17 (2000), US EPA OPPTS 870.3800 (1998)	2007	2060-0013	KCA 5.6.1-001 KCA 5.6.1-002 KCA 5.6.1-003
23	Two-generation oral toxicity study in rats	Rat	OECD 416 (1983), US EPA OPPTS 870.3800, EEC Directive 67/548 (1988)	2000	CTL/P/6332	KCA 5.6.1-004

24	Two-generation oral toxicity study in rats	Rat	OECD 416 (1983), JMAFF (1985), US EPA 83-4 (1984)	1997	IET-96-0031	KCA 5.6.1-05
25	Two-generation oral toxicity study in rats	Rat	OECD 416 (1983)	1993a	885-RP-G2	KCA 5.6.1-06
26	Two-generation oral toxicity study in rats	Rat	OECD 416 (1983), US EPA 83-4 (1982)	1992	CHV 47/911129	KCA 5.6.1-007 KCA 5.6.1-008
27	Two-generation oral toxicity study in rats	Rat	similar to OECD 416	1990	MSL-10387	KCA 5.6.1-010
28	Prenatal developmental toxicity study in rats	Rat	similar to OECD 414	1996	CTL/P/4819	KCA 5.6.2-001
29	Prenatal developmental toxicity study in rats	Rat	OECD 414 (1981), US EPA 83-3, JMAFF (1985)	1995	IET-94-0152	KCA 5.6.2-002
30	Prenatal developmental toxicity study in rabbits	Rabbit	OECD 414 (1981), US EPA 83-3, JMAFF (1985)	1995	IET-94-0153	KCA 5.6.2-011
31	Prenatal developmental toxicity study in rabbits	Rabbit	OECD 414 (1981), US EPA 83-3, JMAFF (1985)	1996	434/020	KCA 5.6.2-010
32	Prenatal developmental toxicity study in rabbits	Rabbit	OECD 414	1996	CTL-P-5009	KCA 5.6.2-009
33	Prenatal developmental toxicity study in rabbits	Rabbit	pre-Guideline; in general compliance with OECD 414 or US EPA 83-3	1980	IR-79-018	KCA 5.6.2-019
34	Prenatal developmental toxicity study in rabbits	Rabbit	OECD 414 (1981)	1993	884-TER-RB	KCA 5.6.2-012 KCA 5.6.2-013
35	Prenatal developmental toxicity study in rabbits	Rabbit	OECD 414 (1981)	1989	1086	KCA 5.6.2-016
36	Repeated dose 28-day oral toxicity study in rodents	Rat	OPPTS 870.7800	2012	WIL-50393	KCA 5.8.2-001
37	ER Binding Assay	Rat, Sprague-Dawley, cytosol from uterus	OPPTS 890.1250 (2009)	2012	6500V-100334ERB	KCA 5.8.3-003

38	Stably Transfected Human ERα Transcriptional Activation Assay (ER STTA)	Human cell line (HeLa-9903)	OECD 455 (2009)	2012	6500V-100334ERTA	KCA 5.8.3-002
39	AR Binding Assay	Rat, Sprague-Dawley, cytosol from prostate	OPPTS 890.1150 (2009)	2012	6500V-100334ARB	KCA 5.8.3-001
40	Aromatase Assay	Human (CYP19 (aromatase) and P450 reductase Supersomes TM)	OPPTS 890.1200	2012	6500V-100334AROM	KCA 5.8.3-004
41	H295R steroidogenesis assay	Human cell line (H295R)	OECD 456	The OECD validation program of the H295R steroidogenesis assay: Phase 3. Final inter-laboratory validation study. Environ Sci Pollut Res (2011) 18:503–515	DOI 10.1007/s11356-010-0396-x	KCA 5.8.3-009
42	Uterotrophic assay	Rat	OECD 440	2012	WIL-843002	KCA 5.8.3-005
43	Hershberger Assay	Rat	OECD 441	2012	WIL-843003	KCA 5.8.3-006
44	Female pubertal assay (PP Male Assay)	Rat	OPPTS 890.1450	2012	WIL-843007	KCA 5.8.3-008
45	Male pubertal assay (PP Male Assay)	Rat	OPPTS 890.1500	2012	WIL-843005	KCA 5.8.3-007
46	Prenatal developmental toxicity study in rabbits	Rabbit	OECD 414	1991	CHV 45-901303	KCA 5.6.2-014 KCA 5.6.2-015
47	Prenatal developmental toxicity study in rabbits	Rabbit	OECD 414	1991	CHV 39-901303	
48	Prenatal developmental toxicity study in rabbits	Rabbit	DRF	1991	CHV 40-901303	
49	Subacute oral toxicity in rats (28 days)	Rat	OECD 407 (1981)	1991	ES.881.28 DDR	KCA 5.3.1/001-003
50	Subacute oral toxicity in rats (28 days)	Rat	OECD 407 (1981)	1989	5626	KCA 5.3.1/004

51	Subacute oral toxicity in dogs	Dog	DRF	1989	5660	KCA 5.3.1/007
52	Repeated dose 90-day oral toxicity study in rodents	Rat	OECD 408	1991	7136	KCA 5.3.2/011
53	Repeated dose 90-day oral toxicity study in rodents	Rat	US EPA 82-1, OECD 408 (1981)	1993	011-0001	KCA 5.3.2/005-007
54	Repeated dose 90-day oral toxicity study in rodents	Rat	OECD 408 (1981)	1992	ES.882.90.OR	KCA 5.3.2/008-010
55	Repeated dose 90-day oral toxicity study in rodents	Rat	similar to OECD 408	1987	ML-86-351	KCA 5.3.2/014
56	Repeated dose 90-day oral toxicity study in rodents	Mouse	OECD 408 (1981), FIFRA 82-1	1991	7024	KCA 5.3.2/018
57	Repeated dose 6-month oral toxicity study in dogs	Dog	similar to OECD 409	1983	810166, ML-81-368	KCA 5.3.2/029
58	Repeated dose 1-year oral toxicity study in dogs	Dog	similar to OECD 452 (1981)	1985	830116, ML-83-137	KCA 5.3.2/036
59	Repeated dose 1-year oral toxicity study in dogs	Dog	similar to OECD 452 (1981)	1990	7502	KCA 5.3.2/035
60	Repeated dose dermal toxicity in rats	Rat	equivalent to OECD 410	1993	7839	KCA 5.3.3/003
61	Repeated dose dermal toxicity in rats	Rat	OECD 410	1996	CTL-P-4985	KCA 5.3.3/001-002
62	Repeated dose dermal toxicity in rabbits	Rabbit	OECD 410	1982	IR-81-195	KCA 5.3.3/008
63	Repeated dose dermal toxicity in rabbits	Rabbit	OECD 410	1994	MUF 214/94	KCA 5.3.3/004-006
64	Prenatal developmental toxicity study	Rat	OECD 414, US EPA 83-3 (1982)	1991	43-90716	KCA 5.6.2-003
65	Prenatal developmental toxicity study	Rat	OECD 414 (1981)	1991	ES.883.TER-R	KCA 5.6.2-004 KCA 5.6.2-005
66	Prenatal developmental toxicity study	Rabbit	similar to OECD 414 ("Teratology study in rabbits")	1980	IR-79-018	KCA 5.6.2-019
67	Carcinogenicity study	Mouse	similar to OECD 451	1989	7793	KCA 5.5-020 KCA 5.5-021

68	Carcinogenicity study	Mouse	no guideline specified; in general compliance with OECD 451	, 1983	77-2061 (BDN-77-420)	KCA 5.5-023
69	One-generation reproduction toxicity study - DRF	Rat	EPA FIFRA Guideline 83-4 (dose-range finder for multigeneration study)	1991	42-90619	KCA 5.6.1-009
70	Multigenerational reproductive toxicity	Rat	Three generation reproduction study	1981	77-2063	KCA 5.6.1-014
71	Repeated dose 28 days	Rat	Range finding study, similar to OECD 407	1989	ML-88-272/EHL 88181/MSL-8921	KCA 5.3.1/005
72	Repeated dose 28 days	Mouse	Range finding study, similar to OECD 408	1978	77-2110	KCA 5.3.1/006
73	Repeates dose 90 days	Mouse	None, similar to OECD 407	1979	77-2111	KCA 5.3.2/019
74	Multigeneration reproductive toxicity	Rat	None	1988	Not provided	KCA 5.6.1-012
75	One-generation reproductive toxicity	Rat	None	1988	Not provided	KCA 5.6.1-011
76	Repeated dose 90 days	Rat	OECD 408	1990	AGC-900914	KCA 5.3.2/012
77	Prenatal developmental toxicity	Rabbit	None	1979	IR-79-017	KCA 5.6.2-018
78	Repeated dose 13 weeks	Rats	None, similar to OECD 408	1992	92-3135 (NIH publication)	NIH publication
79	Repeated dose 13 weeks	Mouse	None, similar to OECD 408	1992	92-3135 (NIH publication)	NIH publication
80	Repeated dose 5 weeks	Rats	None, published study	2016	None, published study	KCA 5.6.1/023
81	Other Steroidogenesis in vitro assay in murine Leydig cells	Mouse in vitro	None, published study	2012	None, published study	KCA 5.6.1/024
82	Other Steroidogenesis in vitro assay in swine granulosa cells	Swine in vitro	None, published study	2018	None, published study	KCA 5.8.3/012
83	In vitro method (general) (Sertoli cell permeability)	Rat in vitro	None, published study	2020	None, published study	KCA 5.6.1/015
84	ER Binding Assay	Human in vitro	None, published study	2017	None, published study	KCA 5.8.3/014
85	Other ER in vitro assay	Human in vitro	None, published study	2013	None, published study	KCA 5.8.3/015
86	In vitro method (general, immature sertoli cell line)	Mouse in vitro	None, published study	2018	None, published study	KCA 5.8.3/013

87	In vitro method (general)	Mouse in vitro	None, published study	2019	None, published study	KCA 5.6.1/019
88	Other Steroidogenesis in vitro assay	Cow in vitro	None, published study	2017	None, published study	KCA 5.6.1/022
89	In vitro estrogen (Estrogen Receptor Transactivation Assay with a variant of a human breast cancer (MCF7) cell line)	Human in vitro	None, published study	2016; Corrigendum 2017	None, published study	KCA 5.8.3/016 (initial article) KCA 5.8.3/017 (corrigendum, 2017)
90	Aromatase Assay	Human in vitro	None, published study	2016	None, published study	KCA 5.8.3/018
91	Subacute oral in rodent	Rat	None, published study	2018	None, published study	KCA 5.6.1/020
92	Pilot study for EOGRTS (description of study design)	Rat	None, published study (one generation, dose range-finder OECD 443)	2018	None, published study	KCA 5.6.1/021
93	Pilot study for EOGRTS (description of ED-relevant parameters)	Rat	None, published study (one generation, dose range-finder OECD 443)	2019	None, published study	KCA 5.6.1/016
94	Subchronic oral toxicity in rodents	Mouse	None, published study	2019	None, published study	KCA 5.6.1/017
95	Subacute oral in rodent	Mouse	None, published study	2019	None, published study	KCA 5.6.1/018
96	Repeated dose 90 days	rat	OECD 408	1989	BY-891002	KCA 5.3.2/013

2.10.2.1 ED assessment for T-modality

Have T-mediated parameters been sufficiently investigated?

T-modality	Sufficiently investigated
T-mediated adversity (i.e. T-mediated parameters)	Based on the requirements of the ECHA/EFSA ED Guidance, potential T-mediated adversity of glyphosate has been sufficiently investigated since the T-mediated parameters thyroid weight and/or histopathology were addressed in several repeated dose toxicity (RDT) studies in dog, mouse, rabbit, and rat including different life stages (study IDs 5-11, 22, 44, 45, 57 - 59, 62 and 1-21, 26, 44, 45, 49, 52 - 59, 63, 67, 68, 70, 73, 74, 76, 93 for weight and histopathology, respectively).
T-related activity (i.e. *in vivo* mechanistic data)	T-mediated potential endocrine activity, i.e. thyroid hormone levels were not investigated in subchronic toxicity studies according to OECD test guidelines (TG) since those were conducted according to former OECD TG versions. However, thyroid hormone levels (i.e. TSH and T4) were addressed in the female and male pubertal assay (study IDs 44, 45), corresponding to subacute exposure periods of the animals as well as in a published pilot study for an EOGRTS (study ID 93).
Overall conclusion on T-modality	Yes, according to the requirements of ECHA/EFSA ED Guidance T-mediated adversity as well as related activity is considered sufficiently investigated based on the available *in vivo* studies as described above.

Note by RMS:
No comments on the information included in the table above. It is noted that RMS concluded that the studies with IDs 54, 70, 74 were unacceptable.

It is agreed that according to the EFSA/ECHA guidance, the T-modality has been sufficiently investigated.

Lines of evidence for adverse effects and endocrine activity related to T-modality
Lines of Evidence (LoE) for T-modality, EAS-modalities as well as for parameters "sensitive to, but not diagnostic of EATS", target organ toxicity and general toxicity are included in the Excel file (Appendix E Table according to ECHA/EFSA ED Guidance).

Note by RMS:
RMS had included the table with lines of evidence for the T-modality below, and adjusted it where necessary. In the Appendix E document, RMS has checked and adjusted the information where necessary (in the tab 'data' and 'data summary').

In the last two columns, the argumentations of the applicants are still included, followed by comments by the RMS.

It is noted that the tables including results for endpoints 'sensitive to but not diagnostic of' and general toxicity are included below in an appendix.

Grouping	Line(s) of evidence	Species	Exposure weeks	Route of exposure	Effect dose	Observed effects (positive and negative)	Assessment of each line of evidence	Assessment of the integrated line of evidence	Modality
Integrated lines of evidence for endocrine activity									
In silico mechanistic	QSAR prediction T-modality	n.a.	n.a.	n.a.	n.a.	No effect The molecular docking method (Endocrine Disruptome) indicates low probability of binding. The results (inconclusive and negative) from the two models available in the Danish QSAR database with regard to TPO are not reliable (out of applicability domain). Given the lack of other models the result should be considered with caution and thus as supporting information only.	No indication for T-related endocrine activity of the test substance is deduced from available in silico models. **RMS**: agreed	Based on the available in vivo mechanistic data and supporting in silico information, it is concluded that the a.s. glyphosate does not possess any T-related endocrine activity. **RMS**: agreed	T
In vivo mechanistic	Hormone levels	Rat (pubertal male)	21 (PND 22 to PND 42)	Oral	>1000 mg/kg bw/day	No effect on T4 or TSH levels	Thyroid hormones were analysed in the male and female pubertal assay as well as in a published pilot study for an EOGRTS. No relevant changes on hormone levels were observed within the pubertal assays. In the pilot study an increase in TSH was observed in F1 males only sacrificed after 6 weeks of exposure. Since no effect on TSH was observed after 13 weeks of exposure as well as in the pubertal assays, covering		
		Rat (pubertal female)	31 (PND 23 to PND 53)	Oral	>1000 mg/kg bw/day	No effect on T4 or TSH			
		Rat	F0: from GD6 to end of lactation; Offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts	Oral	1.75 mg/kg bw/day	Increase TSH A statistically significant increase was observed in male offspring of the 6 weeks exposure group only. No effect was observed after 13 weeks of exposure in males or in females. Moreover, histopathological changes in thyroid were observed neither in the 6 weeks nor in the 13 week exposure group. Moreover, the (male and female) pubertal assays, covering the same live stage as the 6 week period of the current study, did not show any increase in TSH or changes in thyroid weight and histopathology. In addition, no effects were observed in the FOB during the two-generation study (study ID 22). Based on the provided rationale as well as the results of the available repeated dose toxicity studies, no indication for thyroid disrupting effects is provided from this pilot study.			

Grouping	Line(s) of evidence	Species	Exposure weeks	Route of exposure	Effect dose	Observed effects (positive and negative)	Assessment of each line of evidence	Assessment of the integrated line of evidence	Modality
		Mouse	Dams exposed during gestation; Offspring levels were collected on GD19, PND7, PND21	Oral	5000 mg/L	Increase The following serum biochemical indexes were determined: TG, T-CHO, low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) aspartate transaminase (AST), alanine transaminase (ALT). Additionally, TG, T-CHO, LDL-C and HDL-C content was measured in liver homogenate. The concentrations of lipids such as triglycerides (TGs), total cholesterol (T-CHO), and low-density lipoprotein cholesterols (LDL-C) increased to a significant extent in both the serum and livers. Changes in HDL/LDL are considered T-mediated only in combination with other thyroid endpoints. Since no indication for T-related adversity nor activity is provided by the available in vivo studies, the observed increase in some lipid markers in serum and liver is not considered related to an endorine MoA.	the same life stage as the 6 week period of the pilot study, the TSH increase is considered not biologically relevant (for more detail please refer to study ID 93). In conclusion, no indication for T-related endocrine activity of the test substance is deduced from available in vivo mechanistic data in male and female rat. **RMS**: agreed		
Integrated lines of evidence for endocrine adversity									
EATS mediated parameter	Thyroid weight	Dog	90 days	Oral	>1000 mg/kg bw/day	No effect	Thyroid weight and thyroid histopathology were examined in 14 and 41 studies, respectively; including subcabute, subchronic, and chronic exposure periods. A toxicologically relevant effect on either T-mediated parameter was not observed in any study considering four species (dog,	Based on the available in vivo data in four mammalian species after subacute, subchronic and chronic exposure to glyphosate, no T-mediated endocrine adversity was observed. Therefore, the ED criteria with regards to T-modality are not met. **RMS:** No treatment-related adverse effects on thyroid weight or histopathology were seen in either mouse, rat, rabbit or dog.	T
		Dog	90 days	Oral	>10000 ppm	No effect			
		Dog	90 days	Oral	>40000 ppm	No effect			
		Dog	90 days	Oral	2000 ppm	Decrease Relative thyroid weight was reduced in females at 2000 and 10000 ppm. However, this effect showed no dose-response and no histopathological changes were observed in thyroid in dogs of this study. Moreover, no effect on organ weight at similar or higher doses was observed in dog after subchronic (study IDs 6-7) and chronic exposure (study IDs 9-11). Therefore, the reduction in thyroid weight in the current study is considered not toxicologically relevant.			

Grouping	Line(s) of evidence	Species	Exposure weeks	Route of exposure	Effect dose	Observed effects (positive and negative)	Assessment of each line of evidence	Assessment of the integrated line of evidence	Modality
		Dog	1-year	Oral	>500 mg/kg bw/day	No effect	mouse, rabbit, rat) and different life stages in rat. Moreover, carcinogenicity in thyroid was not induced by the test substance in any study. In conclusion, glyphosate does not induce adversity based on T-mediated parameters investigated in the available in vivo studies. **RMS:** Thyroid weight was only affected in one 90-day dog study. However, no dose response was observed and no histopathological changes were found. In none of the other studies in dog, rat, mouse or rabbit an effect on thyroid weight was found.	No T-mediated adversity was observed following exposure to glyphosate.	
		Dog	1-year	Oral	>50000 ppm	No effect			
		Dog	1-year	Oral	>30000 ppm	No effect			
		Rat	10 weeks	Oral	>15000 pm	No effect			
		Rat	21 days (PND 22-42)	Oral	>1000 mg/kg bw/day	No effect			
		Rat	31 days (PND 23-53)	Oral	>1000 mg/kg bw/day	No effect			
		Dog	6 months	Oral	>300 mg/kg bw/day	No effect			
		Dog	1-year	Oral	>500 mg/kg bw/day	No effect			
		Dog	1-year	Oral	>1000 mg/kg bw/day	No effect			
		Rabbit	21 days	Dermal	>5000 mg/kg bw/day	No effect			
	Thyroid (histopathology)	~~Rat~~	~~90 days~~	~~Oral~~	~~>20000 ppm~~	~~No effect~~	Thyroid weight and thyroid histopathology were examined in 14 and 41 studies, respectively; including		
		Rat	90 days	Oral	>50000 ppm	No effect			
		Rat	90 days	Oral	>30000 ppm	No effect			
		Mouse	90 days	Oral	>50000 ppm	No effect			

Grouping	Line(s) of evidence	Species	Exposure weeks	Route of exposure	Effect dose	Observed effects (positive and negative)	Assessment of each line of evidence	Assessment of the integrated line of evidence	Modality
		Dog	90 days	Oral	>1000 mg/kg bw/day	No effect	subcabute, subchronic, and chronic exposure periods. A toxicologically relevant effect on either T-mediated parameter was not observed in any study considering four species (dog, mouse, rabbit, rat) and different life stages in rat. Moreover, carcinogenicity in thyroid was not induced by the test substance in any study. In conclusion, glyphosate does not induce adversity based on T-mediated parameters investigated in the available in vivo studies. **RMS:** It is noted that RMS removed the results from three studies (IDs 54, 70, 74), as RMS considered these studies to be unacceptable.		
		Dog	90 days	Oral	>10000 ppm	No effect			
		Dog	90 days	Oral	>40000 ppm	No effect			
		Dog	90 days	Oral	>50000 ppm	No effect			
		Dog	1-year	Oral	>500 mg/kg bw/day	No effect			
		Dog	1-year	Oral	>50000 ppm	No effect			
		Dog	1-year	Oral	>30000 ppm	No effect			
		Dog	1-year	Oral	>20000 ppm	No effect			
		Rat	2 years	Oral	>10000 ppm	No effect			
		Rat	2 years	Oral	>30000 ppm	No effect			
		Rat	2 years	Oral	>20000 ppm	No effect			
		Rat	2 years	Oral	>1000 mg/kg bw/day	No effect			
		Rat	2 years	Oral	>20000 ppm	No effect			
		Rat	2 years	Oral	>15000 ppm	No effect			
		Mouse	18 months	Oral	>10000 ppm	No effect			
		Mouse	18 months	Oral	>5000 ppm	No effect			
		Mouse	18 months	Oral	>40000 ppm	No effect			
		Rat	10 days prior to mating, continue until termination	Oral	>10000 ppm	No effect			
		Rat	21 days (PND 22-42)	Oral	>1000 mg/kg bw/day	No effect			

Grouping	Line(s) of evidence	Species	Exposure weeks	Route of exposure	Effect dose	Observed effects (positive and negative)	Assessment of each line of evidence	Assessment of the integrated line of evidence	Modality
		Rat	31 days (PND 23-53)	Oral	>1000 mg/kg bw/day	No effect	No treatment-related effects on thyroid histopathology were found in studies in the mouse, rat, rabbit or dog.		
		Rat	28 days	Oral	>20000 ppm	No effect			
		Rat	90 days	Oral	>1000 mg/kg bw/day	No effect			
		Rat	90 days	Oral	>20000 ppm	No effect			
		Rat	90 days	Oral	>20000 ppm	No effect			
		Rat	90 days	Oral	>20000 ppm	No effect			
		Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect			
		Dog	6 months	Oral	>300 mg/kg bw/day	No effect			
		Dog	1 year	Oral	>500 mg/kg bw/day	No effect			
		Dog	1 year	Oral	>1000 mg/kg bw/day	No effect			
		Rabbit	28 days	Dermal	>2000 mg/kg bw/day	No effect			
		Mouse	2 years	Oral	>1000 mg/kg bw/day	No effect			
		Mouse	2 years	Oral	>30000 ppm	No effect			
		~~Rat~~	~~Life-time, all 3 generations~~	~~Oral~~	~~>30 mg/kg bw/day~~	~~No effect~~			
		Rat	21 days (PN 0-21, exposure though milk)	Oral	>30 mg/kg bw/day	No effect			
		Mouse	90 days	Oral	>50000 ppm	No effect			
		~~Rat~~	~~F0 (M 20; F20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Oral~~	~~>3000 ppm~~	~~No effect~~			

Grouping	Line(s) of evidence	Species	Exposure weeks	Route of exposure	Effect dose	Observed effects (positive and negative)	Assessment of each line of evidence	Assessment of the integrated line of evidence	Modality
		Rat	90-92 days	Oral	>7500 ppm	No effect			
		Rat	F0: from GD6 to end of lactation; Offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts	Oral	>1.75 mg/kg bw/day	No effect			
		Rat	90 days	Oral	>7500 ppm	No effect			
Evidence of general toxicity	see tables below (appendix)	See table below (appendix)							

Assessment of the integrated lines of evidence and weight of evidence for T-mediated adversity and endocrine activity

Relevant data and Lines of Evidence (LoE) including detailed discussions of specific endpoints/parameters per study on potential T-mediated endocrine disrupting properties are included in Appendix E (attached to chapter 2.1.2). A summary and analysis of the results on adversity and activity based on a weight of evidence approach are provided in Table 3 and Table 4, respectively.

Table 3: WoE for T-mediated adversity

- Toxicologically relevant changes on thyroid weight were not observed in 14 repeated dose toxicity studies. These studies were performed in three species including subacute (rabbit: study ID 62; pubertal rat: study IDs 44, 45), subchronic (dog: study IDs 5 - 8, 57; rat: study ID 22) and chronic exposure periods (dog: study IDs 9 - 11, 58, 59).

- No relevant histopathological changes in thyroid were observed after subacute (rabbit: study ID 63; pubertal rat: study IDs 44, 45; rat: study ID 49), subchronic (dog: study IDs 5 – 8, 57; mouse: study IDs 4, 56, 73; rat: study IDs 1 – 3, 52 - 55, 76) and chronic (dog: study IDs 9 - 11, 58, 59; mouse: study IDs 19-21, 67, 68; rat: study IDs 12-18) exposure, as well as in a rat reproductive toxicity studies (study ID 26, 70, 74, 93). Therefore, a test substance induced hypertrophy or hyperplasia of follicular cells in thyroid, which could be linked to potential endocrine disruption, was not observed in four mammalian species after glyphosate exposure.

- Carcinogenicity in thyroid was not observed in five mouse (study IDs 19 - 21, 67, 68) and six rat (study IDs 12-18) studies after chronic glyphosate exposure. In addition, neoplasia in dog were not observed after chronic exposure (study IDs 9 - 11, 58, 59).

- No toxicologically relevant and consistent effects on parameters "sensitive to but not diagnostic of EATS", such as:
  - adrenal weight (44 studies) and histopathology (45 studies)
  - pituitary weight (20 studies) and histopathology (41 studies)
  - foetal and pup development, fertility and pregnancy parameters (in eleven and four prenatal developmental studies in rabbit and rat, respectively, as well as one one-generation, six two-generation and two three-generation studies in rat)
  - neurological development: brain weights and histopathology, functional observation battery

  were observed after subchronic, chronic as well as multi-generation toxicity studies.

- In 52 repeated dose toxicity studies in four species, i.e. dog, mouse, rabbit, rat no toxicologically relevant histopathological changes in liver, which can be associated with changes in thyroid, such as centrilobular hypertrophy, were observed after glyphosate exposure.

→ T-mediated adversity of glyphosate is not observed.

Table 4: WoE for T-mediated endocrine activity

- No relevant effects on mean serum T4 levels were observed in the male (study ID 45) and female (study ID 44) pubertal assay.

- TSH levels were analysed in the male (study ID 45) and female (study ID 44) pubertal assays as well as a published pilot study for an EOGRTS (study ID 93). No relevant changes on

hormone levels were observed within the pubertal assays. In the pilot study an increase in TSH was observed in F1 males only sacrificed after 6 weeks of exposure post weaning. Since no effect on TSH was observed after 13 weeks of post-weaning exposure as well as in the pubertal assays, covering the same life stage as the 6 week period of the pilot study, the observed TSH increase is considered not biologically relevant (for more detail please refer to the LoE).

- Results of the *in silico* modeling do not indicate thyroid receptor binding properties (for details refer to QSAR report (report no 110517-1, KCA 5.8.3-11)).

→ T-related endocrine activity of glyphosate is not observed.

Thyroid weight and thyroid histopathology were examined in 14 and 43 studies, respectively; including subcabute, subchronic, and chronic exposure periods. A toxicologically relevant effect on either T-mediated parameter was not observed in any study considering four species (dog, mouse, rabbit, rat) and different life stages in rat. Moreover, carcinogenicity in thyroid was not induced by the test substance in mouse and rat.

Additionally, *in silico* models do not provide any indication for thyroid receptor binding of glyphosate and no relevant effect on thyroid hormones (TSH, T4) was observed in *in vivo* studies (study IDs 44, 45, 93).

In conclusion, glyphosate does not induce T-mediated adversity and no indication for T-related endocrine activity was observed *in silico* and *in vivo*.

Note by RMS:
In table 3 above, the applicant discusses the weight of evidence for T-mediated adversity. It is noted that RMS concluded that the studies with IDs 54, 70, 74 were unacceptable.

Regarding the third bullet point, RMS notes the following:

In one of the carcinogenicity studies in rats (ID 17), historical control data were provided upon request, which showed that the incidence in mid and high dose males and females were outside these HCD.

In this study there was no progression to carcinomas and no effect on non-neoplastic precursors was observed. In fact, the thyroid does not appear to be a target organ for glyphosate in any of the repeated dose toxicity studies in rats.

Regarding the fourth bullet point, RMS notes the following regarding pituitary histopathology: In one the studies (ID 18) pituitary adenomas were observed in rats. Overall, RMS concluded: When considering the results from the available carcinogenicity studies in the rat together it is clear that pituitary adenomas are very common in rats. No progression to carcinomas was observed and no effect on concomitant non-neoplastic findings were observed. Therefore, it is concluded that glyphosate has no effect on pituitary adenomas. (see Vol. 1, section 2.6.5.1)

It is agreed that considering all available information, glyphosate does not induce T-mediated adversity or T-related endocrine activity.

Initial analysis of the evidence and identification of relevant scenario for the ED assessment of T-modality

Table 5: Selection of relevant scenario

Adversity based on T-mediated parameters	**Positive mechanistic OECD CF level 2/3 Test**	**Scenario**	**Next step of the assessment**	**Scenario selected**
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is not "**T-mediated**" adversity	**X**
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no **T-mediated endocrine activity** observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

MoA analysis for T-modality

Not applicable (according to scenario 1a in Table 5, selected based on the available data on glyphosate, a MoA analysis is not required).

Note by RMS:
Agreed that a Mode of Action analysis is not required.

Conclusion of the assessment of T-modality

Potential effects of glyphosate on the HPT axis were addressed in several repeat dose toxicity studies of subacute to chronic exposure also considering different life stages in rat (level 4 and 5 studies of the OECD conceptual framework) where thyroid weight and histopathology were analysed. Moreover, a male and female pubertal assay (level 4 studies of the OECD conceptual framework), where hormone levels (T4, TSH) in addition to thyroid weight and histology were investigated, were performed. Data from *in vitro* assays regarding potential T-related endocrine activity are not available but *in silico* investigations were performed.

The general profile of effects for thyroid-active compounds include decreased T4, increased TSH, increased thyroid weight and/or altered thyroid histopathology (follicular cell hypertrophy/hyperplasia with decreased amounts of colloid). Within the repeated dose toxicity studies, relevant and consistent effects on thyroid weights (14 studies) and thyroid histopathology (43 studies) were not observed in four mammalian species (dog, mouse, rabbit, rat). Moreover, there were no treatment-related effects on thyroid hormone levels (T4 and TSH) in a published pilot study for an EOGRTS and the female pubertal assay as well as in the male pubertal assay in the absence of overt toxicity. Furthermore, no indication

for thyroid receptor binding is deduced from *in silico* modelling. Therefore, it is concluded that glyphosate does not perturb or adversely influence the thyroid pathways in mammalian species. This conclusion is in line with the current Peer review of the pesticide risk assessment of the potential endocrine disrupting properties of glyphosate (EFSA Journal 2017;15(9):4979) as well as with the conclusion from EPA's WoE of the Endocrine Screening Program (EDSP) Tier l assays (US EPA, 2015 "EDSP Weight of Evidence Conclusions on the Tier 1 Screening Assays for the List 1 Chemicals").

Based on the requirements of the ECHA/EFSA ED Guidance, potential T-mediated adversity is sufficiently investigated, if the thyroid parameters foreseen to be investigated in the following studies have been measured and the results included in the dossier: OECD TG 407, 408, 409, 416, and 451-3.

T-mediated parameters, i.e. thyroid weight and/or histopathology, were addressed in several repeated dose toxicity studies conducted with glyphosate in dog, mouse, rabbit, and rat including different life stages (study IDs 5-11, 22, 44, 45, 57 - 59, 62 and 1-21, 26, 44, 45, 49, 52 - 59, 63, 67, 68, 70, 73, 74, 76, 93 for weight and histopathology, respectively). T-mediated potential endocrine activity, i.e. thyroid hormone levels were not investigated in the available OECD TG studies since those were conducted according to former OECD TG versions. However, thyroid hormone levels (i.e. TSH and T4) were addressed in the female and male pubertal assay (study IDs 44, 45), corresponding to subacute exposure periods of the animals as well as in a published pilot study for an EOGRTS (study ID 93), where immature rats were exposed through pubertal development (subacute exposure period) and in adulthood (study ID 93 only). Since thyroid weights and histopathology were investigated in several RDT studies and no T-mediated adversity was observed, the dataset on potential T-mediated adversity is considered sufficient based on the requirements of ECHA/EFSA ED Guidance.

According to the ED criteria laid down in Regulation (EU) 2018/605, endocrine mediated adversity as well as activity and the biological link between those two must be apparent to identify a substance as an endocrine disruptor. Since glyphosate does not induce T-mediated adversity, which is considered sufficiently investigated according to ECHA/EFSA ED Guidance and no indication for T-related endocrine activity was observed in *in silico* and *in vivo*, it is concluded that the ED criteria with regard to T-modality in mammalian species are not fulfilled for glyphosate (Scenario 1a, Table 5).

Assessment and conclusion by RMS:
It is agreed with overall conclusion of the applicant regarding the T-modality. RMS considers the T-modality to be sufficiently investigated and no adversity was observed.
Based on the available data on glyphosate, the ED criteria for the T-modality are not met.

2.10.2.2 ED assessment for EAS-modalities

Have EAS-mediated parameters been sufficiently investigated?

EAS-modalities	Sufficiently investigated
EAS-mediated adversity (i.e. EAS-mediated parameters)	Parameters for EAS-mediated adversity were investigated in repeated dose toxicity studies including six two-generation (study IDs 22 - 27), four one-generation (study IDs 69, 75, 93, 94) and two three-generation (study IDs 70, 74) reproductive toxicity studies. One two-Generation study (study ID 22) was performed according to the current version of OECD TG 416 (2001) investigating all relevant EAS-mediated parameters as referenced in the ECHA/EFSA ED Guidance (Table 14). A second two-Generation study (study ID 23) was performed similar to the current version of OECD TG 416 (2001) except for the following parameters: anogenital distance (not assessed since sex ratio and sexual maturation was not affected), pre-implantation loss, specific pup development parameters (investigations restricted to body weight, vaginal opening and preputial separation; no FOB). Therefore, EAS-mediated adversity of glyphosate is considered sufficiently investigated according to ECHA/EFSA ED Guidance.

EAS-modalities	Sufficiently investigated
EAS-related (i.e. *in vivo* and *in vitro* mechanistic data)	E: Potential E-related endocrine activity was addressed with the Uterotrophic Assay (study ID 42) which is the required study type for sufficient investigation of E-related endocrine activity according to the ECHA/EFSA ED Guidance (chapter 3.4.2). In addition, two *in vitro* assays (study ID 37: OPPTS 890.1250 (2009), study ID 38: OECD TG 455) were performed. Thus, E-related endocrine activity is sufficiently investigated for glyphosate. A: Potential A-related endocrine activity was addressed with the Hershberger Assay (study ID 43) which is the required study type to sufficiently investigate A-related endocrine activity according to the ECHA/EFSA ED Guidance (chapter 3.4.2). In addition, an AR Binding assay (study ID 39: OPPTS 890.1150 (2009)) was performed *in vitro*. Thus, A-related endocrine activity is sufficiently investigated for glyphosate. S: Potential S-related endocrine activity was addressed with the Aromatase Assay (study ID 40: OPPTS 890.1200) and the H295R Steroidogenesis Assay (study ID 41: OECD TG 456) which are the required study types for sufficient investigation of S-related endocrine activity according to the ECHA/EFSA ED Guidance (chapter 3.4.3). Additionally, results for E- and A-modality, which are considered sufficiently investigated, are considered. Thus, S-related endocrine activity is sufficiently investigated for glyphosate.
Overall conclusion on EAS-modalities	Yes, EAS-mediated adversity as well as EAS-related activity is considered sufficiently investigated based on the available *in vitro* and *in vivo* studies as described above.

Note by RMS:
Regarding the reproductive toxicity studies mentioned in the table above:

Indeed there is one 2-generation study available which was conducted in full compliance with the 2001 version of OECD guideline 416 (study ID 22). It is noted that RMS concluded that the multigeneration studies with IDs 70, 74 and 75 were unacceptable.

Regarding the E-modality, indeed an Uterotrophic assay is available, and in addition two *in vitro* studies. RMS does note however, that the *in vitro* study regarding estrogen receptor transcriptional activation (study ID 38) was considered unacceptable.

RMS has no comments regarding the studies indicated in the table above for the A- and S-modalities.

Lines of evidence for adverse effects and endocrine activity related to EAS-modalities
Lines of Evidence (LoE) for T-modality, EAS-modalities as well as for parameters "sensitive to, but not diagnostic of EATS", target organ toxicity and general toxicity are included in the attached excel file (Appendix E Table according to ECHA/EFSA ED Guidance). Please refer to chapter 2.1.2.

Note by RMS:

RMS has included the table with lines of evidence for the EAS-modality below, and adjusted it where necessary. In the Appendix E document, RMS has checked and adjusted the information where necessary (in the tab 'data' and 'data summary').

In the last two columns, the argumentations of the applicants are still included, followed by comments by the RMS.

It is noted that three additional studies from public literature are available, which were submitted at a later time point. These studies (B.6.8.3.17, B.6.8.3.18, B.6.8.3.19) were not included in appendix E by the applicant. ***The applicant is requested to add these studies to appendix E.***

In the study described in B.6.8.3.17, the effect of glyphosate was investigated in an *in vivo* study with C57BL/6 J female mice (PND 42). Body weight, cyclicity, follicle number, circulating ovarian steroid hormone levels and ovarian intracellular signaling parameters (representative for folliculogenesis and steroidogenesis) were tested in all animals during and after the dosing period. No difference between the treated and control animals were seen for any parameter following the 5 or 10 week exposure period. RMS concluded this study to be reliable with restrictions.
In the study described in section B.6.8.3.18, glyphosate and the positive control E2 induced Ishikawa endometrial cancer cell migration and invasion, as well as the downregulation of E-cadherin mRNA expression. Since these observations were reversed by the addition of fulvestrant, the results indicate that these processes are estrogen receptor-dependent. The results also indicate that glyphosate and E2 caused epithelial-mesenchymal-transition-related changes, being an indicator for initiation of metastasis. RMS concluded this study to be reliable.
In the study described in section B.6.8.3.19, the effects of glyphosate on testosterone secretion and the role of endoplasmic reticulum stress in the process were investigated in TM3 cells *in vitro*. Results showed that exposure to glyphosate at concentrations below 200 mg/L had no effect on cell viability, while glyphosate at concentrations above 0.5 mg/L could inhibit the testosterone secretion in TM3 cells. Treatment of TM3 cells with glyphosate at 5 mg/L not only reduced the protein levels of testosterone synthase StAR and CYP17A1 but also inhibited testosterone secretion. RMS concluded this study to be reliable with restrictions.
The results from these two *in vitro* studies do not match the results found in *in vivo* studies. The *in vivo* study described in B.6.8.3.17 was negative and supports the overall conclusions (see 2.2.5 below).

It is noted that the tables including results for endpoints 'sensitive to but not diagnostic of' and general toxicity are included below in an appendix.

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Route of administration	Lowest Effect dose	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
n.a.	in silico	Estrogen receptor	n.a.	n.a.	n.a.	n.a.	No effect	Considering the results of the predictions in a weight of evidence approach, no indication for an estrogenic activity is observed. The overall weight of the CERAPP predictions is considered highest due a) the consensus approach and b) the extensive training and validation set derived within the CERAPP project. The CERAPP consensus predictions coincide well with the CERAPP potency for binding derived from Literature (https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID1024122#bioactivity-toxcast-models). Furthermore, glyphosate is part of the training set of ER binding tests showing negative results. The results of inconclusive predictions (Danish QSAR DB) are considered less relevant because predictions are out of the applicability domain of the model. Otherwise, all other models also show no indication for an estrogenic activity potential (for a detailed description of the results please refer to the QSAR report).	No indication for E-related endocrine activity of the test substance is deduced from available in silico models. RMS: Agreed	**In conclusion, no EAS-related endocrine activity is deduced for glyphosate based on *in silico*, *in vitro* as well as *in vivo* mechanistic data.**	**E**
37	In vitro mechanistic	Estrogen receptor	Rat, Sprague-Dawley, cytosol from uterus	16-20 Hours	Uptake from the medium (in vitro)	> 10-03 M	No effect	Glyphosate demonstrated no evidence for ER binding in the estrogen receptor binding (rat uterine cytosol) screening assay since the test substance was identified as "non-interacting" in three valid independent runs.	Based on the results of 6 in vitro tests, including 2 Guideline studies (study IDs 37, 38), glyphosate does not show any relevant estrogenic activity.		
38	In vitro mechanistic	Estrogen receptor	Human cell line (HeLa-9903)	24 hours	Uptake from the medium (in vitro)	> 10-03 M	No effect	Based on the results of two valid transcriptional activation assays, it can be concluded that glyphosate is not an agonist of human estrogen receptor alpha (hERα) over the concentration range (maximum concentration 10-3 M) tested in the HeLa-9903 model system.			

84	in vitro mechanistic	Estrogen receptor	Human	Multiple exposure times (hours)	Uptake from the medium (in vitro)	>2500 µg a.i./L	No effect	Increased cell proliferation was observed in MCF-7 and T47D cells (but not in hormone-independent MDA-MB-231 cells) at 10,000 µg/L to 1,000,000 µg/L. Glyphosate stimulated ERE-mediated transcription of the luciferase reporter gene starting at a concentration of 1,000 µg/L. The analysis of gene ontology confirms that genes having their expression altered by treatment of MCF-7 cells with glyphosate were involved in cell cycle regulation, stimulation by steroid hormones and cell death through apoptosis. ONIOM binding energy assessment implies that binding of glyphosate to the ER is weak and unstable, suggesting that glyphosate is unlikely to bind to ERα. This study has demonstrated that glyphosate activates ERα through a ligand-independent pathway only at high concentrations that are not encountered at typical exposure levels. Glyphosate was reported to induce ERTA only at high concentrations (10,000 and 20,000 µg/L or 59 and 118 µM) and induction was concluded to result from an unknown ligand-independent ER mechanism. However, this result is inconsistent with the EDSP Tier 1 ERTA assay tested up to 1000 µM glyphosate.	RMS: Agreed, but notes that study ID 38 is not an acceptable study		
85	in vitro mechanistic	Estrogen receptor		24 hours	Uptake from the medium (in vitro)	1,00E-06 µM	Change	A 5 to 13-fold relative induction to controls for ER-driven transcriptional activity in T47D cells was described at the levels by glyphosate ranging from 10^-6 to 10^-12 M. Induction was blocked by the addition of 10 nM of the ER antagonist ICI 182780. In addition, proliferation in T47D cells after 5 d of exposure was reported to be 40% as measured by the MTT assay as an indirect assessment of cell number whereas cell number in proliferations assays is best assessed by directly measuring cell number with flow cytometry. The increase in ER-driven transcriptional activity is highly inconsistent with the Uterotrophic Assay results and published studies. The current study reports that glyphosate has greater estrogenic effect than a maximally inducing dose of 17β-estradiol, which is a highly questionable result based on what is known about structure and activity information for glyphosate. This finding led Mesnage et al. (2017; study ID 84) to conclude that the results of the current study are not biologically plausible and speculate that this result reflected an estrogenic contaminant in the assay. Based on this rationale, the reported effect is considered not biologically relevant and no indication for E-related endocrine activity is deduced from this study.			

89	In vitro mechanistic	Estrogen receptor	Human in vitro	24 hours	Uptake from the medium (in vitro)	>10 µM	No effect	Glyphosate did not show any estrogenic activity at a concentration of 10 µM in two cell lines or via the two human estrogen receptor (hER) subtypes, hERα and hERβ. Based on the OECD 455 guideline for the BG1 assay, relative activity for the test substance that is <20% of the response of a maximally inducing concentration of E2 is considered to be negative. Therefore, glyphosate is conlcluded to have no ERα, ERβ agonistic activities, in vitro. It needs to be noted that according to the published Corrigendum, the cell lines used were a variant of human breast cancer cell line MCF7. Thus, the recombinant cell lines are VM7Luc4E2 and VM7ERβc9.			
87	[Not in list]	[Not in list]	Mouse	14 hours	Uptake from the medium (in vitro)	500 µM	Change	In vitro intracellular changes in Kunming mice oocytes were evaluated after being cultured in medium supplemented with 200 µM glyphosate. Findings included: decreased germinal vesicle breakdown, decreased first polar body extrusion, increased mRNA expression of anti-oxidant enzyme-related genes, abnormal spindle morphology, increased DNA double strand breaks, aggregated mitochondria, decreased mitochondrial membrane potential, increased protein expression of apoptosis factors, increased mRNA expression of apoptosis related genes and decreased autophagy-related genes. No dose-response could be determined as only one concentration was tested, far in excess of that considered biologically relevant. Whilst some evaluations were conducted on oocytes harvested from a wider data set of 24 mice (protein expression levels of apoptosis factors by Western blot analysis), a number of the assessments were conducted on oocytes from just 12 mice (mRNA expression of oxidative stress-related, apoptosis-related and autophagy-related genes) or 6 mice (mitochondrial staining, measurement of mitochondrial membrane potential). This narrow source of oocytes limits the robustness of certain conclusions. Furthermore, there are insufficient details reported in the methods to establish whether mice were of the same age before oocyte harvesting or the purity of the glyphosate tested. **Based on the rationale provided and also considering that the assessed endpoints are not considered EATS-related, no indication for endocrine-related activity is deduced from this in vitro assay**.			
42	In vivo mechanistic	Uterus weight (UT assay)	Rat	3 days	Oral	> 1000 mg/kg bw/day	No effect	Mean uterine weights (wet and blotted, including luminal fluid) were not affected in the Uterotrophic Assay (OECD TG 440; study ID 42).	**No EAS-related endocrine activity was observed in vivo, based on the results of an uterotrophic assay as**		**E, A**

80	In vivo mechanistic	Estradiol level	Rat	5 weeks	Oral	>500 mg/kg bw/day	No effect		**well as in vivo hormone level measurements of published literature studies.** RMS: Agreed		
93	In vivo mechanistic	Estradiol level	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	<1.75 mg/kg bw/day	No effect	F1: 17β-estradiol (E2). No statistically relevant effect observed in males (effect in females not possible to evaluate statistically due to insufficient sample size considering the different stages of estrous cycle).			
80	In vivo mechanistic	Progesterone level	Rat	5 weeks	Oral	>500 mg/kg bw/day	No effect				
93	In vivo mechanistic	Luteinizing Hormone (LH) level	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	<1.75 mg/kg bw/day	No effect				
93	In vivo mechanistic	Follicle Stimulating Hormone (FSH) level	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts,	Oral	<1.75 mg/kg bw/day	No effect				

				respectively							
93	In vivo mechanistic	Prolactin	Rat	F0: from GD 6 to end of lactation; Offsping: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	<1.75 mg/kg bw/day	No effect				
93	In vivo mechanistic	Other hormones	Rat	F0: from GD 6 to end of lactation; Offsping: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	<1.75 mg/kg bw/day	No effect	Further hormones: sex hormone binding globuline (SHBG), growth hormone (GH), adrenocorticotropic hormone (ACTH), brain-derived neurotrophic factor (BDNF) levels were not affected in both F1 exposure groups.			
n.a.	in silico	Androgen receptor	n.a.	n.a.	n.a.	n.a.	No effect	Considering the results of the predictions as provided above in a weight of evidence, glyphosate is considered to have no potential for androgenic activity. The overall weight of the CoMPARA predictions is considered highest due a) the consensus approach and b) the extensive training and validation set derived within the COMPARA project (https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID1024122#bioactivity-toxcast-models). Furthermore, in the Danish (Q)SAR Database Glyphosate was included in the training set and tested negative for antagonistic effect on the human androgen receptor in vitro (for a detailed description of the results please refer to the QSAR report).	No indication for A-related endocrine activity of the test substance is deduced from available in silico models. RMS: Agreed		**A**

39	In vitro mechanistic	Androgen receptor	Rat, Sprague-Dawley, cytosol from prostate	16-20 hours	Uptake from the medium (in vitro)	> 10^-03 M	No effect	Glyphosate demonstrated no evidence for AR binding in the androgen receptor binding (rat prostate cytosol) screening assay since the test substance was identified as "non-binder" in three valid independent runs.	Based on the results of the available data, no androgenic activity was observed in vitro. RMS: Agreed		**A**
86	In vitro mechanistic	Cellular proliferation	Mouse	24 hours	Uptake from the medium (in vitro)	>10000 ppm	No effect	In this study the effect of glyphosate on murine TM4 Sertoli cells was investigated in vitro. The endpoints were cytotoxicity, glutathione transferase activity and lipid accumulation. Glyphosate was found to have no impact on cell viability after 24 hours of exposure at concentrations ranging from 10 ppm to 10,000 ppm. Glyphosate reduced succinate dehydrogenase to some extent over the entire concentration range from 10 (approx. 85 % of control) to 10,000 ppm (approx.75 % of control) with no dose-effect relationship and was found to have no impact on glutathione transferase activity. Exposure of TM4 cells to glyphosate for 24 hours at 2,500 or 5,000 ppm induces an increase in cytoplasmic lipid droplets. These concentrations are far beyond what is physiologically feasible in vivo.			

83	In vitro mechanistic	[Not in list]	Rat	Multiple exposure times (hours)	Uptake from the medium (in vitro)		Change	In vitro exposure of Sertoli cells to glyphosate was reported to alter Sertolli cell junction barrier permeability and to decrease testosterone-stimulated TER. Further, a redistribution of claudin11 was observed. However, since this is an isolated finding in a single in vitro study which cannot easily be transferred to the in vivo situation and since and no effects on male fertility (e.g. sperm parameters) were observed in the available multi-generation studies, the result of this in vitro study is considered not biologically relevant (for further details please refer to the paragraph below). (Glyphosate did not modify the expression of the androgen receptor or intercellular junction proteins (claudin11, occludin and ZO-1). Further, intracellular signalling via P-p38-MAPK and P-ERK1/2 pathways were not affected. Lactate production, glucose uptake, GLUT1, FA oxidation, or FAT/CD36 and CPT1 expression was unaffected by glyphosate. Thus, the conducted molecular and cell biological investigations indicate that glyphosate does not influence testicular function due to disturbances of nutritional function or metabolism in Sertolli cells. In vitro exposure to glyphosate at non-cytotoxic concentrations (10 - 100 ppm) altered Sertoli cell junction barrier permeability and decreased testosterone-stimulated TER. Further, redistribution of claudin11 at the zone of contact between cells was detected after glyphosate stimulation. If the effects observed on Sertolli cell junction barrier permeability may contribute to a postulated effect on male reproductive function cannot be finally assessed. In general, an evaluation of such highly specific cell biological endpoints for hazard assessment is rather difficult as they cannot be transferred easily to intact organisms. As the biological in vivo relevance of such “isolated” in vitro/ex vivo findings is not validated for intact organisms, an interpretation of the obtained results on the redistribution of one special protein and cell junction barrier permeability is difficult and not considered sufficiently conclusive. In addition, when considering that no effects on male fertility were observed in the available multi-generation studies, the result of this single in vitro study is considered not biologically relevant.)			
43	In vivo mechanistic	Cowpers glands weight (Hershberger)	Rat	10 days	Oral	> 1000 mg/kg bw/day	No effect		No A-related effect on Cowpers glands weight was observed. RMS: Agreed		**A**
43	EATS-mediated	Coagulating gland weight	Rat	10 days	Oral	> 1000 mg/kg bw/day	No effect		No A-related effect on coagulating gland weight was observed. RMS: Agreed		
43	In vivo mechanistic	Glans penis weight	Rat	10 days	Oral	> 1000 mg/kg bw/day	No effect		No A-related effect on glans penis weight was observed.		

		(Hershberger)							RMS: Agreed		
43	In vivo mechanistic	LABC weight (Hershberger)	Rat	10 days	Oral	> 1000 mg/kg bw/day	No effect		No A-related effect on glans penis weight was observed. RMS: Agreed		
43	In vivo mechanistic	Prostate weight (Hershberger)	Rat	10 days	Oral	> 1000 mg/kg bw/day	No effect		No A-related effect on prostate weight was observed. RMS: Agreed		
43	In vivo mechanistic	Seminal vesicles weight (Hershberger)	Rat	10 days	Oral	> 1000 mg/kg bw/day	No effect		No A-related effect on seminal vesicles weight was observed. RMS: Agreed		
45	In vivo mechanistic	Testosterone level	Rat	31 days (PND 23-53)	Oral	>1000 mg/kg bw/day	No effect	Mean serum hormone level was not statistically significantly decreased at 1000 mg/kg bw/day; a dose showing overt toxicity (1 mortality, rales, body weight gain decrease >10%) which confounds interpretation of reproductive system-related endpoints in the pubertal assay. No dose-response was observed and no histological changes were observed in testes. Therefore, the decrease is considered not treatment-related.	Relevant and consistent treatment-related changes in serum testosterone levels in vivo were not observed in rat. A decrease in hormone testosterone level was observed in 35 day old male mouse offspring after exposure in utero. However, since no dose-response was observed and testosterone levels were not affected in 8 months old male mice of the same study, no indication of EAS-relates endocrine activity is derived. RMS: Agreed		**E, A, S**
80	In vivo mechanistic	Testosterone level	Rat	5 weeks		>500 mg/kg bw/day	No effect	Although there was a trend towards decreased serum concentrations with dose, no statistically significant changes were noted.			
91	In vivo mechanistic	Testosterone level	Rat	14 days	Oral	>25 mg/kg bw/day	No effect	Intra-testicular testosterone level was investigated.			
93	In vivo mechanistic	Testosterone level	Rat	F0: from GD 6 to end of lactation; Offsping: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	<1.75 mg/kg bw/day	No effect	Total testosterone levels in dams were not affected.			

93	In vivo mechanistic	Testosterone level	Rat	F0: from GD 6 to end of lactation; Offsping: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	<1.75 mg/kg bw/day	No effect	F1: Serum concentration of free (fT) and total testosterone (TT), 5α-dihydrotestosterone (DHT) were analysed in both cohorts (6 and 13 weeks). No statistically significant differences in serum TT, fT and DHT concentrations were observed in males or females belonging to both cohorts. A non-statistically significant increase in TT was observed in females of both cohorts only and fT was decreased after 6 weeks but not 13 weeks of exposure.			
94	In vivo mechanistic	Testosterone level	Mouse	Dams: Day of vaginal plug detection (embryonic day 10.5) to 20 days post-partum Offspring termination: PND 5, 20, 35 and 8 months old animals	Oral	0,5 mg/kg bw/day	**Decrease**	Serum testosterone level was statistically significantly decreased in the low and high dose group in 35 day old males. However, no dose-response was observed. No significant effect was observed in 8 months old mice.			
n.a.	in silico	Steroidogenesis	n.a.	n.a.	n.a.	n.a.	No effect	There are three results available for steroid receptors: glucocorticoid receptor (GR), glucocorticoid receptor antagonism, and mineralocorticoid receptor (MR). No activity is predicted for these receptors by the molecular docking method (Endocrine Disruptome).	No indication for S-related endocrine activity of the test substance is deduced from available in silico models.		**S**
41	In vitro mechanistic	Steroidogenesis (genes/enzyme changes) (in vitro)	Human cell line (H295R)	48 hours	Uptake from the medium (in vitro)	> 10^-04 M	No effect	Glyphosate did not alter 17ß-estradiol and testosterone production in the H295R steroidogenesis assay.	The observed increase in progesterone as well as decreases in in vitro estradiol levels, observed in single published non-TG		

81	In vitro mechanistic	Testosterone synthesis	Mouse	4 hours	Uptake from the medium (in vitro)	>600 µM	No effect	Forgacs et al. (2012) evaluated the effect of 4 h exposures of glyphosate on testosterone production in BLTK1 murine Leydig cells in the presence and absence of an inducing dose of recombinant human chorionic gonadotropin (rhCG). Glyphosate at the maximum concentration of 300 µM did not alter rhCG induced testosterone concentrations in BLTK1 murine Leydig cells. Moreover, basal testosterone levels were not altered at a maximum concentration of 600 µM.	studies, showed no dose-response. Based on this and on the fact that no effect on estradiol level was observed in an OECD TG 456 steroidogenesis assay, the non-dose-related effects in non-TG studies published in scientific literature provide no conclusive indication on S-related endocrine activity of glyphosate. Thus, it is concluded that the results of two in vitro guideline tests as well as six published study addressing steroid hormone synthesis, do not show any relevant effect of glyphosate on steroidogenesis including aromatase. RMS: Agreed		
82	In vitro mechanistic	Estradiol level (in vitro)	Swine	48 hours	Uptake from the medium (in vitro)	0,2 µM	**Decrease**	17-ß-estradiol (E2) secretion was statistically significantly inhibited ($p < 0.05$) at all tested concentrations but without a concentration-response relationship in swine granulosa cells.			
88	in vitro mechanistic	Estradiol level (in vitro)	Cow	24-48 hours	Uptake from the medium (in vitro)	5 mg/L	**Decrease**	In the presence of FSH only, glyphosate had no effect on estradiol production. In the presence of FSH and IGF1, estradiol production was reduced at 5 µg/mL only, but not at any other dose in granulosa cells.			
82	In vitro mechanistic	Progesterone level (in vitro)	Swine	48 hours	Uptake from the medium (in vitro)	0,2 µM	**Increase**	Progesteron (P4) secretion was statistically significantly increased ($p < 0.05$) at all tested concentrations but without a concentration-response relationship in swine granulosa cells.			
88	In vitro mechanistic	Progesterone level (in vitro)	Cow	24-48 hours	Uptake from the medium (in vitro)	>5 mg/L	No effect	Progesterone production was neither affected in granulosa nor in theca cells.			
88	In vitro mechanistic	Androstenedione (in vitro)	Cow	24-48 hours	Uptake from the medium (in vitro)	>5 mg/L	No effect	Glyphosate at 5 µg/mL had no effect on the theca cell (TC) production of androstenedione.			
82	In vitro mechanistic	Cellular proliferation	Swine	48 hours	Uptake from the medium (in vitro)	0,2 µM	**Decrease**	Glyphosate statistically significantly decreased cell proliferation ($p < 0.001$) as evaluated by BrdU incorporation and cell viability ($p < 0.05$) as measured by ATP production without a concentration-response relationship in swine granulosa cells.			
88	in vitro mechanistic	Cellular proliferation	Cow	24-48 hours	Uptake from the medium (in vitro)	0,5 mg/L	**Change**	Statistically significant effects have been observed at 0.5 and 5 µg/mL on cell proliferation in FSH/IGF1 stimulated granulosa cells (In the presence of FSH only, glyphosate had no effect on granulosa cell (GC) viability. In the presence of FSH and IGF1, glyphosate reduced GC proliferation without a dose-response at 0.5 and 5 µg/mL but not at lower test concentrations. Without FSH or IGF1, 1.7 µg/mL of glyphosate slightly increased GC proliferation in response to serum (≤11 %).) However, no effect on theca cell proliferation was observed.			
40	In vitro mechanistic	CYP19	Human (CYP19 (aromatase) and P450 reductase Supersomes TM)	15 minutes	Uptake from the medium (in vitro)	> 10^-03 M	No effect	Based on 3 independent assay runs, glyphosate is classified as a "non-inhibitor" of aromatase activity in the human recombinant aromatase assay.			

88	in vitro mechanistic	CYP19	Cow	24-48 hours	Uptake from the medium (in vitro)	>5 mg/L	No effect	The combined IGF1 plus FSH treatment increased (P<0.05) CYP19A1 and CYP11A1 mRNA abundance by threefold and twofold, respectively, above untreated control GC. Glyphosate (5µg/mL) had no significant effect on CYP19A1 or CYP11A1 mRNA in GC co-treated with FSH and IGF1.			
90	In vitro mechanistic	CYP19	Human	24 hours	Uptake from the medium (in vitro)	>2000 ppm	No effect	Glyphosate did not significantly inhibit aromatase activity at non-cytotoxic concentrations (up to approximately 2000 ppm [mg/L]).			
91	in vivo mechanistic	Steroidogenesis (genes/enzyme changes)	Rat	14 days	Oral	>25 mg/kg bw/day	No effect	The Leydig cell-specific steroidogenesis factors CYP11A1 and STAR were both expressed at comparative levels between the glyphosate treated animals and the controls. Also no difference in expression and distribution was noted between glyphosate treated groups and controls for the steroidogenic enzyme HSD3B1 and the germ cell-specific factor DDX4.			
94	in vivo mechanistic	Steroidogenesis (genes/enzyme changes)	Mouse	Dams: Day of vaginal plug detection (embryonic day 10.5) to 20 days post-partum Offspring termination: PND 5, 20, 35 and 8 months old animals	Oral	>50 mg/kg bw/day	No effect	Aromatase and Cyp11A1 mRNA levels were not affected.			
22	EATS-mediated	Age at Vaginal opening	Rat	10 weeks	Oral	>15000 ppm	No effect		No EAS-mediated effects on the age at vaginal opening were observed in three two-generation studies, a dose-reange finding study for an EOGRTS as well as in a female pubertal assay in rat. **In conclusion, EAS-mediated adversity with regard to vaginal**	**Under consideration of all available studies in four species up to chronic exposure period, adversity based on EAS-**	**EAS**
23	EATS-mediated	Age at Vaginal opening	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
26	EATS-mediated	Age at Vaginal opening	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				

44	EATS-mediated	Age at Vaginal opening	Rat	21 days (PND 22-42)	Oral	> 1000 mg/kg bw/day	No effect		**opening is not observed.** **RMS:** agreed	**mediated parameters is not observed. In conclusion, glyphosate does not induce EAS-mediated adversity.**	
93	EATS-mediated	Age at Vaginal opening	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect				
44	EATS-mediated	Age at first estrus (female pubertal assay)	Rat	21 days (PND 22-42)	Oral	> 1000 mg/kg bw/day	No effect		No EAS-related endocrine activity on the age at first estrus was observed in a female pubertal assay in rat as well as in a dose-range finding study for an EOGRTS. **RMS:** agreed		
93	EATS-mediated	Age at first estrus	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Female offspring in the control- and glyphosate-treated groups presented the FE within 6 days from the VO. (The female rats belonging to the developmental cohort (8F/group) were also monitored for the time to first estrous (FE), defined as the first day on which only cornified epithelial cells were observed on a vaginal smear, determined by vaginal cytology for 14 consecutive days, starting 3 days after vaginal opening was observed.)			
22	EATS-mediated	Estrus cyclicity	Rat	10 weeks	Oral	>15000 ppm	No effect		No relevant effect on estrous cyclicity was observed. The increased estrous cycle length observed in 1/8 studies (study ID 78) is attributed to general systemic toxicity		

23	EATS-mediated	Estrus cyclicity	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect		(reduced body weight gain and diarrhea) and a dose exceeding the current applicable limit dose by a factor of three. Moreover, none of the other 7/8 studies (study IDs 22 – 24, 26, 79) including four two-generation studies did show any effects on fertility. In conclusion, no EAS-mediated adversity on estrous cyclicity is observed. **RMS:** only in one of the studies an increased cycle length was observed, however at a very high dose level exceeding the MTD. In 7 other studies no effects were seen. Overall, it is concluded that there is no EAS-mediated adversity on estrous cyclicity.		
24	EATS-mediated	Estrus cyclicity	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
26	EATS-mediated	Estrus cyclicity	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				
44	EATS-mediated	Estrus cyclicity	Rat	21 days (PND 22-42)	Oral	> 1000 mg/kg bw/day	No effect				
78	EATS-mediated	Estrus cyclicity	Rat	90 days	Oral	50000 ppm	**Increase**	Increased estrous cycle length was observed at 50000 ppm which is equivalent to 3393 mg/kg bw/day and thus, more than three times the limit dose of 1000 mg/kg bw/day. In addition general systemic toxicity was observed at this dose level (such as reduced body weight gain compared to control and diarrhea in the first 50 study days).			
79	EATS-mediated	Estrus cyclicity	Mouse	90 days	Oral	>50000 ppm	No effect				
93	EATS-mediated	Estrus cyclicity	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect				

1	EATS-mediated	Ovary histopathology	Rat	90 days	Oral	>20000 ppm	No effect		Relevant effects on ovary weight were not observed in dog (8 studies), rabbit (2 studies), rat (18 studies), and mouse (6 studies). Moreover, no relevant effects with regard to histopathology were observed in dog (10 studies), rabbit (2 studies), rat (27 studies), and mouse (8 studies) after subchronic and chronic exposure as well as exposure over different life stages. **In conclusion, EAS-mediated adversity with regard to effects on ovaries is not observed.** **RMS:** It is noted that RMS removed one study from the results on ovary histopathology (study ID 74, rat) as this study was considered unacceptable. In the available and acceptable studies in mouse, rat, rabbit and dog no effect on ovarian histopathology was found.		
2	EATS-mediated	Ovary histopathology	Rat	90 days	Oral	>50000 ppm	No effect				
3	EATS-mediated	Ovary histopathology	Rat	90 days	Oral	>30000 ppm	No effect				
4	EATS-mediated	Ovary histopathology	Mouse	90 days	Oral	>50000 ppm	No effect				
5	EATS-mediated	Ovary histopathology	Dog	90 days	Oral	>1000 mg/kg bw/day	No effect				
6	EATS-mediated	Ovary histopathology	Dog	90 days	Oral	>10000 ppm	No effect				
7	EATS-mediated	Ovary histopathology	Dog	90 days	Oral	>40000 ppm	No effect				
8	EATS-mediated	Ovary histopathology	Dog	90 days	Oral	>50000 ppm	No effect				
9	EATS-mediated	Ovary histopathology	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
10	EATS-mediated	Ovary histopathology	Dog	1 year	Oral	>50000 ppm	No effect				
11	EATS-mediated	Ovary histopathology	Dog	1 year	Oral	>30000 ppm	No effect				
12	EATS-mediated	Ovary histopathology	Rat	1 year	Oral	>20000 ppm	No effect				
13	EATS-mediated	Ovary histopathology	Rat	2 years	Oral	>10000 ppm	No effect				
14	EATS-mediated	Ovary histopathology	Rat	24 months	Oral	>30000 ppm	No effect				

15	EATS-mediated	Ovary histopathology	Rat	2 years	Oral	>20000 ppm	No effect				
16	EATS-mediated	Ovary histopathology	Rat	2 years	Oral	>1000 mg/kg bw/day	No effect				
17	EATS-mediated	Ovary histopathology	Rat	2 years	Oral	>20000 ppm	No effect				
18	EATS-mediated	Ovary histopathology	Rat	2 years	Oral	>15000 ppm	No effect				
19	EATS-mediated	Ovary histopathology	Mouse	18 months	Oral	>10000 ppm	No effect				
20	EATS-mediated	Ovary histopathology	Mouse	18 months	Oral	>5000 ppm	No effect				
21	EATS-mediated	Ovary histopathology	Mouse	18 months	Oral	>40000 ppm	No effect				
22	EATS-mediated	Ovary histopathology	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Ovary histopathology	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Ovary histopathology	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
25	EATS-mediated	Ovary histopathology	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to	Oral	>10000 ppm	No effect				

				weaning of F2							
26	EATS-mediated	Ovary histopathology	Rat	10 weeks prior to mating, continued until termination	Oral	>10000 ppm	No effect				
27	EATS-mediated	Ovary histopathology	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				
44	EATS-mediated	Ovary histopathology	Rat	21 days (PND 22-42)	Oral	> 1000 mg/kg bw/day	No effect				
49	EATS-mediated	Ovary histopathology	Rat	28 days	Oral	>20000 ppm	No effect				
52	EATS-mediated	Ovary histopathology	Rat	90 days	Oral	>1000 mg/kg bw/day	No effect	Fallopian tubes were also examined.			
53	EATS-mediated	Ovary histopathology	Rat	90 days	Oral	>20000 ppm	No effect				
~~*54*~~	~~*EATS-mediated*~~	~~*Ovary histopathology*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000 ppm*~~	~~*No effect*~~				
55	EATS-mediated	Ovary histopathology	Rat	90 days	Oral	>20000 ppm	No effect				
56	EATS-mediated	Ovary histopathology	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				
57	EATS-mediated	Ovary histopathology	Dog	6 months	Oral	>300 mg/kg bw/day	No effect				
58	EATS-mediated	Ovary histopathology	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
59	EATS-mediated	Ovary histopathology	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect				

60	EATS-mediated	Ovary histopathology	Rat	21 days	Dermal	>1000 mg/kg bw/day	No effect		**RMS:**. In the available studies in mouse, rat, rabbit and dog no effect on ovarian weight was found. As no effects on either ovary histopathology or weight were found, it can be concluded that no EAS-mediated adversity was seen on ovaries following exposure to glyphosate.		
62	EATS-mediated	Ovary histopathology	Rabbit	21 days	Dermal	>5000 mg/kg bw/day	No effect				
63	EATS-mediated	Ovary histopathology	Rabbit	28 days	Dermal	>2000 mg/kg bw/day	No effect				
67	EATS-mediated	Ovary histopathology	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect				
68	EATS-mediated	Ovary histopathology	Mouse	2 years	Oral	> 30000 ppm	No effect				
~~*70*~~	~~*EATS-mediated*~~	~~*Ovary histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				
~~*70*~~	~~*EATS-mediated*~~	~~*Ovary histopathology*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				
73	EATS-mediated	Ovary histopathology	Mouse	90 days	Oral	>50000 ppm	No effect				
~~*74*~~	~~*EATS-mediated*~~	~~*Ovary histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300 ppm*~~	~~*No effect*~~	~~*No effects in F1 observed.*~~			
~~*74*~~	~~*EATS-mediated*~~	~~*Ovary histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300 ppm*~~	~~*No effect*~~	~~*No effects in F2 observed.*~~			
76	EATS-mediated	Ovary histopathology	Rat	90-92 days	Oral	>7500 ppm	No effect				
93	EATS-mediated	Ovary histopathology	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and	Oral	>1.75 mg/kg bw/day	No effect	F0			

				PND 125±2 for the 6 and 13 weeks cohorts, respectively							
93	EATS-mediated	Ovary histopathology	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			
2	EATS-mediated	Ovary weight	Rat	90 days	Oral	>50000 ppm	No effect				
5	EATS-mediated	Ovary weight	Dog	90 days	Oral	>1000 mg/kg bw/day	No effect				
7	EATS-mediated	Ovary weight	Dog	90 days	Oral	>40000 ppm	No effect				
8	EATS-mediated	Ovary weight	Dog	90 days	Oral	>50000 ppm	No effect				
9	EATS-mediated	Ovary weight	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
10	EATS-mediated	Ovary weight	Dog	1 year	Oral	>50000 ppm	No effect				
13	EATS-mediated	Ovary weight	Rat	2 years	Oral	>10000 ppm	No effect				
15	EATS-mediated	Ovary weight	Rat	2 years	Oral	>20000 ppm	No effect				
16	EATS-mediated	Ovary weight	Rat	2 years	Oral	>1000 mg/kg bw/day	No effect				
18	EATS-mediated	Ovary weight	Rat	2 years	Oral	>15000 ppm	No effect				
19	EATS-mediated	Ovary weight	Mouse	18 months	Oral	>10000 ppm	No effect				

20	EATS-mediated	Ovary weight	Mouse	18 months	Oral	>5000 ppm	No effect				
22	EATS-mediated	Ovary weight	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Ovary weight	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Ovary weight	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
26	EATS-mediated	Ovary weight	Rat	10 weeks prior to mating, continued until termination	Oral	>10000 ppm	No effect				
27	EATS-mediated	Ovary weight	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				
30	EATS-mediated	Ovary weight	Rabbit	13 days (GD 6-18)	Oral	>300 mg/kg bw/day	No effect				
44	EATS-mediated	Ovary weight	Rat	21 days (PND 22-42)	Oral	> 1000 mg/kg bw/day	No effect				
49	EATS-mediated	Ovary weight	Rat	28 days	Oral	>20000 ppm	No effect				
52	EATS-mediated	Ovary weight	Rat	90 days	Oral	>1000 mg/kg bw/day	No effect				
53	EATS-mediated	Ovary weight	Rat	90 days	Oral	>20000 ppm	No effect				
~~*54*~~	~~*EATS-mediated*~~	~~*Ovary weight*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000 ppm*~~	~~*No effect*~~				
56	EATS-mediated	Ovary weight	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				

57	EATS-mediated	Ovary weight	Dog	6 months	Oral	>300 mg/kg bw/day	No effect				
58	EATS-mediated	Ovary weight	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
59	EATS-mediated	Ovary weight	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect				
62	EATS-mediated	Ovary weight	Rabbit	21 days	Dermal	>5000 mg/kg bw/day	No effect				
67	EATS-mediated	Ovary weight	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect				
68	EATS-mediated	Ovary weight	Mouse	2 years	Oral	> 30000 ppm	No effect				
~~70~~	~~EATS-mediated~~	~~Ovary weight~~	~~Rat~~	~~21 days (PND0-21, exposure through milk)~~	~~Oral~~	~~>30 mg/kg bw/day~~	~~No effect~~				
~~70~~	~~EATS-mediated~~	~~Ovary weight~~	~~Rat~~	~~life-time, all three generations~~	~~Oral~~	~~>30 mg/kg bw/day~~	~~No effect~~				
73	EATS-mediated	Ovary weight	Mouse	90 days	Oral	>50000 ppm	No effect				
93	EATS-mediated	Ovary weight	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	F0			
93	EATS-mediated	Ovary weight	Rat	F0: from GD 6 to end of lactation;	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			

				Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively							
1	EATS-mediated	Uterus histopathology (with cervix)	Rat	90 days	Oral	>20000 ppm	No effect		Relevant effects on uterus weight were not observed in dog (3 studies), rabbit (4 studies), rat (13 studies), and mouse (2 studies). Moreover, no relevant effects with regard to histopathology of uterus and cervix were observed in dog (10 studies), rabbit (2 studies), rat (28 studies), and mouse (8 studies) after subchronic and chronic exposure as well as exposure over different life stages. **In conclusion, EAS-mediated adversity with regard to to effects on uterus and cervix is not observed.** **RMS:** It is noted that RMS removed one study from the results on uterus histopathology (study ID 74, rat) as this study was considered unacceptable. Only in one study in dog an effect on uterus histopathology was observed. However, this		
2	EATS-mediated	Uterus histopathology (with cervix)	Rat	90 days	Oral	>50000 ppm	No effect				
3	EATS-mediated	Uterus histopathology (with cervix)	Rat	90 days	Oral	>30000 ppm	No effect				
4	EATS-mediated	Uterus histopathology (with cervix)	Mouse	90 days	Oral	>50000 ppm	No effect				
5	EATS-mediated	Uterus histopathology (with cervix)	Dog	90 days	Oral	1000 mg/kg bw/day	**Change**	Decreased uterus size at macroscopical examination at 1000 mg/kg bw/day was observed: uterine atrophy in 3/3 females. However this finding was judged to be secondary to systemic toxicity as reduced body weight and body weight gain, reduced food consumption and diarrhea were observed at 1000 mg/kg. Furthermore, studies performed in the same species with similar or even higher dose groups for the same period of time, did not reveal any effects on uterus size. Moreover, no effect on uterine size was observed after an exposure period of 1 year at similar doses in the same species. In conclusion, the observed macroscopic effect is an isolated finding, not toxicologically relevant.			
6	EATS-mediated	Uterus histopathology (with cervix)	Dog	90 days	Oral	>10000 ppm	No effect				
7	EATS-mediated	Uterus histopathol	Dog	90 days	Oral	>40000 ppm	No effect				

		ogy (with cervix)							effects was concluded to be secondary to systemic toxicity in this study. In addition, in none of the other dog studies, with similar dose levels, were effects seen. In the mouse, rat and rabbit no effects were observed. Overall it is considered that there is no adverse effect o uterus histopathology following exposure to glyphosate.		
8	EATS-mediated	Uterus histopathology (with cervix)	Dog	90 days	Oral	>50000 ppm	No effect				
9	EATS-mediated	Uterus histopathology (with cervix)	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
10	EATS-mediated	Uterus histopathology (with cervix)	Dog	1 year	Oral	>50000 ppm	No effect				
11	EATS-mediated	Uterus histopathology (with cervix)	Dog	1 year	Oral	>30000 ppm	No effect				
12	EATS-mediated	Uterus histopathology (with cervix)	Rat	1 year	Oral	>20000 ppm	No effect				
13	EATS-mediated	Uterus histopathology (with cervix)	Rat	2 years	Oral	>10000 ppm	No effect				
14	EATS-mediated	Uterus histopathology (with cervix)	Rat	2 years	Oral	>30000 ppm	No effect				
15	EATS-mediated	Uterus histopathology (with cervix)	Rat	2 years	Oral	>20000 ppm	No effect				
16	EATS-mediated	Uterus histopathology (with cervix)	Rat	2 years	Oral	>1000 mg/kg bw/day	No effect				
17	EATS-mediated	Uterus histopathology (with cervix)	Rat	2 years	Oral	>20000 ppm	No effect				
18	EATS-mediated	Uterus histopathology (with cervix)	Rat	2 years	Oral	>15000 ppm	No effect				

19	EATS-mediated	Uterus histopathology (with cervix)	Mouse	18 months	Oral	>10000 ppm	No effect				
20	EATS-mediated	Uterus histopathology (with cervix)	Mouse	18 months	Oral	>5000 ppm	No effect				
21	EATS-mediated	Uterus histopathology (with cervix)	Mouse	18 months	Oral	>40000 ppm	No effect				
22	EATS-mediated	Uterus histopathology (with cervix)	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Uterus histopathology (with cervix)	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Uterus histopathology (with cervix)	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
25	EATS-mediated	Uterus histopathology (with cervix)	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000 ppm	No effect				
26	EATS-mediated	Uterus histopathology (with cervix)	Rat	10 weeks; prior to mating, continued	Oral	>10000 ppm	No effect				

				until termination							
27	EATS-mediated	Uterus histopathology (with cervix)	Rat	11 weeks; prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				
31	EATS-mediated	Uterus histopathology (with cervix)	Rabbit	13 days (GD 7-19)	Oral	400 mg/kg bw/day	No effect				
44	EATS-mediated	Uterus histopathology (with cervix)	Rat	21 days (PND 22-42)	Oral	> 1000 mg/kg bw/day	No effect				
49	EATS-mediated	Uterus histopathology (with cervix)	Rat	28 days	Oral	>20000 ppm	No effect				
52	EATS-mediated	Uterus histopathology (with cervix)	Rat	90 days	Oral	>1000 mg/kg bw/day	No effect				
53	EATS-mediated	Uterus histopathology (with cervix)	Rat	90 days	Oral	>20000 ppm	No effect	Cervix, uterus and vagina were fixed together.			
~~*54*~~	~~*EATS-mediated*~~	~~*Uterus histopathology (with cervix)*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000 ppm*~~	~~*No effect*~~				
55	EATS-mediated	Uterus histopathology (with cervix)	Rat	90 days	Oral	>20000 ppm	No effect				
56	EATS-mediated	Uterus histopathology (with cervix)	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				
57	EATS-mediated	Uterus histopathol	Dog	6 months	Oral	>300 mg/kg bw/day	No effect				

		ogy (with cervix)									
58	EATS-mediated	Uterus histopathology (with cervix)	Dog	1 year	Oral	>500 mg/kg bw/day	No effect		**RMS:** In the available studies in mouse, rat, rabbit and dog no effect on uterus weight was found. Considering the results for uterus histopathology and weight, it can be concluded that no EAS-mediated adversity was seen on uterus following exposure to glyphosate.		
59	EATS-mediated	Uterus histopathology (with cervix)	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect				
62	EATS-mediated	Uterus histopathology (with cervix)	Rabbit	21 days	Dermal	>5000 mg/kg bw/day	No effect				
67	EATS-mediated	Uterus histopathology (with cervix)	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect				
68	EATS-mediated	Uterus histopathology (with cervix)	Mouse	2 years	Oral	> 30000 ppm	No effect	Uterus histopathology was performed including uterine horns and cervix.			
~~*70*~~	~~*EATS-mediated*~~	~~*Uterus histopathology (with cervix)*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				
~~*70*~~	~~*EATS-mediated*~~	~~*Uterus histopathology (with cervix)*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				
73	EATS-mediated	Uterus histopathology (with cervix)	Mouse	90 days	Oral	>50000 ppm	No effect				
~~*74*~~	~~*EATS-mediated*~~	~~*Uterus histopathology (with cervix)*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300 ppm*~~	~~*No effect*~~	~~*No effects in F1 observed.*~~			
~~*74*~~	~~*EATS-mediated*~~	~~*Uterus histopathology (with cervix)*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300 ppm*~~	~~*No effect*~~	~~*No effects in F2 observed.*~~			

76	EATS-mediated	Uterus histopathology (with cervix)	Rat	90-92 days	Oral	>7500 ppm	No effect		**RMS:** In the available studies in mouse, rat and dog no effect on cervix histopathology was found.		
93	EATS-mediated	Uterus histopathology (with cervix)	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	F0			
93	EATS-mediated	Uterus histopathology (with cervix)	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			
5	EATS-mediated	Uterus weight (with cervix)	Dog	90 days	Oral	>1000 mg/kg bw/day	No effect				
9	EATS-mediated	Uterus weight (with cervix)	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
15	EATS-mediated	Uterus weight (with cervix)	Rat	2 years	Oral	>20000 ppm	No effect				
16	EATS-mediated	Uterus weight (with cervix)	Rat	2 years	Oral	>1000 mg/kg bw/day	No effect				

18	EATS-mediated	Uterus weight (with cervix)	Rat	2 years	Oral	>15000 ppm	No effect				
22	EATS-mediated	Uterus weight (with cervix)	Rat	10 weeks	Oral	>15000 ppm	No effect				
22	EATS-mediated	Uterus weight (with cervix)	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Uterus weight (with cervix)	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Uterus weight (with cervix)	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
28	EATS-mediated	Uterus weight (with cervix)	Rat	10 days (GD 7-16)	Oral	>1000 mg/kg bw/day	No effect				
29	EATS-mediated	Uterus weight (with cervix)	Rat	10 days (GD 6-15)	Oral	>1000 mg/kg bw/day	No effect				
30	EATS-mediated	Uterus weight (with cervix)	Rabbit	13 days (GD 6-18)	Oral	>300 mg/kg bw/day	No effect				
32	EATS-mediated	Uterus weight (with cervix)	Rabbit	13 days (GD 8-20)	Oral	> 300 mg/kg bw/day	No effect				
34	EATS-mediated	Uterus weight (with cervix)	Rabbit	13 days (GD 6-18)	Oral	> 500 mg/kg bw/day	No effect				
35	EATS-mediated	Uterus weight (with cervix)	Rabbit	13 days (GD 6-18)	Oral	> 500 mg/kg bw/day	No effect				

44	EATS-mediated	Uterus weight (with cervix)	Rat	21 days (PND 22-42)	Oral	> 1000 mg/kg bw/day	No effect				
52	EATS-mediated	Uterus weight (with cervix)	Rat	90 day	Oral	>1000 mg/kg bw/day	No effect				
56	EATS-mediated	Uterus weight (with cervix)	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				
59	EATS-mediated	Uterus weight (with cervix)	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect				
65	EATS-mediated	Uterus weight (with cervix)	Rat	10 days (GD 6-15)	Oral	>1000 mg/kg bw/day	No effect				
67	EATS-mediated	Uterus weight (with cervix)	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect				
93	EATS-mediated	Uterus weight (with cervix)	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	F0			
93	EATS-mediated	Uterus weight (with cervix)	Rat	F0: from GD 6 to end of lactation; Offsping: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts,	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			

				respectively							
1	EATS-mediated	Cervix histopathology	Rat	90 days	Oral	>20000 ppm	No effect				
2	EATS-mediated	Cervix histopathology	Rat	90 days	Oral	>50000 ppm	No effect				
3	EATS-mediated	Cervix histopathology	Rat	90 days	Oral	>30000 ppm	No effect				
4	EATS-mediated	Cervix histopathology	Mouse	90 days	Oral	>50000 ppm	No effect				
5	EATS-mediated	Cervix histopathology	Dog	90 days	Oral	>1000 mg/kg bw/day	No effect				
8	EATS-mediated	Cervix histopathology	Dog	90 days	Oral	>50000 ppm	No effect				
11	EATS-mediated	Cervix histopathology	Dog	1 year	Oral	>30000 ppm	No effect				
12	EATS-mediated	Cervix histopathology	Rat	1 year	Oral	>20000 ppm	No effect				
15	EATS-mediated	Cervix histopathology	Rat	2 years	Oral	>20000 ppm	No effect				
17	EATS-mediated	Cervix histopathology	Rat	2 years	Oral	>20000 ppm	No effect				
18	EATS-mediated	Cervix histopathology	Rat	2 years	Oral	>15000 ppm	No effect				
19	EATS-mediated	Cervix histopathology	Mouse	18 months	Oral	>10000 ppm	No effect				
21	EATS-mediated	Cervix histopathology	Mouse	18 months	Oral	>40000 ppm	No effect				
22	EATS-mediated	Cervix histopathology	Rat	10 weeks	Oral	>15000 ppm	No effect				

23	EATS-mediated	Cervix histopathology	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Cervix histopathology	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
26	EATS-mediated	Cervix histopathology	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				
53	EATS-mediated	Cervix histopathology	Rat	90 days	Oral	>20000 ppm	No effect				
55	EATS-mediated	Cervix histopathology	Rat	90 days	Oral	>20000 ppm	No effect				
56	EATS-mediated	Cervix histopathology	Mouse	90 day	Oral	>4500 mg/kg bw/day	No effect				
58	EATS-mediated	Cervix histopathology	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
76	EATS-mediated	Cervix histopathology	Rat	90-92 days	Oral	>7500 ppm	No effect				
2	EATS-mediated	Vagina histopathology	Rat	90 days	Oral	>50000 ppm	No effect		No relevant effects with regard to histopathology of vagina were observed in dog (1 study), rat (12 studies), and mouse (3 studies) after subchronic and chronic exposure as well as exposure over different life stages. Moreover, no changes were observed in vaginal smears. **In conclusion, EAS-mediated adversity with regard to effects**		
3	EATS-mediated	Vagina histopathology	Rat	90 days	Oral	>30000 ppm	No effect				
4	EATS-mediated	Vagina histopathology	Mouse	90 days	Oral	>50000 ppm	No effect				
9	EATS-mediated	Vagina histopathology	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
14	EATS-mediated	Vagina histopathology	Rat	24 months	Oral	>30000 ppm	No effect				

17	EATS-mediated	Vagina histopathology	Rat	24 months	Oral	>20000 ppm	No effect		**on vagina is not observed.**		
18	EATS-mediated	Vagina histopathology	Rat	2 years	Oral	>15000 ppm	No effect		**RMS:** agreed		
20	EATS-mediated	Vagina histopathology	Mouse	18 months	Oral	>5000 ppm	No effect				
21	EATS-mediated	Vagina histopathology	Mouse	18 months	Oral	>40000 ppm	No effect				
22	EATS-mediated	Vagina histopathology	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Vagina histopathology	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Vagina histopathology	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
25	EATS-mediated	Vagina histopathology	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000 ppm	No effect				
26	EATS-mediated	Vagina histopathology	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				

27	EATS-mediated	Vagina histopathology	Rat	11 weeks; prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				
53	EATS-mediated	Vagina histopathology	Rat	90 days	Oral	>20000 ppm	No effect				
93	EATS-mediated	Vagina histopathology	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	F0			
93	EATS-mediated	Vagina histopathology	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			
22	EATS-mediated	Vaginal smears	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Vaginal smears	Rat	10 days (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Vaginal smears	Rat	10 weeks for pre-mating	Oral	>30000 ppm	No effect				

				rearing 8 weeks for subsequent breeding							
25	EATS-mediated	Vaginal smears	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000 ppm	No effect				
26	EATS-mediated	Vaginal smears	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				
~~*70*~~	~~*EATS-mediated*~~	~~*Accessory sex organs histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~	~~*Clitoral gland investigated for F0 only. No microscopic findings were considered compound related.*~~	**In conclusion, EAS-mediated adversity with regard to effects on clitoral gland is not observed.** **RMS:** RMS considered this study to be unacceptable. Therefore, no acceptable data on clitoral gland is available		
22	EATS-mediated	Ano-Genital distance	Rat	10 weeks	Oral	>15000 ppm	No effect		The AGD was assessed in a two-generation study and was not affected by glyphosate exposure (study ID 22). The AGD was not investigated in further		

93	EATS-mediated	Ano-Genital distance	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	1,75 mg/kg bw/day	**Increase**	AGD was measured on PND 4 (including bw determination). AGD was statistically significantly increased in males only (absolute values: 4.26 mm vs 4.02 mm in control) and the author also reports this for the AGD adjusted for body weight. However, the numbers for the AGD index as well as the body weight data are not provided. Moreover, when taking into account the provided box plots and dot plots regarding AGD and AGD index, a significant increase in AGD index is not obvious. Moreover, the increase in anogenital distance was not correlated with increased testosterone levels or changes in any male reproductive endpoints (e.g., age at PPS, testes weight, accessory sexual tissue weights, sperm parameters). No endpoints were statistically significant with female rats. In the in vivo mechanistic and multi-generational studies there were no indication of effects on the androgen pathway that would result in an increase on anogenital distance in male rats. Therefore, the reported increase in AGD in males only is considered toxicologically not related to an endocrine pathway. RMS: the study was considered reliable with restrictions as only one (low) dose was tested, small group sizes, blood sampling done only once and timing of sampling.	available two-generation studies since those were performed according to former test guideline versions and no effect on sex ratio was observed (study ID 23). The increase in AGD observed in males in one published study is considered not related to an endocrine pathway, since no other male parameters (e.g., age at PPS, testes weight, accessory sexual tissue weights, sperm parameters) were affected in this study. Moreover, there is no consistency with regard to a potential androgenic effect when also considering the results of the in vivo mechanistic as well as the multi-generation studies. **In conclusion, EAS-mediated adversity with regard to effects on anogenital distance is not observed.** **RMS:** the result found in a public literature study, which was considered reliable with restrictions, was not replicate in a fully OECD and GLP compliant study conducted at higher dose levels. It is agreed that EAS mediated adversity was not seen on anogenitial distance.		

22	EATS-mediated	Age at balanopreputial separation	Rat	10 weeks	Oral	15000 ppm	**Increase**	Preputial separation (PPS) was statistically significantly delayed at 15000 ppm (about 1000 mg/kg bw/d), which is the limit dose of the test system according to OECD TG 416. The age at PPS was increased to 45.9 ± 3.1 days versus 43.0 ± 2.3 days in control group with no further signs of developmental retardation, hence, a higher mean bodyweight was noted at attainment of PPS. The delay of PPS is of marginal magnitude and considered to be based on biological variation. There were no differences in mating performance, sperm parameters and histopathological examinations did not reveal any changes in the testis or epididymis. Therefore, in isolation, this finding was considered to be unrelated to treatment which is supported by two further studies performed in rats at similar doses (study IDs 23, 26) which did not show a delay in PPS. Moreover, the PPS observed in the high dose group is only slightly above the range provided in OECD GD 43 and 151, according to which onset of puberty in the rat occurs around postnatal days 40-45. In addition, a delay in PPS was not reproduced in the second generation (F2 generation). Therefore, the increase in age at PPS in the F1 generation is not considered an anti-androgenic effect.	3/5 studies investigating balanopreputial separation (PPS) did not show any effect of glyphosate exposure including one two-generation study tested up to the limit dose of 1000 mg/kg bw/day (study ID 23) and conducted similar to OECD TG 416 (2001). Within the male pubertal assay (study ID 45), a delayed age at PPS was shown only at the high dose where also overt toxicity (one mortality, lung rales, body weight gain decrease >10%) was observed. Since overt toxicity confounds interpretation of reproductive system-related endpoints in the pubertal assay, the delay in PPS is not considered an antiandrogenic effect (further details please refer to study ID 45). In one two-generation study (study ID 22) a marginal but statistically significant delay in PPS was observed at the limit		
23	EATS-mediated	Age at balanopreputial separation	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
26	EATS-mediated	Age at balanopreputial separation	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				

45	EATS-mediated	Age at balanopreputial separation	Rat	31 days (PND 23-53)	Oral	1000 mg/kg bw/day	**Increase**	A statistically non-significant delay in the mean age at attainment of balanopreputial separation was observed in the high dose group (48.0 days). However, the body weight on the day of attainment of complete balanopreputial separation (PPS) in the 1000 mg/kg/day group was similar to the control group. However, the body weight was decreased at several time points by about 10% and the overall body weight change was reduced by 12.4% at 1000 mg/kg bw/day. Thus, the delay of PPS is considered an effect secondary to reduced body weight gain. Moreover, when adjusting the day of attainment for those males with three or more consecutive days of incomplete separation (persistent threads), no statistically significant delay in the mean age of attainment of preputial separation was noted for the 1000 mg/kg bw/day dose group when compared to the control group. There were 6, 11, 9, and 9 males in the control, 100, 300, and 1000 mg/kg bw/day dose group, respectively, with incomplete PSS for more than three days. No test substance related effects were observed at doses not causing overt toxicity. Therefore, the increase in age at PPS is not considered and anti-androgenic effect.	test dose of 1000 mg/kg bw/day in the F1 but not the F2 generation. Since further parameters, such as mating performance, sperm parameters and histopathological examinations of testis or epididymis did not reveal any changes and the effect was not reproduced in two further two-generation studies at similar doses, the delay of PPS was considered an isolated finding, not relevant for deducing an antiandrogenic effect of glyphosate. This rationale is in line with the conclusion of the EFSA Peer Review (EFSA Journal 2017;15(9):4979) as well as with the conclusion of EPA on the Endocrine Screening Program (EDSP) Tier 1 (US EPA, 2015). **In conclusion, glyphosate does not induce an adverse EAS-mediated effect on PPS.** **RMS:** Agreed		
93	EATS-mediated	Age at balanopreputial separation	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect				
20	EATS-mediated	Accessory sex organs histopathology	Mouse	18 months	Oral	>5000 ppm	No effect		**In conclusion, EAS-mediated adversity with regard to effects on the preputial gland is not observed.** **RMS:** agreed. It is noted that RMS considered study ID 70 to be unacceptable. Therefore, only acceptable data on		
~~*70*~~	~~*EATS-mediated*~~	~~*Accessory sex organs histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				

									preputial gland from one study is available.		
3	EATS-mediated	Coagulating gland histopathology	Rat	90 days	Oral	>30000 ppm	No effect		In 1/3 studies, relative but not absolute coagulating gland weight was reduced. No effect on coagulating gland weight was observed in 2/3 toxicity studies in rat with higher doses (e.g. study ID 22, 23). Moreover, no relevant effects with regard to histopathology of coagulating gland were observed in rat (11 studies), and mouse (4 studies) after subchronic and chronic exposure as well as exposure over different life stages. **In conclusion, EAS-mediated adversity with regard to effects on coagulating gland is not observed.** **RMS:** agreed		
4	EATS-mediated	Coagulating gland histopathology	Mouse	90 days	Oral	>50000 ppm	No effect				
13	EATS-mediated	Coagulating gland histopathology	Rat	24 months	Oral	>10000 ppm	No effect				
14	EATS-mediated	Coagulating gland histopathology	Rat	24 months	Oral	>30000 ppm	No effect				
19	EATS-mediated	Coagulating gland histopathology	Mouse	18 months	Oral	>10000 ppm	No effect				
20	EATS-mediated	Coagulating gland histopathology	Mouse	18 months	Oral	>5000 ppm	No effect				
21	EATS-mediated	Coagulating gland histopathology	Mouse	18 months	Oral	>40000 ppm	No effect				
22	EATS-mediated	Coagulating gland histopathology	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Coagulating gland histopathology	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Coagulating gland	Rat	10 weeks for pre-mating	Oral	>30000 ppm	No effect				

		histopathology		rearing 8 weeks for subsequent breeding							
25	EATS-mediated	Coagulating gland histopathology	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000 ppm	No effect				
26	EATS-mediated	Coagulating gland histopathology	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				
49	EATS-mediated	Coagulating gland histopathology	Rat	28 days	Oral	>20000 ppm	No effect				
~~*54*~~	~~*EATS-mediated*~~	~~*Coagulating gland histopathology*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000 ppm*~~	~~*No effect*~~				
93	EATS-mediated	Coagulating gland histopathology	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect				

22	EATS-mediated	Coagulating gland weight	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Coagulating gland weight	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
80	EATS-mediated	Coagulating gland weight	Rat	5 weeks	Oral	500 mg/kg bw/day	**Decrease**	A significant decrease in absolute (but not relative) weight of the coagulating gland(weighed together with seminal vesicles) was observed, which may be attributed to the non statistically significant reduced final body weight. Since no effect on coagulating gland weight and histopathology was observed in further toxicity studies in rat with higher doses (e.g. study ID 22, 23), and no effect on relative organ weight was observed in the current study, the decrease in absolute organ weight is not considered toxicologically relevant.			
1	EATS-mediated	Epididymis histopathology	Rat	90 days	Oral	>20000 ppm	No effect		Relevant effects on epididymis weights were not observed in dog (6 studies), rat (14 studies), and mouse (3 studies). Moreover, no relevant effects with regard to histopathology of epididymis were observed in dog (9 studies), rabbit (1 study), rat (23 studies), and mouse (9 studies) after subchronic and chronic exposure as well as exposure over different life stages (for rat). **In conclusion, EAS-mediated adversity with regard to effects on epididymis is not observed.** **RMS:** In the available studies in mouse, rat, rabbit and dog no effect on epididymis histopathology was found.		
3	EATS-mediated	Epididymis histopathology	Rat	90 days	Oral	>30000 ppm	No effect				
4	EATS-mediated	Epididymis histopathology	Mouse	90 days	Oral	>50000 ppm	No effect				
5	EATS-mediated	Epididymis histopathology	Dog	90 days	Oral	>1000 mg/kg bw/day	No effect				
7	EATS-mediated	Epididymis histopathology	Dog	90 days	Oral	>40000 ppm	No effect				
8	EATS-mediated	Epididymis histopathology	Dog	90 days	Oral	>50000 ppm	No effect				
9	EATS-mediated	Epididymis histopathology	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
10	EATS-mediated	Epididymis histopathology	Dog	1 year	Oral	>50000 ppm	No effect				
11	EATS-mediated	Epididymis histopathology	Dog	1 year	Oral	>30000 ppm	No effect				
12	EATS-mediated	Epididymis histopathology	Rat	1 year	Oral	>20000 ppm	No effect				

13	EATS-mediated	Epididymis histopathology	Rat	2 years	Oral	>10000 ppm	No effect				
14	EATS-mediated	Epididymis histopathology	Rat	2 years	Oral	>30000 ppm	No effect				
15	EATS-mediated	Epididymis histopathology	Rat	2 years	Oral	>20000 ppm	No effect				
16	EATS-mediated	Epididymis histopathology	Rat	2 years	Oral	>1000 mg/kg bw/day	No effect				
17	EATS-mediated	Epididymis histopathology	Rat	2 years	Oral	>20000 ppm	No effect				
18	EATS-mediated	Epididymis histopathology	Rat	2 years	Oral	>15000 ppm	No effect				
19	EATS-mediated	Epididymis histopathology	Mouse	18 months	Oral	>10000 ppm	No effect				
20	EATS-mediated	Epididymis histopathology	Mouse	18 months	Oral	>5000 ppm	No effect				
21	EATS-mediated	Epididymis histopathology	Mouse	18 months	Oral	>40000 ppm	No effect				
22	EATS-mediated	Epididymis histopathology	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Epididymis histopathology	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Epididymis histopathology	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
25	EATS-mediated	Epididymis histopathology	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in	Oral	>10000 ppm	No effect				

				F0 and continued for 2 successive generations up to weaning of F2							
26	EATS-mediated	Epididymis histopathology	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				
27	EATS-mediated	Epididymis histopathology	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				
45	EATS-mediated	Epididymis histopathology	Rat	31 days (PND 23-53)	Oral	> 1000 mg/kg bw/day	No effect				
52	EATS-mediated	Epididymis histopathology	Rat	90 days	Oral	>1000 mg/kg bw/day	No effect				
53	EATS-mediated	Epididymis histopathology	Rat	90 days	Oral	>20000 ppm	No effect				
55	EATS-mediated	Epididymis histopathology	Rat	90 days	Oral	>20000 ppm	No effect	Epididymides were examined together with testes.			
56	EATS-mediated	Epididymis histopathology	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				
57	EATS-mediated	Epididymis histopathology	Dog	6 months	Oral	>300 mg/kg bw/day	No effect	Examined together with testes.			
58	EATS-mediated	Epididymis histopathology	Dog	1 year	Oral	>500 mg/kg bw/day	No effect		**RMS:** In one study in rat, a decreased absolute weight was found at the mid- and high dose,		
59	EATS-mediated	Epididymis histopathology	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect				

60	EATS-mediated	Epididymis histopathology	Rat	21 days	Dermal	>1000 mg/kg bw/day	No effect		which was considered secondary to lower body weight. In addition, the high dose level exceeded the MTD. No histopathological changes were found in this rat study. In none of the other studies in rat, mouse, or dog an effect on epididymis weight was seen. Overall, it is agreed that EAS-mediated adversity on epididymis is not observed.		
62	EATS-mediated	Epididymis histopathology	Rabbit	21 days	Dermal	>5000 mg/kg bw/day	No effect				
67	EATS-mediated	Epididymis histopathology	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect				
68	EATS-mediated	Epididymis histopathology	Mouse	2 years	Oral	> 30000 ppm	No effect				
~~*70*~~	~~*EATS-mediated*~~	~~*Epididymis histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				
~~*70*~~	~~*EATS-mediated*~~	~~*Epididymis histopathology*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				
73	EATS-mediated	Epididymis histopathology	Mouse	90 days	Oral	>50000 ppm	No effect				
80	EATS-mediated	Epididymis histopathology	Rat	5 weeks	Oral	>500 mg/kg bw/day	No effect				
93	EATS-mediated	Epididymis histopathology	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			
5	EATS-mediated	Epididymis weight	Dog	90 days	Oral	>1000 mg/kg bw/day	No effect				
8	EATS-mediated	Epididymis weight	Dog	90 days	Oral	>50000 ppm	No effect				

9	EATS-mediated	Epididymis weight	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
11	EATS-mediated	Epididymis weight	Dog	1 year	Oral	>30000 ppm	No effect				
12	EATS-mediated	Epididymis weight	Rat	1 year	Oral	>20000 ppm	No effect				
15	EATS-mediated	Epididymis weight	Rat	2 years	Oral	>20000 ppm	No effect				
18	EATS-mediated	Epididymis weight	Rat	2 years	Oral	>15000 ppm	No effect				
20	EATS-mediated	Epididymis weight	Mouse	18 months	Oral	>5000 ppm	No effect				
22	EATS-mediated	Epididymis weight	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Epididymis weight	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Epididymis weight	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
27	EATS-mediated	Epididymis weight	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				

45	EATS-mediated	Epididymis weight	Rat	31 days (PND 23-53)	Oral	300 mg/kg bw/day	**Decrease**	Lower mean absolute left and right epididymis weight (9.5-9.9% and 3.8-7.1% for 1000 and 300 mg/kg bw/day dose group, respectively) was observed (not statistically significant). The effect was considered secondary to body weight decreases. For the high dose overt toxicity (1 mortality, rales, body weight gain decrease >10%) was observed. Body weight decreases > 10% have been shown to confound the interpretation of reproductive system-related endpoints in the pubertal assays (Fed Reg. 74(71):17570-17585). Therefore, for the 1000 mg/kg bw/day dose group, interpretation of endocrine endpoints was confounded by overt and systemic toxicity and considered not relevant for a WoE analysis for the androgen pathway as per the USEPA and EFSA guidance. In addition, no histopathological changes were observed in the current study and no effects on reproduction were observed in one-, two- and three-generation studies. Thus, decreased organ weight is not considered relevant for EAS-mediated adversity.			
53	EATS-mediated	Epididymis weight	Rat	90 days	Oral	>20000 ppm	No effect	Testes and epididymis were weighed together.			
55	EATS-mediated	Epididymis weight	Rat	90 days	Oral	>20000 ppm	No effect	Testes and epididymis were weighed together.			
56	EATS-mediated	Epididymis weight	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect	Testes and epididymis were weighed together.			
58	EATS-mediated	Epididymis weight	Dog	1 year	Oral	>500 mg/kg bw/day	No effect	Testes and epididymis were weighed together.			
59	EATS-mediated	Epididymis weight	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect	Testes and epididymis were weighed together.			
60	EATS-mediated	Epididymis weight	Rat	21 days	Dermal	>1000 mg/kg bw/day	No effect				
67	EATS-mediated	Epididymis weight	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect	Testes and epididymis were weighed together.			
78	EATS-mediated	Epididymis weight	Rat	90 days	Oral	>50000 ppm	No effect				
93	EATS-mediated	Epididymis weight	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND	Oral	<1.75 mg/kg bw/day	No effect				

				73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively							
94	In vivo mechanistic	Epididymis weight	Mouse	Dams: Day of vaginal plug detection (embryonic day 10.5) to 20 days post-partum Offspring termination: PND 5, 20, 35 and 8 months old animals	Oral	>50 mg/kg bw/day	No effect	Epididymides weights were determined in 35 day and 8 months old males and no statistically significant effect was observed.			
45	EATS-mediated	LABC weight	Rat	31 days (PND 23-53)	Oral	1000 mg/kg bw/day	**Decrease**	Statistically significantly decreased mean absolute LABC weight (15.9%) was observed at the high dose showing overt toxicity (1 mortality, rales, body weight gain decrease >10%). Body weight decreases > 10% have been shown to confound the interpretation of reproductive system-related endpoints in the pubertal assays (Fed Reg. 74(71):17570-17585). Therefore, for the 1000 mg/kg bw/day dose group, interpretation of endocrine endpoints was confounded by overt and systemic toxicity and considered not relevant for a WoE analysis for the androgen pathway as per the USEPA and EFSA guidance. In addition, no effects on reproduction were observed in one-, two- and three-generation studies.	An effect on LABC weight was observed at overt systemic toxicity only. Therefore, no indication for endocrine-related adversity can be deduced. **RMS:** the decrease seen was at a dose level exceeding the MTD. Therefore, no direct EAS-mediated adversity on LABC weight was observed.		
2	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	90 days	Oral	>50000 ppm	No effect		Relevant effects on prostate weight were not observed in dog (5 studies), rat (9 studies), and mouse (2 studies). Moreover, no relevant effects with regard to histopathology of prostate were observed in dog (9 studies), rabbit		
3	EATS-mediated	Prostate histopathol	Rat	90 days	Oral	>30000 ppm	No effect				

		ogy (with seminal vesicles and coagulating glands)							(1 study), rat (22 studies), and mouse (8 studies) after subchronic and chronic exposure as well as exposure over different life stages (for rat). **No EAS-mediated adversity was observed for the prostate in four species.** **RMS:** It is noted that RMS removed one study in rat (study ID 54) from the results on prostate pathology, as RMS concluded this study to be unacceptable. In a 90-day study in the dog, prostate atrophy was observed at the high dose, however, this dose exceeded the MTD. No effect was observed in the other studies in dog. In one of the long-term studies in rat, increased firmness was seen at the high dose during gross necropsy. No adverse effects were found during histopathological examination in this study. In none of the other rat studies an effect on histopathology was observed. It is agreed that no EAS-mediated adversity on prostate histopathology was observed.		
4	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Mouse	90 days	Oral	>50000 ppm	No effect				
5	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Dog	90 days	Oral	1000 mg/kg bw/day	**Change**	Prostate atrophy was observed in 2/3 animals at 1000 mg/kg bw/day. However, at the same dose reduced mean body weight (-28%) and lower weight gain (+4% vs +31% in controls) was observed. Moreover, clinical signs such as diarrhea were observed and one animal was sacrificed prior to study termination. Furthermore, chronic toxicity studies in dogs, using similar dose groups did not reveal any effects on the histopathology of the prostate (study IDs 7-11). Therefore, the observed effect on prostate is considered secondary to general toxicity at this dose level and not related to an endocrine MoA**.**			
7	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Dog	90 days	Oral	>40000 ppm	No effect				
8	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Dog	90 days	Oral	>50000 ppm	No effect				
9	EATS-mediated	Prostate histopathology (with seminal vesicles	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				

		and coagulating glands)									
10	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Dog	1 year	Oral	>50000 ppm	No effect				
11	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Dog	1 year	Oral	>30000 ppm	No effect				
12	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	1 year	Oral	>20000 ppm	No effect				
13	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	2 years	Oral	>10000 ppm	No effect				
14	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	2 years	Oral	>30000 ppm	No effect				

15	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	2 years	Oral	20000 ppm	**Change**	Gross necropsy: increased (3/64) firmness at 20000 ppm Histopathology, non-neoplastic findings: Prostatitis at 20000 ppm, increased incidences compared to concurrent control but within historical control range. Histopathology, neoplastic findings: no treatment-related findings The findings during gross necropsy are of very low magnitude and are therefore considered as a result of normal biological variation. In addition, histopathological changes were within the range of historical control data. Moreover, further chronic studies in rat exposed to similar doses did not show any effect on prostate (study IDs 13, 14). In conclusion, prostatitis as well as the increased firmness were not considered treatment-related.			
16	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	2 years	Oral	>1000 mg/kg bw/day	No effect				
17	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	2 years	Oral	>20000 ppm	No effect				
18	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	2 years	Oral	>15000 ppm	No effect				
19	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Mouse	18 months	Oral	>10000 ppm	No effect				

20	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Mouse	18 months	Oral	>5000 ppm	No effect				
21	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Mouse	18 months	Oral	>40000 ppm	No effect				
22	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
25	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and	Oral	>10000 ppm	No effect				

				continued for 2 successive generations up to weaning of F2							
26	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				
27	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	11 weeks; prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				
49	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	28 days	Oral	>20000 ppm	No effect				
52	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	90 days	Oral	>1000 mg/kg bw/day	No effect				
53	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	90 days	Oral	>20000 ppm	No effect		**RMS:** In one 90-day dog study, a decrease in absolute and relative prostate weight, however, this effect was seen at a dose level		

~~*54*~~	~~*EATS-mediated*~~	~~*Prostate histopathology (with seminal vesicles and coagulating glands)*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000 ppm*~~	~~*No effect*~~		exceeding the MTD. In the other dog studies no effects were seen. In a 2-generation study in rats (ID 24) a decrease in absolute an relative prostate weight was seen in F1 males only. No histopathological changes were seen and the effect on weight was seen at a dose which induced general toxicity. No effects were seen in the other generational studies. In the male pubertal assay (ID 45), absolute prostate weight was decreased at a dose level exceeding the MTD. In the other studies no effects on prostate weight were observed. Overall, it is agreed that no EAS-mediated adversity was seen in the prostate.		
55	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	90 days	Oral	>20000 ppm	No effect				
56	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				
57	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Dog	6 months	Oral	>300 mg/kg bw/day	No effect				
58	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
59	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect				

62	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rabbit	21 days	Dermal	>5000 mg/kg bw/day	No effect				
67	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect				
68	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Mouse	2 years	Oral	> 30000 ppm	No effect				
~~*70*~~	~~*EATS-mediated*~~	~~*Prostate histopathology (with seminal vesicles and coagulating glands)*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				
~~*70*~~	~~*EATS-mediated*~~	~~*Prostate histopathology (with seminal vesicles and coagulating glands)*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				
73	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Mouse	90 days	Oral	>50000 ppm	No effect				

76	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	90-92 days	Oral	>7500 ppm	No effect				
93	EATS-mediated	Prostate histopathology (with seminal vesicles and coagulating glands)	Rat	F0: from GD 6 to end of lactation; Offsping: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			
5	EATS-mediated	Prostate weight	Dog	90 days	Oral	1000 mg/kg bw/day	**Decrease**	Absolute and relative organ weights were decreased at 1000 mg/kg bw/day (-68 and -56%; statistical significance only for absolute weight). The weight reduction correlates with the observed atrophy. However, at the same dose reduced mean body weight (-28%) and lower weight gain (+4% vs +31% in controls) was observed. Moreover, clinical signs such as diarrhea were observed and one animal was sacrificed prior to study termination. Furthermore, chronic toxicity studies in dogs, using similar dose groups did not reveal any effects on the histopathology or weight of the prostate (study IDs 7-11). Therefore, the observed organ weight decrease is considered secondary to general toxicity at this dose level and not related to an endocrine MoA.			
7	EATS-mediated	Prostate weight	Dog	90 days	Oral	>40000 ppm	No effect				
9	EATS-mediated	Prostate weight	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
10	EATS-mediated	Prostate weight	Dog	1 year	Oral	>50000 pm	No effect				
16	EATS-mediated	Prostate weight	Rat	2 years	Oral	>1000 mg/kg bw/day	No effect				
22	EATS-mediated	Prostate weight	Rat	10 weeks	Oral	>15000 ppm	No effect				

23	EATS-mediated	Prostate weight	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Prostate weight	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	30000 ppm	**Decrease**	Statistically significant decrease in absolute and relative prostate weight was observed at 30000 ppm in F1 males only (no effect in F0 males). The histopathological examination of the prostate in F1 males did not reveal any effects. Moroever, signs of general toxicity such as decreased body weight gain and loose stool was observed at this dose level. Moreover, in further two-generation studies (study IDs 22, 23, 26) prostate weight was not affected. Therefore, changes in prostate weight are attributed to systemic toxicity and not related to an endocrine MoA.			
26	EATS-mediated	Prostate weight	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				
45	EATS-mediated	Prostate weight	Rat	31 days (PND 23-53)	Oral	1000 mg/kg bw/day	**Decrease**	Statistically significantly lower mean absolute ventral prostate weight (22.6%) were observed in the high dose group. Weight change of the ventral prostate was only observed at the high dose also inducing overt toxicity (significant body wight decrease >10% and clinical signs) and thus, was considered secondary to general toxicity not related to EAS-mediated adversity. Mean dorsolateral prostate weight was significantly reduced with glyphosate at the mid-dose group, 300 mg/kg bw/day, compared to control. However, this change was not observed at the high or low dose groups, so in the absence of a dose-response and coupled with none of the other reproductive organ weights were altered, this isolated finding is not considered to be endocrine-mediated.			
52	EATS-mediated	Prostate weight	Rat	90 days	Oral	>1000 mg/kg bw/day	No effect				

56	EATS-mediated	Prostate weight	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				
59	EATS-mediated	Prostate weight	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect				
67	In vivo mechanistic	Prostate weight	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect				
80	EATS-mediated	Prostate weight	Rat	5 weeks	Oral	>500 mg/kg bw/day	No effect				
93	EATS-mediated	Prostate weight	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect				
2	EATS-mediated	Seminal vesicles histopathology	Rat	90 days	Oral	>50000 ppm	No effect		Relevant effects on seminal vesicles weight were not observed in rat and mouse. In 2/8 rat studies a decrease in absolute organ weight was observed. In both cases, the effect cannot be attributed to glyphosate treatment: 1) Within the pubertal assay overt toxicity is observed at the same dose level; 2) Only relative but not absolute organ weight was		
3	EATS-mediated	Seminal vesicles histopathology	Rat	90 days	Oral	>30000 ppm	No effect				
4	EATS-mediated	Seminal vesicles histopathology	Mouse	90 days	Oral	>50000 ppm	No effect				
12	EATS-mediated	Seminal vesicles histopathology	Rat	1 year	Oral	>20000 ppm	No effect				

13	EATS-mediated	Seminal vesicles histopathology	Rat	2 years	Oral	>10000 ppm	No effect		significantly decreased without corresponding histopathological changes. In addition, organ weight was not decreased in further studies in rat at higher doses and longer exposure period (e.g. study ID 22, 23). Moreover, no relevant effects with regard to histopathology of seminal vesicles were observed in rabbit (1 study), rat (23 studies), and mouse (8 studies) after subchronic and chronic exposure as well as exposure over different life stages (for rat). **No EAS-mediated adverse was observed on seminal vesicles in three species.** **RMS:** It is noted that RMS removed one rat study from the results on seminal vesicle histopathology (ID 74), as RMS considered this study to be unacceptable. No effects on seminal vesicle histopathology were observed following exposure to glyphosate.		
14	EATS-mediated	Seminal vesicles histopathology	Rat	2 years	Oral	>30000 ppm	No effect				
15	EATS-mediated	Seminal vesicles histopathology	Rat	2 years	Oral	>20000 ppm	No effect				
17	EATS-mediated	Seminal vesicles histopathology	Rat	2 years	Oral	>20000 ppm	No effect				
18	EATS-mediated	Seminal vesicles histopathology	Rat	2 years	Oral	>15000 ppm	No effect				
19	EATS-mediated	Seminal vesicles histopathology	Mouse	18 months	Oral	>10000 ppm	No effect				
20	EATS-mediated	Seminal vesicles histopathology	Mouse	18 months	Oral	>5000 ppm	No effect				
21	EATS-mediated	Seminal vesicles histopathology	Mouse	18 months	Oral	>40000 ppm	No effect				
22	EATS-mediated	Seminal vesicles histopathology	Rat	10 weeks	Oral	>15000 ppm	No effect				

23	EATS-mediated	Seminal vesicles histopathology	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Seminal vesicles histopathology	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
25	EATS-mediated	Seminal vesicles histopathology	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000 ppm	No effect				
26	EATS-mediated	Seminal vesicles histopathology	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				
27	EATS-mediated	Seminal vesicles histopathology	Rat	11 weeks; prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				
49	EATS-mediated	Seminal vesicles histopathology	Rat	28 days	Oral	>20000 ppm	No effect				
52	EATS-mediated	Seminal vesicles	Rat	90 days	Oral	>1000 mg/kg bw/day	No effect				

		histopathology							**RMS:** in the pubertal male assay (ID 45), a decrease in absolute seminal vesicle weight was seen. However, this effect was seen at a dose level exceeding the MTD. In a public literature study in rat (ID 80) a decrease in absolute weight was seen, with no effect on relative weight and no effects on histopathology. In the other studies in rat (with longer duration) no effects was seen. Also in the mouse no effect on seminal vesicle weight was found. Overall, it is agreed that there is no EAS-mediated adversity seen on seminal vesicles following exposure to glyphosate.		
~~54~~	~~EATS-mediated~~	~~Seminal vesicles histopathology~~	~~Rat~~	~~90 days~~	~~Oral~~	~~>20000 ppm~~	~~No effect~~				
55	EATS-mediated	Seminal vesicles histopathology	Rat	90 days	Oral	>20000 ppm	No effect				
56	EATS-mediated	Seminal vesicles histopathology	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				
62	EATS-mediated	Seminal vesicles histopathology	Rabbit	21 days	Dermal	>5000 mg/kg bw/day	No effect				
~~74~~	~~EATS-mediated~~	~~Seminal vesicles histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Oral~~	~~>300 ppm~~	~~No effect~~	~~No effects in F1 observed.~~			
~~74~~	~~EATS-mediated~~	~~Seminal vesicles histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Oral~~	~~>300 ppm~~	~~No effect~~	~~No effects in F2 observed.~~			
80	EATS-mediated	Seminal vesicles histopathology	Rat	5 weeks	Oral	>500 mg/kg bw/day	No effect				
93	EATS-mediated	Seminal vesicles histopathology	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Seminal vesicles and coagulating gland (assessed for both F1 exposure groups).			

2	EATS-mediated	Seminal vesicles weight	Rat	90 days	Oral	>50000 ppm	No effect				
22	EATS-mediated	Seminal vesicles weight	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Seminal vesicles weight	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Seminal vesicles weight	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
45	EATS-mediated	Seminal vesicles weight	Rat	31 days (PND 23-53)	Oral	1000 mg/kg bw/day	**Decrease**	Statistically significantly lower mean absolute seminal vesicle (with coagulating gland and fluid 18.5% and without 16.4%) weight were observed in the 1000 mg/kg/day group also showing overt toxicity (1 mortality, rales, body weight gain decrease >10%). Body weight decreases > 10% have been shown to confound the interpretation of reproductive system-related endpoints in the pubertal assays (Fed Reg. 74(71):17570-17585). Therefore, for the 1000 mg/kg bw/day dose group, interpretation of endocrine endpoints was confounded by overt and systemic toxicity and considered not relevant for a WoE analysis for the androgen pathway as per the USEPA and EFSA guidance. In addition, no effects on reproduction were observed in one-, two- and three-generation studies.			
53	EATS-mediated	Seminal vesicles weight	Rat	90 days	Oral	>20000 ppm	No effect				
80	EATS-mediated	Seminal vesicles weight	Rat	5 weeks	Oral	500 mg/kg bw/day	**Decrease**	A significant decrease in absolute (but not relative) weight of the seminal vesicle gland (weighed together with coagulating gland) was observed, which was reported together with non statistically significant reduced final body weight. Histopathological changes on seminal vesicles were not observed within the current study. In addition, further studies with higher and longer exposure to glyphosate (e.g. study ID 22, 23) did not result in reduction of seminal vesicles weight. Based on the rationale provided and the lacking consistent effect on organ weight, the reduction of absolute seminal vesicles weigh only, is not considered endocrine-related.			
93	EATS-mediated	Seminal vesicles weight	Rat	F0: from GD 6 to end of	Oral	>1.75 mg/kg bw/day	No effect				

				lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively							
94	EATS-mediated	Seminal vesicles weight	Mouse	Dams: Day of vaginal plug detection (embryonic day 10.5) to 20 days post-partum Offspring termination: PND 5, 20, 35 and 8 months old animals	Oral	>50 mg/kg bw/day	No effect	Seminal vesicles weights were determined in 35 day and 8 months old males and no statistically significant effect was observed.			
22	EATS-mediated	Sperm numbers	Rat	10 weeks	Oral	*15000 ppm*	*Decrease*	*A lower number of homogenization resistant spematid was present in the cauda epididymis in F0 males at 15000 ppm. No effect was observed in the F1 males and there was no effect on reproductive performance or fertility.*	No relevant effect on sperm numbers was observed in rat and mouse (stud ID 94). A decrease in sperm numbers was observed in 2/6 studies. The decreased number in the subchronic study (study ID 78) is attributed to overt systemic toxicity and not associated with any decrease in testes weights. The decrease in		
23	EATS-mediated	Sperm numbers	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Sperm numbers	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				

78	EATS-mediated	Sperm numbers	Rat	90 days	Oral	25000 ppm	**Decrease**	A decrease in sperm numbers was observed from 25000 ppm. At the same dose level a significant reduction of body weight gain was observed (terminal body weight M 50000 ppm= -18% compared to control). Histopathology of testes was not performed within this study but a decrease in testes weight was not observed. The decreased count of sperm number is not considered to be endocrine-related but rather secondary to systemic toxicity. Furthermore, studies at similar doses did not show any effects on sperm parameters. In addition, no effects on fertility were observed in the available two-generation studies.	epididymal sperm count observed in a literature study is considered incidental since no effects on testis weight and histopathology were observed in the same study. Moreover, none of the other six studies (study IDs 22 – 24, 79, 93, 94) including two-generation studies did show any effects on sperm or fertility parameters. **In conclusion, no EAS-mediated adversity on sperm numbers is observed.** **RMS:** In a 2-generation study (ID 22) a decrease in number of homogenization resistant spematid in the cauda epididymis was seen in F0 males only and without affecting reproductive performance. In a 90-day study in the rat (ID 78), a decrease in sperm number was seen, however this was at a dose level exceeding the MTD. In another study in rat (ID 80) a decrease in total sperm count was seen, however, without an effect on testis weight or histopathology. In none of the other studies in rat or mouse an effect was seen. Overall, it is agreed that there is no EAS-mediated adversity		
79	EATS-mediated	Sperm numbers	Mouse	90 days	Oral	>50000 ppm	No effect				
80	EATS-mediated	Sperm numbers	Rat	5 weeks	Oral	500 mg/kg bw/day	**Decrease**	Total sperm count was decreased (epididymal sperm) which is considered incidental since no effects on testis weight and histopathology were observed.			
93	EATS-mediated	Sperm numbers	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			
94	In vivo mechanistic	Sperm numbers	Mouse	Dams: Day of vaginal plug detection (embryonic day 10.5) to 20 days post-partum Offspring termination: PND 5, 20, 35 and 8 months old animals	Oral	>50 mg/kg bw/day	No effect	Spermatozoa number was not statistically significantly affected.			

									regarding sperm numbers.		
22	EATS-mediated	Sperm motility	Rat	10 weeks	Oral	>15000 ppm	No effect		**No EAS-mediated adversity on sperm motility is observed in rat (5 studies including two 2-generation studies and mouse (1 study) after subchronic exposure.** **RMS:** Agreed		
23	EATS-mediated	Sperm motility	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Sperm motility	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
78	EATS-mediated	Sperm motility	Rat	90 days	Oral	>50000 ppm	No effect				
79	EATS-mediated	Sperm motility	Mouse	90 days	Oral	>50000 ppm	No effect				
93	EATS-mediated	Sperm motility	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Sperm transit time was calculated (assessed for both F1 exposure groups).			
22	EATS-mediated	Sperm morphology	Rat	10 weeks	Oral	>15000 ppm	No effect		**No EAS-mediated adversity on sperm morphology is observed in rat (5 studies including 2 2-generation studies and mouse (1 study) after subchronic exposure.** **RMS:** Agreed		
23	EATS-mediated	Sperm morphology	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Sperm morphology	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				

78	EATS-mediated	Sperm morphology	Rat	90 days	Oral	>50000 ppm	No effect				
79	EATS-mediated	Sperm morphology	Mouse	90 days	Oral	>50000 ppm	No effect				
93	EATS-mediated	Sperm morphology	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			
1	EATS-mediated	Testis histopathology	Rat	90 days	Oral	>20000 ppm	No effect		Relevant effects on testis weight were not observed in dog (10 studies), rabbit (2 studies), rat (30 studies), and mouse (10 studies). In isolated studies testes weight increases were observed in rat. However, these were mostly attributed to body weight decreases. A decrease in relative weight was observed in one published non-TG study in mouse. The isolated weight changes were neither consistent within one species over different exposure periods (no time coherence) nor in the four species investigated. Moreover, no relevant effects with regard to histopathology were observed in dog		
2	EATS-mediated	Testis histopathology	Rat	90 days	Oral	>50000 ppm	No effect				
3	EATS-mediated	Testis histopathology	Rat	90 days	Oral	>30000 ppm	No effect				
4	EATS-mediated	Testis histopathology	Mouse	90 days	Oral	>50000 ppm	No effect				
5	EATS-mediated	Testis histopathology	Dog	90 days	Oral	>1000 mg/kg bw/day	No effect				
6	EATS-mediated	Testis histopathology	Dog	90 days	Oral	>10000 ppm	No effect				
7	EATS-mediated	Testis histopathology	Dog	90 days	Oral	>40000 ppm	No effect				
8	EATS-mediated	Testis histopathology	Dog	90 days	Oral	>50000 ppm	No effect				
9	EATS-mediated	Testis histopathology	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				

10	EATS-mediated	Testis histopathology	Dog	1 year	Oral	>50000 ppm	No effect		(10 studies), rabbit (2 studies), rat (32 studies), and mouse (9 studies) after subchronic and chronic exposure as well as exposure over different life stages. **In conclusion, EAS-mediated adversity with regard to effects on testis is not observed.** **RMS:** It is noted that RMS removed two rat studies from the results on testis histopathology (ID's 74 and 75), as RMS concluded these studies were unacceptable. No effects on testis histopathology were observed.		
11	EATS-mediated	Testis histopathology	Dog	1 year	Oral	>30000 ppm	No effect				
12	EATS-mediated	Testis histopathology	Rat	1 year	Oral	>20000 ppm	No effect				
13	EATS-mediated	Testis histopathology	Rat	2 years	Oral	>10000 ppm	No effect				
14	EATS-mediated	Testis histopathology	Rat	2 years	Oral	>30000 ppm	No effect				
15	EATS-mediated	Testis histopathology	Rat	2 years	Oral	20000 ppm	No effect				
16	EATS-mediated	Testis histopathology	Rat	2 years	Oral	>1000 mg/kg bw/day	No effect				
17	EATS-mediated	Testis histopathology	Rat	2 years	Oral	>20000 ppm	No effect				
18	EATS-mediated	Testis histopathology	Rat	2 years	Oral	>15000 ppm	No effect				
19	EATS-mediated	Testis histopathology	Mouse	18 months	Oral	>10000 ppm	No effect				

20	EATS-mediated	Testis histopathology	Mouse	18 months	Oral	>5000 ppm	No effect				
21	EATS-mediated	Testis histopathology	Mouse	18 months	Oral	>40000 ppm	No effect				
22	EATS-mediated	Testis histopathology	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Testis histopathology	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Testis histopathology	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
25	EATS-mediated	Testis histopathology	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000 ppm	No effect				
26	EATS-mediated	Testis histopathology	Rat	10 weeks; prior to mating, continued	Oral	>10000 ppm	No effect				

				until termination							
27	EATS-mediated	Testis histopathology	Rat	11 weeks; prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				
45	EATS-mediated	Testis histopathology	Rat	31 days (PND 23-53)	Oral	> 1000 mg/kg bw/day	No effect				
49	EATS-mediated	Testis histopathology	Rat	28 days	Oral	>20000 ppm	No effect				
52	EATS-mediated	Testis histopathology	Rat	90 days	Oral	>1000 mg/kg bw/day	No effect				
53	EATS-mediated	Testis histopathology	Rat	90 days	Oral	>20000 ppm	No effect				
~~*54*~~	~~*EATS-mediated*~~	~~*Testis histopathology*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000 ppm*~~	~~*No effect*~~				
55	EATS-mediated	Testis histopathology	Rat	90 days	Oral	>20000 ppm	No effect				
56	EATS-mediated	Testis histopathology	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				
57	EATS-mediated	Testis histopathology	Dog	6 months	Oral	>300 mg/kg bw/day	No effect				
58	EATS-mediated	Testis histopathology	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
59	EATS-mediated	Testis histopathology	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect				
60	EATS-mediated	Testis histopathology	Rat	21 days	Dermal	>1000 mg/kg bw/day	No effect				

62	EATS-mediated	Testis histopathology	Rabbit	21 days	Dermal	>5000 mg/kg bw/day	No effect		**RMS:** It is noted that RMS added an additional study in the results for testis weight (study ID 96). In one long-term study in the rat, an increase in relative testis weight was seen, which was considered secondary to decreased body weight. In addition, no histopathological changes were seen in this study. In one long-term study in the mouse (ID 68) an increase in testis weight was seen at a very high dose level, which also caused systemic toxicity (e.g. -11% bw; liver and kidney effects). In 90-day studies in the rat (ID 78) and mouse (ID 79), an increase in relative testis weight was seen but was considered secondary to lower body weight in both studies.		
63	EATS-mediated	Testis histopathology	Rabbit	28 days	Dermal	>2000 mg/kg bw/day	No effect				
67	EATS-mediated	Testis histopathology	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect				
68	EATS-mediated	Testis histopathology	Mouse	2 years	Oral	> 30000 ppm	No effect				
~~70~~	~~EATS-mediated~~	~~Testis histopathology~~	~~Rat~~	~~life-time, all three generations~~	~~Oral~~	~~>30 mg/kg bw/day~~	~~No effect~~				
~~70~~	~~EATS-mediated~~	~~Testis histopathology~~	~~Rat~~	~~21 days (PND0-21, exposure through milk)~~	~~Oral~~	~~>30 mg/kg bw/day~~	~~No effect~~				
73	EATS-mediated	Testis histopathology	Mouse	90 days	Oral	>50000 ppm	No effect				
~~74~~	~~EATS-mediated~~	~~Testis histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Oral~~	~~>300 ppm~~	~~No effect~~	~~No effects in F0 observed.~~			
~~74~~	~~EATS-mediated~~	~~Testis histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Oral~~	~~>300 ppm~~	~~No effect~~	~~No effects in F1 observed.~~			
~~74~~	~~EATS-mediated~~	~~Testis histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Oral~~	~~>300 ppm~~	~~No effect~~	~~No effects in F2 observed.~~			
~~75~~	~~EATS-mediated~~	~~Testis histopathology~~	~~Rat~~	~~Males: 60 days prior to mating; females: 14~~	~~Oral~~	~~>10 mg/kg bw/day~~	~~No effect~~				

				~~*days prior to mating until end of lactation (PND 21) or until sacrifice GD 13*~~					In a public literature study in the mouse (ID 94), a decrease in relative testis weight was observed, however, without a dose response. Overall, it is agreed that there was no EAS-mediated adversity on testis.		
76	EATS-mediated	Testis histopathology	Rat	90-92 days	Oral	>7500 ppm	No effect				
80	EATS-mediated	Testis histopathology	Rat	5 weeks	Oral	500 mg/kg bw/day	No effect				
93	EATS-mediated	Testis histopathology	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			
94	EATS-mediated	Testis histopathology	Mouse	Dams: Day of vaginal plug detection (embryonic day 10.5) to 20 days post-partum Offspring termination: PND 5, 20, 35 and 8 months old animals	Oral	>50 mg/kg bw/day	No effect				

1	EATS-mediated	Testis weight	Rat	90 days	Oral	>20000 ppm	No effect				
2	EATS-mediated	Testis weight	Rat	90 days	Oral	*>50000 ppm*	*No effect*				
3	EATS-mediated	Testis weight	Rat	90 days	Oral	>30000 ppm	No effect				
4	EATS-mediated	Testis weight	Mouse	90 days	Oral	>50000 ppm	No effect				
5	EATS-mediated	Testis weight	Dog	90 days	Oral	>1000 mg/kg bw/day	No effect				
6	EATS-mediated	Testis weight	Dog	90 days	Oral	>10000 ppm	No effect				
7	EATS-mediated	Testis weight	Dog	90 days	Oral	>40000 ppm	No effect				
8	EATS-mediated	Testis weight	Dog	90 days	Oral	>50000 ppm	No effect				
9	EATS-mediated	Testis weight	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
10	EATS-mediated	Testis weight	Dog	1 year	Oral	>50000 ppm	No effect				
11	EATS-mediated	Testis weight	Dog	1 year	Oral	>30000 ppm	No effect				
12	EATS-mediated	Testis weight	Rat	1 year	Oral	>20000 ppm	No effect				
13	EATS-mediated	Testis weight	Rat	2 years	Oral	>10000 ppm	No effect				
14	EATS-mediated	Testis weight	Rat	2 years	Oral	>30000 ppm	**Increase**	Increased relative weight was observed in males at 30000 ppm in week 26 which is considered secondary to decreased body weight. In addition general systemic toxicity such as decreased food consumtion and decreased motoractivity were observed. Moreover, no histopathological changes were observed in testes. Therefore, the decreased relative weight is not considered relevant for EAS-mediated adversity assessment.			

15	EATS-mediated	Testis weight	Rat	2 years	Oral	2000 ppm	No effect				
16	EATS-mediated	Testis weight	Rat	2 years	Oral	>1000 mg/kg bw/day	No effect				
17	EATS-mediated	Testis weight	Rat	2 years	Oral	>20000 ppm	No effect				
18	EATS-mediated	Testis weight	Rat	2 years	Oral	>15000 ppm	No effect				
19	EATS-mediated	Testis weight	Mouse	18 months	Oral	>10000 ppm	No effect				
20	EATS-mediated	Testis weight	Mouse	18 months	Oral	>5000 ppm	No effect				
21	EATS-mediated	Testis weight	Mouse	18 months	Oral	>40000 ppm	No effect				
22	EATS-mediated	Testis weight	Rat	10 weeks	Oral	>15000 ppm	No effect				
23	EATS-mediated	Testis weight	Rat	10 weeks (pre-mating)	Oral	>10000 ppm	No effect				
24	EATS-mediated	Testis weight	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
26	EATS-mediated	Testis weight	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000 ppm	No effect				
27	EATS-mediated	Testis weight	Rat	11 weeks; prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				

45	EATS-mediated	Testis weight	Rat	31 days (PND 23-53)	Oral	> 1000 mg/kg bw/day	No effect				
49	EATS-mediated	Testis weight	Rat	28 days	Oral	>20000 ppm	No effect				
50	EATS-mediated	Testis weight	Rat	28 days	Oral	>2500 mg/kg bw/day	No effect				
52	EATS-mediated	Testis weight	Rat	90 days	Oral	>1000 mg/kg bw/day	No effect				
53	EATS-mediated	Testis weight	Rat	90 days	Oral	>20000 ppm	No effect				
~~*54*~~	~~*EATS-mediated*~~	~~*Testis weight*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000 ppm*~~	~~*No effect*~~				
55	EATS-mediated	Testis weight	Rat	90 days	Oral	>20000 ppm	No effect				
56	EATS-mediated	Testis weight	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				
57	EATS-mediated	Testis weight	Dog	6 months	Oral	>300 mg/kg bw/day	No effect				
58	EATS-mediated	Testis weight	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
59	EATS-mediated	Testis weight	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect				
60	EATS-mediated	Testis weight	Rat	21 days	Dermal	>1000 mg/kg bw/day	No effect				
61	EATS-mediated	Testis weight	Rat	21 days	Dermal	>1000 mg/kg bw/day	No effect				
62	EATS-mediated	Testis weight	Rabbit	21 days	Dermal	>5000 mg/kg bw/day	No effect				

63	EATS-mediated	Testis weight	Rabbit	28 days	Dermal	>2000 mg/kg bw/day	No effect				
67	EATS-mediated	Testis weight	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect				
68	EATS-mediated	Testis weight	Mouse	2 years	Oral	30000 ppm	**Increase**	At terminal sacrifice, the mean absolute and relative weights (to brain and body weight) of the testes were elevated at 30000 ppm (5342.4 mg/kg bw current limit dose would be 1000 mg/kg bw/day). (Epididymis was not weighed.) No histopathological changes were observed . Two further studies in mice using similar doses for 90 days and 2 years (study IDs 67 and 56) did not reveal any effects on testes weight. Since the effect is not reproducibel neither in mouse nor in any other species, the increased organ weight is not considered relevant for EAS-mediated adversity assessment.			
~~*70*~~	~~*EATS-mediated*~~	~~*Testis weight*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				
~~*70*~~	~~*EATS-mediated*~~	~~*Testis weight*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				
73	EATS-mediated	Testis weight	Mouse	90 days	Oral	>50000 ppm	No effect				
76	EATS-mediated	Testis weight	Rat	90-92 days	Oral	>7500 ppm	No effect				
78	EATS-mediated	Testis weight	Rat	90 days	Oral	25000 ppm	**Increase**	An increase in relative but not absolute organ weight was observed at 25000 ppm and 50000 ppm. The increase was considered secondary to extensively decreased body weights (-18%). Histopathology was not performed within this study. However, in another subchronic toxicity study (study ID 2) , no histopathological changes were observed. Moreover, no effects on histopathology were observed in testes after chronic exposure (study IDs 13-18). In addition, the assessment of absolute testes weight is of more relevance, since testis weight is normally conserved despite body weight loss (JRC (2016) Screening methodology to identify potential endocrine disruptors according to different options in the context of an impact assessment.). Therefore, the increase of relative testes weight is considered not relevant for EAS-mediated adversity.			

79	EATS-mediated	Testis weight	Mouse	90 days	Oral	25000 ppm	**Increase**	An increase in relative but not absolute organ weight was observed at 25000 ppm and 50000 ppm. The increase was considered secondary to decreased body weights (>10%). Histopathology was not performed within this study. However, in another subchronic toxicity study (study ID 4) , no histopathological changes were observed. Moreover, no effects on histopathology were observed in testes after chronic exposure (study IDs 19-21). In addition, the assessment of absolute testes weight is of more relevance, since testis weight is normally conserved despite body weight loss (JRC (2016) Screening methodology to identify potential endocrine disruptors according to different options in the context of an impact assessment.). Therefore, the increase of relative testes weight is considered not relevant for EAS-mediated adversity.			
80	EATS-mediated	Testis weight	Rat	5 weeks	Oral	500 mg/kg bw/day	No effect				
93	EATS-mediated	Testis weight	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect				
94	EATS-mediated	Testis weight	Mouse	Dams: Day of vaginal plug detection (embryonic day 10.5) to 20 days post-partum Offspring termination: PND 5, 20, 35 and 8 months old animals	Oral	0,5 mg/kg bw/day	**Decrease**	Relative testes weight was not affected in 20 day old males. A decrease in relative weight was observed in the low and mid dose group aged 35 days reaching statistical significance for the low dose only. In 8 months old rats a decrease in relative testes weight was observed for the low and the high dose group achieving statistical significance for the low dose only. Since no dose-response was observed and the absolute testes weight is not provided (which would be more relevant based on OECD GD 151 (2013)), the effects on testes weight are considered isolated findings.			

96	*EATS-mediated*	*Testis weight*	*Rat*	*90 days*	*Oral*	*>7500 ppm*	*No effect*				
22	EATS-mediated	Genital abnormalities	Rat	10 weeks	Oral	>15000 ppm	No effect		Genital abnormalities were not observed in rat and rabbit in prenatal developmental or 2-generation studies. **In conclusion, EAS-mediated adversity inducing genital abnormalities is not observed.** **RMS:** agreed		
24	EATS-mediated	Genital abnormalities	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000 ppm	No effect				
64	EATS-mediated	Genital abnormalities	Rat	10 days (GD 6-15)	Oral	>3500 mg/kg bw/day	No effect	No treatment-related effect on genitals was observed during sex determination, visceral examination, as well as gonadal inspection.			
66	EATS-mediated	Genital abnormalities	Rabbit	22 days (GD 6-27)	Oral	>350 mg/kg bw/day	No effect	Each fetus was first examined for external malformations and variations and subsequently dissected, internally sexed, and examined for visceral malformations and variations. No genital abnormalities were reported.			
2	EATS-mediated	Mammary gland histopathology (female)	Rat	90 days	Oral	>50000 ppm	No effect		Relevant effects on mammary gland histopathology of male and female animals were not observed in dog (9 studies), rat (16 studies), and mouse (7 studies) after subchronic and chronic exposure as well as exposure over different life stages. **In conclusion, EAS-mediated adversity with regard to effects**		
3	EATS-mediated	Mammary gland histopathology (female)	Rat	90 days	Oral	>30000 ppm	No effect				
4	EATS-mediated	Mammary gland histopathology (female)	Mouse	90 days	Oral	>50000 ppm	No effect				

5	EATS-mediated	Mammary gland histopathology (female)	Dog	90 days	Oral	>1000 mg/kg bw/day	No effect		**on mammary gland is not observed.** **RMS:** Agreed		
7	EATS-mediated	Mammary gland histopathology (female)	Dog	90 days	Oral	>40000 ppm	No effect				
8	EATS-mediated	Mammary gland histopathology (female)	Dog	90 days	Oral	>50000 ppm	No effect				
9	EATS-mediated	Mammary gland histopathology (female)	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
10	EATS-mediated	Mammary gland histopathology (female)	Dog	1 year	Oral	>50000 ppm	No effect				
11	EATS-mediated	Mammary gland histopathology (female)	Dog	1 year	Oral	>30000 ppm	No effect				
12	EATS-mediated	Mammary gland histopathology (female)	Rat	1 year	Oral	>20000 ppm	No effect				
13	EATS-mediated	Mammary gland histopathology (female)	Rat	2 years	Oral	>10000 ppm	No effect				
14	EATS-mediated	Mammary gland histopathology (female)	Rat	2 years	Oral	>30000 ppm	No effect				
15	EATS-mediated	Mammary gland	Rat	2 years	Oral	>20000 ppm	No effect				

		histopathology (female)									
16	EATS-mediated	Mammary gland histopathology (female)	Rat	2 years	Oral	>1000 mg/kg bw/day	No effect				
17	EATS-mediated	Mammary gland histopathology (female)	Rat	2 years	Oral	>20000 ppm	No effect				
18	EATS-mediated	Mammary gland histopathology (female)	Rat	2 years	Oral	>15000 ppm	No effect				
19	EATS-mediated	Mammary gland histopathology (female)	Mouse	18 months	Oral	>10000 ppm	No effect				
20	EATS-mediated	Mammary gland histopathology (female)	Mouse	18 months	Oral	>5000 ppm	No effect				
21	EATS-mediated	Mammary gland histopathology (female)	Mouse	18 months	Oral	>40000 ppm	No effect				
27	EATS-mediated	Mammary gland histopathology (female)	Rat	11 weeks; prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				
52	EATS-mediated	Mammary gland histopathology (female)	Rat	90 days	Oral	>1000 mg/kg bw/day	No effect				

53	EATS-mediated	Mammary gland histopathology (female)	Rat	90 days	Oral	>20000 ppm	No effect				
55	EATS-mediated	Mammary gland histopathology (female)	Rat	90 days	Oral	>20000 ppm	No effect				
56	EATS-mediated	Mammary gland histopathology (female)	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				
57	EATS-mediated	Mammary gland histopathology (female)	Dog	6 months	Oral	>300 mg/kg bw/day	No effect				
58	EATS-mediated	Mammary gland histopathology (female)	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
59	EATS-mediated	Mammary gland histopathology (female)	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect				
67	EATS-mediated	Mammary gland histopathology (female)	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect				
68	EATS-mediated	Mammary gland histopathology (female)	Mouse	2 years	Oral	> 30000 ppm	No effect				
~~*70*~~	~~*EATS-mediated*~~	~~*Mammary gland histopathology (female)*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				

~~*70*~~	~~*EATS-mediated*~~	~~*Mammary gland histopathology (female)*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30 mg/kg bw/day*~~	~~*No effect*~~				
76	EATS-mediated	Mammary gland histopathology (female)	Rat	90-92 days	Oral	>7500 ppm	No effect				
93	EATS-mediated	Mammary gland histopathology (female)	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	F0			
93	EATS-mediated	Mammary gland histopathology (female)	Rat	F0: from GD 6 to end of lactation; Offsping: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			
2	EATS-mediated	Mammary gland histopathology (male)	Rat	90 days	Oral	>50000 ppm	No effect				
3	EATS-mediated	Mammary gland histopathology (male)	Rat	90 days	Oral	>30000 ppm	No effect				

5	EATS-mediated	Mammary gland histopathology (male)	Dog	90 days	Oral	>1000 mg/kg bw/day	No effect				
7	EATS-mediated	Mammary gland histopathology (male)	Dog	90 days	Oral	>40000 ppm	No effect				
9	EATS-mediated	Mammary gland histopathology (male)	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
10	EATS-mediated	Mammary gland histopathology (male)	Dog	1 year	Oral	>50000 ppm	No effect				
14	EATS-mediated	Mammary gland histopathology (male)	Rat	2 years	Oral	>30000 ppm	No effect				
16	EATS-mediated	Mammary gland histopathology (male)	Rat	2 years	Oral	>1000 mg/kg bw/day	No effect				
17	EATS-mediated	Mammary gland histopathology (male)	Rat	2 years	Oral	>20000 ppm	No effect				
18	EATS-mediated	Mammary gland histopathology (male)	Rat	2 years	Oral	>15000 ppm	No effect				
20	EATS-mediated	Mammary gland histopathology (male)	Mouse	18 months	Oral	>5000 ppm	No effect	(Only two animals were examined.)			
27	EATS-mediated	Mammary gland histopathology (male)	Rat	11 weeks; prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000 ppm	No effect				

52	EATS-mediated	Mammary gland histopathology (male)	Rat	90 days	Oral	>1000 mg/kg bw/day	No effect				
53	EATS-mediated	Mammary gland histopathology (male)	Rat	90 days	Oral	>20000 ppm	No effect				
55	EATS-mediated	Mammary gland histopathology (male)	Rat	90 days	Oral	>20000 ppm	No effect				
56	EATS-mediated	Mammary gland histopathology (male)	Mouse	90 days	Oral	>4500 mg/kg bw/day	No effect				
57	EATS-mediated	Mammary gland histopathology (male)	Dog	6 months	Oral	>300 mg/kg bw/day	No effect				
58	EATS-mediated	Mammary gland histopathology (male)	Dog	1 year	Oral	>500 mg/kg bw/day	No effect				
59	EATS-mediated	Mammary gland histopathology (male)	Dog	1 year	Oral	>1000 mg/kg bw/day	No effect				
67	EATS-mediated	Mammary gland histopathology (male)	Mouse	2 years	Oral	> 1000 mg/kg bw/day	No effect				
68	EATS-mediated	Mammary gland histopathology (male)	Mouse	2 years	Oral	> 30000 ppm	No effect				
93	EATS-mediated	Mammary gland histopathology (male)	Rat	F0: from GD 6 to end of lactation; Offspring: up to PND 73±2 and PND 125±2 for the 6 and 13 weeks	Oral	>1.75 mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			

				cohorts, respectively							

Assessment of the integrated lines of evidence and weight of evidence for EAS-mediated adversity and endocrine activity

Relevant data and Lines of Evidence (LoE) including detailed discussions of specific endpoints/parameters per study on potential EAS-mediated parameters are included in Appendix E (attached to chapter 2.1.2). A summary and analysis of the results on adversity and activity based on a weight of evidence approach are provided in Table 6 and Table 7, respectively.

Table 6: WoE for EAS-mediated adversity

- EAS-mediated carcinogenicity in organs related to endocrine activity (e.g. testis, mammary gland, ovaries, uterus) was not observed in chronic/carcinogenicity studies in dog (6 - 12 months: study IDs 9 - 11, 57 - 59), mouse (18 months; study IDs 19 - 21, 2 years: 67 - 68) and rat (1 - 2 years: study IDs 12 - 18).

- No relevant effects were observed on **EAS-mediated parameters** including organ weights as well as reproductive toxicity parameters within the available repeated dose toxicity studies with glyphosate in dog, mouse, rabbit, and rat.

  - <u>Sexual maturation (rat study IDs 22, 23, 26, 44, 45, 93)</u>
    Neither the age at first oestrus (investigated in the female pubertal assay, study ID 44 and a published EOGRTS pilot study, study ID 93) nor the age at vaginal opening (investigated in three 2-generation studies, study IDs 22, 23, 26, the female pubertal assay, study ID 44 and a published EOGRTS pilot study, study ID 93) were affected by glyphosate exposure.
    Three (study IDs 23, 26, 93) out of five studies investigating balanopreputial separation (PPS) did not show any effect of glyphosate exposure including one two-generation study (study ID 23), conducted similar to OECD TG 416 (2001), exposing up to the limit dose of 1000 mg/kg bw/day.
    Within the male pubertal assay (study ID 45), a delayed age at PPS was shown only at the high dose where also overt toxicity (one mortality, lung rales, body weight gain decrease >10%) was observed. Since overt toxicity confounds interpretation of reproductive system-related endpoints in the pubertal assay, the delay in PPS is not considered an anti-androgenic effect (further details and rationale are provided in the LoE).
    In one two-generation study (study ID 22) a marginal but statistically significant delay in PPS was observed at the limit test dose of 1000 mg/kg bw/day in the F1 but not the F2 generation. Since further parameters, such as mating performance, sperm parameters and histopathological examinations of testis or epididymis did not reveal any changes and the effect was not reproduced in two further two-generation studies at similar doses (study IDs 23, 26), the delay of PPS was considered an isolated finding, not relevant for deducing an anti-androgenic effect of glyphosate. This rationale is in line with the conclusion of the EFSA Peer Review (EFSA Journal 2017; 15(9):4979) as well as with the conclusion of EPA on the Endocrine Screening Program (EDSP) Tier l (US EPA, 2015). Thus, glyphosate does not induce an adverse EAS-mediated effect on PPS.
    In conclusion, sexual maturation was neither affected in male nor in female rats.

  - <u>Anogenital distance (AGD) (rat study ID 22, 93)</u>
    The AGD was assessed in a two-generation study and was not affected by glyphosate exposure (study ID 22). The AGD was not investigated in further available two-generation studies since those were performed according to former test guideline versions and no effect on sex ratio was observed (study ID 23). The increase in AGD observed in males in one published EOGRTS pilot study (study ID 93) is considered not related to an endocrine pathway, since no other male parameters (e.g., age at PPS, testes weight, accessory sexual tissue weights, sperm parameters) were affected in this study. Moreover, there is no consistency with regard to a potential androgenic effect when also considering the results

Table 6: WoE for EAS-mediated adversity

of the *in vivo* mechanistic as well as the multi-generation studies.

- Sperm parameters (mouse study ID 79, rat study IDs 22 – 24, 78, 80, 93)
  No relevant effect on sperm numbers was observed. The decrease in sperm numbers observed in one subchronic study (study ID 78) was attributed to general systemic toxicity and not associated with any decrease in testes weights. The decrease in epididymal sperm count observed in a published subacute study (study ID 80) is considered incidental since no effects on testis weight and histopathology were observed in the same study. Moreover, none of six further studies (study IDs 22 – 24, 79, 93, 94) including three two-generation studies did show any effects on sperm or fertility parameters. In conclusion, no EAS-mediated adversity on sperm numbers is observed.
  No effect on sperm motility and morphology were observed in rat (study IDs 22 – 24, 78, 93) and mouse (study ID 79). In conclusion, no EAS-mediated adversity on sperm parameters was deduced.

- Oestrous cyclicity (mouse study ID 79, rat study IDs 22 – 24, 26, 44, 78, 93)
  No relevant effect on oestrous cyclicity was observed. The increase in oestrous cycle length observed in one (study ID 78) out of seven studies is attributed to general systemic toxicity (reduced body weight gain and diarrhea) and a dose exceeding the current applicable limit dose by a factor of three. Moreover, none of the other six studies (study IDs 22 – 24, 26, 44, 79) including four two-generation studies did show any effects on fertility. In conclusion, no EAS-mediated adversity on oestrous cyclicity is observed.

- Female reproductive organs (dog, mouse, rabbit, rat)
  - Vaginal smears and/or **vagina** histopathology were unaffected by exposure to glyphosate in dog (study ID 9), mouse (study IDs 4, 20, 21), and rat (study IDs 2, 3, 14, 17, 18, 22 – 27, 93) after subchronic and chronic exposure as well as exposure over different life stages (in rat).
  - An effect on **clitoral gland** was not observed in rat of the F0 generation of a three-generation study (study ID 70).
  - No effects on **uterus** weights, as well as uterus and cervix histopathology were observed in dog (study IDs 5 - 11, 57 - 59), mouse (study IDs 4, 19 - 21, 56, 67, 68, 73), rabbit (study IDs 30 - 32, 34, 35, 62) and rat (study IDs 1 - 3, 12 - 18, 22 - 28, 44, 49, 52 - 55, 65, 70, 74, 76, 93) after subchronic and chronic exposure as well as exposure over different life stages (in rat).
  - No effects on **ovary** weights and histopathology were observed in dog (study IDs 5 - 11, 57 - 59), mouse (study IDs 4, 19 - 21, 56, 67, 68, 73), rabbit (study IDs 62, 63) and rat (study IDs 1 - 3, 12 - 18, 22 - 27, 44, 49, 52 - 55, 60, 70, 74, 76, 93) after subchronic and chronic exposure as well as exposure over different life stages (in rat).
  - No effect on **mammary gland** histopathology was observed in dog (study IDs 5, 7 - 11, 57 - 59), mouse (study IDs 4, 19 - 21, 56, 67, 68), and rat (study IDs 2, 3, 12 - 18, 27, 52, 53, 55, 70, 76, 93) after subchronic and chronic exposure as well as exposure over different life stages (in rat).

  → EAS-mediated adversity on female reproductive organs was not observed in four species (dog, mouse, rabbit, and rat).

- Male reproductive organs (dog, mouse, rabbit, rat)
  - No relevant effects on **testis** weights and histopathology were observed in dog (study IDs 5 - 11, 57 - 59), mouse (study IDs 4, 19 - 21, 56, 67, 68, 73, 79), rabbit (study ID 62, 63), and rat (study IDs 1 - 3, 12 - 18, 22 - 27, 45, 49, 52 - 55, 60, 70, 74 - 76, 78, 80, 93, 94) after subchronic and chronic exposure, as well as exposure

Table 6: WoE for EAS-mediated adversity

over different life stages (in rat). In isolated studies, relative testis weight increases were observed. However, these were mostly attributed to concurrent body weight decreases. Moreover, the weight changes were neither consistent within one species over different exposure periods (no time coherence) nor in the four species investigated and did not correlate with histopathological changes.

- No relevant effects on **epididymis** weights and histopathology were observed in dog (study IDs 5, 7 - 11, 57 - 59), mouse (study IDs 4, 19 - 21, 56, 67, 68, 73), rabbit (study ID 62), and rat (study IDs 1, 3, 12 - 18, 22 - 27, 45, 52, 53, 55, 60, 70, 80, 93) after subchronic and chronic exposure as well as exposure over different life stages (in rat).

- **Accessory sex organs**:
  - In 1/3 studies assessing coagulating gland weight, relative but not absolute coagulating gland weight was reduced (study ID 80). No effect on coagulating gland weight was observed in 2/3 toxicity studies in rat exposed to higher doses (e.g. study ID 22, 23). Moreover, no effects on **coagulating gland** weights and histopathology were observed in mouse (study IDs 4, 19 - 21) and rat (study IDs 3, 13, 14, 22 - 26, 49, 54, 93) after subchronic and chronic exposure as well as exposure over different life stages (in rat).
  - Statistically significant decreased mean absolute **LABC** weight (15.9%) was observed at the high dose of the male pubertal assay (study ID 45). At this dose level overt toxicity (one mortality, rales, body weight gain decrease > 10%) was observed. Body weight decreases > 10% have been shown to confound the interpretation of reproductive system-related endpoints in the pubertal assays (Fed Reg. 74(71):17570-17585). Therefore, for the high dose group, interpretation of endocrine endpoints was confounded by overt and systemic toxicity and considered not relevant for a WoE analysis for the androgen pathway as per the USEPA and EFSA guidance. In addition, no effects on reproduction were observed in one-, two- and three-generation studies.
  - An effect on the **preputial gland** was not observed in mouse and rat (F0, F1, F2) after chronic exposure (study ID 20) and within a three-generation study (study ID 70), respectively.
  - No relevant effect on **prostate** weight and histopathology were observed in dog (study IDs 5, 7 - 11, 57 - 59), mouse (study IDs 4, 19 - 21, 56, 67, 68, 73), rabbit (study ID 62) and rat (study IDs 2, 3, 11 - 18, 22 - 27, 52 - 55, 70, 76, 80, 93) after subchronic and chronic exposure as well as exposure over different life stages (in rat)
  - Relevant effects on **seminal vesicles** weight were not observed in rat and mouse. In 2/8 rat studies a decrease in absolute organ weight was observed. In both cases, the effect is not considered linked to an endocrine effect induced by glyphosate treatment: 1) Within the pubertal assay (study ID 45) overt toxicity is observed at the same dose level; 2) Only relative but not absolute organ weight was significantly decreased without corresponding histopathological changes (study ID 80). In addition, organ weight was not decreased in further studies in rat at higher doses and longer exposure periods (e.g. study ID 22, 23). Moreover, no relevant effects on seminal vesicles weight and histopathology were observed in mouse (study IDs 4, 19 - 21, 56), rabbit (study ID 62) and rat (study IDs 2, 3, 12 - 15, 17, 18, 22 - 27, 49, 52, 54, 74, 80 (histopathology only), 94 (weight only), 93) after subchronic and chronic exposure as well as exposure over different life stages (in rat).

Table 6: WoE for EAS-mediated adversity

- No effect on **mammary gland** histopathology was observed in dog (study IDs 5, 7, 9, 10, 57 - 59), mouse (study IDs 20, 56, 67, 68), and rat (study IDs 2, 3, 14, 16, 17, 18, 27, 52, 53, 55, 93) after subchronic and chronic exposure as well as exposure over different life stages (in rat).

→ EAS-mediated adversity on male reproductive organs was not observed in four species (dog, mouse, rabbit, and rat).

- Genital abnormalities
  Genital abnormalities were not observed in any two-generation study (study IDs 22, 24), or during sexing in prenatal developmental studies (study IDs 64 (rat), 66 (rabbit)).

→ Under consideration of all available studies up to chronic exposure in four species, adversity based on EAS-mediated parameters is not observed.

- No relevant and consistent effects on "**parameters sensitive to but not diagnostic of EATS**" were observed:
  - organ weights and histopathology
    - No relevant effects on **adrenal** weight and histopathology were observed in 44 and 45 repeated dose toxicity studies, respectively, in four species, i.e. dog, mouse, rabbit, rat.
    - No relevant effects on **pituitary** weight and histopathology were observed in 19 and 39 repeated dose toxicity studies, respectively, in four species, i.e. dog, mouse, rabbit, rat.
    - No relevant effects on **brain** weight (34 studies) and histopathology (23 studies) were observed in four species in adult animals (dog, mouse, rabbit, and rat). Moreover, no effects on brain development were observed in two-, and three-generation studies in rat (study IDs 22, 26, 70, 74).

  - Development and reproduction
    - **Dystocia** was reported for two single animals (one animal each in the F0 and F1 generation of the low dose group) within one two-generation study (study ID 25). These were considered isolated incidental findings. Moreover, dystocia was not reported within the other available multi-generation studies (study IDs 22 – 27, 70, 74, 75) and thus, dystocia is not induced by glyphosate treatment.
    - **Fertility** parameters such as pre-coital interval, time to mating, fertility index, and pregnancy index were not relevantly affected in multi-generation studies in rat (study IDs 22 – 27, 70, 74).
    - **Reproduction** parameters such as gestation length, number of ovarian follicles, were not relevantly affected in multi-generation studies in rat (study IDs 22 – 27, 70, 74, 93). Moreover, numbers of implantations and corpora lutea, numbers of embryonic and foetal deaths and viable foetuses, pre- and post-implantation loss were not relevantly affected in prenatal developmental toxicity studies (study IDs 28 – 35, 46, 47, 46 – 66, 75, 77) in rat and rabbit in the absence of maternal toxicity as well as in two-generation studies (study IDs 22, 23) in rat.
    - **Developmental parameters** such as the presence of anomalies, foetal and pup development, litter/pup weight, pup survival, litter viability, litter size were not relevantly affected by glyphosate exposure in the absence of maternal toxicity (prenatal developmental toxicity studies: study IDs 28 – 35, 46, 47, 46 – 66, 75, 77, multi-generation studies: study IDs 22 – 27, 70, 74, 75, 93). Moreover, no effect was observed on neurological development as shown in the functional observation battery investigation within a two-generation study (study ID 22).

Table 6: WoE for EAS-mediated adversity

- No effect on **sex ratio** was observed in prenatal toxicity studies (study IDs 30-34, 46, 47, 66 and 28, 29, 64, 65 for rabbit and rat, respectively) as well as in multi-generation studies in rat (study IDs 22-24, 26, 69, 70, 93).

→ **Under consideration of all available studies up to chronic exposure in four species, adversity based on "parameters sensitive to, but not diagnostic of EATS" is not observed.**

→ **In conclusion, no EAS-mediated adversity is deduced for glyphosate based on 79 *in vivo* OECD TG studies as well as five published studies in four species including different life stages and different exposure periods up to chronic exposure.**

Note by RMS:
Regarding Table 6 above describing WoE EAS-mediated adversity:

It is noted that RMS concluded that the studies with IDs 54, 70, 74 and 75 were unacceptable.

- Clitoral gland:

The only study that investigated the clitoral gland was the study with ID 70. This study did not indicate any effect, however, RMS considered this study to be unacceptable.

- Preputial gland:

Possible effects on preputial gland were investigated in a chronic study (ID 20) and a 3-generation study (ID 70). No effects were observed, however, RMS considered study ID 70 to be unacceptable.

- Sperm parameters:

There is an additional study available (NTP 1992), which was not submitted by the applicants. In this study in F344/N rats, a decrease of 20% in sperm counts was found in groups exposed to 25000 and 50000 ppm glyphosate. Left caudal, epididymal and testicular weights, epididymal sperm motility, total spermatid heads/testes and total spermatid head/g caudal tissue were not different from controls. At these two high dose levels, reduced body weight gains were seen in males. In B6C3F1 mice no effect on sperm motility was observed up to a dose level of 50000 ppm.

In a 2-generation study (ID 22) a decrease in number of homogenization resistant spematid in the cauda epididymis was seen in F0 males only and without affecting reproductive performance.
In a 90-day study in the rat (ID 78), a decrease in sperm number was seen, however this was at a dose level exceeding the MTD.
In another study in rat (ID 80) a decrease in total sperm count was seen, however, without an effect on testis weight or histopathology. In none of the other studies in rat or mouse an effect was seen.
Overall, it is agreed that there is no EAS-mediated adversity regarding sperm numbers.
Furthermore, RMS notes that nipple retention (androgen-mediated) was not examined specifically in any of the studies. However, this does not impact the outcome of the ED assessment as it is considered that this endpoint has been sufficiently investigated.

Table 7: WoE for EAS-mediated endocrine activity

E-modality:

- *in silico*
  The available *in silico* data provide supporting evidence that glyphosate does not possess (anti)estrogenic activity based on QSAR model predictions including CERAPP consensus

Table 7: WoE for EAS-mediated endocrine activity

predictions (for details refer to QSAR report (report no 110517-1, KCA 5.8.3-11)).

- *in vitro*
  Potential *in vitro* mechanistic effects related to E-modality were investigated in the following two *in vitro* Guideline assays showing no estrogenic activity: ER Binding Assay (study ID 37: OPPTS 890.1250 (2009)) and Stably Transfected Human ERα Transcriptional Activation Assay (study ID 38: OECD TG 455). No consistent and relevant effect was observed in further published non-Guideline *in vitro* studies (for details on study IDs 84, 85, 87, 89 please refer to LoE).

- *in vivo*
  Potential endocrine activity was investigated in the Uterotrophic Assay (OECD TG 440; study ID 42). Glyphosate did not affect terminal body weight or body weight gains at any dose. No treatment-related clinical and macroscopic findings were noted in uterus from either the glyphosate or positive control group. Mean uterine absolute and relative weights (wet and blotted) for the glyphosate group were similar the vehicle control group. Significantly higher mean wet and blotted uterine weights (8.6- and 288 3.6-fold, respectively) compared to the vehicle control group were measured in the positive control group demonstrating the expected estrogenic effect. Based on these results, E-related endocrine activity is not deduced for glyphosate.
  Moreover, several hormone levels (estradiol, progesterone, FSH, LH, prolactin, sex hormone binding globuline (SHBG), growth hormone (GH), adrenocorticotropic hormone (ACTH), brain-derived neurotrophic factor (BDNF) measured in 2 published *in vivo* studies (study IDs 80, 93) were not affected.

A-modality:

- *in silico*
  The available *in silico* data provide supporting evidence that glyphosate does not possess (anti)androgenic activity based on QSAR model predictions including COMPARA consensus predictions (for details refer to QSAR report (report no 110517-1, KCA 5.8.3-11)).

- *in vitro*
  Potential *in vitro* mechanistic effects related to A-modality were investigated in the AR Binding assay (study ID 39: OPPTS 890.1150 (2009)) showing no androgenic activity. No consistent and relevant effect was observed in further published non-Guideline *in vitro* studies (for details on study IDs 83, 86 please refer to LoE).

- *in vivo*
  Potential endocrine activity was investigated in the Hershberger Assay (study ID 43: OECD TG 441) as well as the male pubertal assay. In addition testosterone levels were measured in three published rat (study IDs 80, 91, 93) and one mouse (study ID 94) study.
  Serum testosterone levels in mouse were decreased in the low and high dose group of 35 day old males where dams had been exposed to glyphosate (study ID 94). However, no dose-response was observed and testosterone levels of eight months old mice of the same study were not affected.
  Mean serum testosterone levels of the high dose group were decreased in the male pubertal assay (study ID 45), where also overt toxicity was observed. However, the decrease was statistically not significant and not dose-dependent. Moreover, no histopathological changes were observed and organ weights were not affected at doses without overt toxicity. Thus, the testosterone decrease is not considered treatment-related which is also supported by the

Table 7: WoE for EAS-mediated endocrine activity

conclusion of the EPA on the Endocrine Screening Program (EDSP) Tier l (US EPA, 2015) as well as the current EFSA Peer Review (EFSA Journal 2017;15(9):4979). Moreover, testosterone levels in serum (study IDs 80, 93) and testes (study ID 91, 93) were not affected in three published rat studies.
The Hershberger assay serves as a mechanistic *in vivo* screening assay for androgen agonists, androgen antagonists and 5α-reductase inhibitors. Glyphosate had no effect on mean body weight, body weight gain, or produced any clinical or macroscopic findings after treatment with the limit dose (1000 mg/kg bw/day). No significant effects were observed on the weights of male accessory sex organs (bulbourethral glands, glans penis, Levator ani and bulbocavernosus (LABC) muscle group, seminal vesicles with coagulating glands and ventral prostate) in the androgen agonist portion of the assay.
Glyphosate did not produce anti-androgenic activity in peripubertal orchidepididy-mectomized male rats that had co-administration of a daily dose of the reference androgen testosterone propionate.
Based on the results of the Hershberger Assay and the hormone measurements of the male pubertal assay as well as the published RDT studies, an (anti)androgenic activity of glyphosate *in vivo* is not deduced.

S-modality:

- *in silico*
  The available *in silico* data provide supporting evidence that glyphosate does not possess activity to affect steroidogenesis based on molecular docking method for glucocorticoid receptor, glucocorticoid receptor antagonism, and mineralocorticoid receptor (for details refer to QSAR report (report no 110517-1, KCA 5.8.3-11)).

- *in vitro*
  Potential *in vitro* mechanistic effects related to S-modality were investigated in the aromatase assay (study ID 40: OPPTS 890.1200) and the H295R steroidogenesis assay (study ID 41: OECD TG 456) showing no endocrine disrupting activity related to steroidogenesis. Moreover, several published assays are available partly showing increases and decreases in *in vitro* hormone levels (e.g. estradiol and progesterone). However, no OECD TG were followed and consistent effects were not observed. In addition, publications investigating effects on aromatase (study IDs 88, 90) did not show any effects on enzyme activity or mRNA levels.

- *in vivo*
  In vivo tests specifically investigating effect on steroidogenesis are currently not available. However, S-modality is partially covered in the Hershberger Assay by examining potential effects on 5 alpha-hydroxylase. Based on the negative result of this assay, no indication for S-related endocrine activity can be deduced for glyphosate. Moreover, the Leydig cell-specific steroidogenesis factors CYP11A1 and STAR as well as expression and distribution of the steroidogenic enzyme HSD3B1 were not affected in a subacute rat study (study ID 91). Additionally, aromatase mRNA levels were not affected in mouse dams exposed to glyphosate from GD 1 to PND 20 (study ID 94).

→ **In conclusion, no EAS-related endocrine activity is deduced for glyphosate based on *in silico, in vitro* as well as *in vivo* mechanistic data.**

Note by RMS:

Regarding Table 7 above describing WoE EAS-mediated endocrine activity:

E-modality, *in vitro*: It is noted that RMS concluded that the Transfected Human ERα Transcriptional Activation Assay (study ID 38: OECD TG 455) was not acceptable.

A review of the mammalian guideline studies as well as studies available from scientific literature conducted with glyphosate revealed no carcinogenicity or any other EAS-mediated adverse effects from a diverse set of biological markers (e.g. organ weights, growth parameters, sexual maturation, reproductive indices, histopathology of estrogen- and androgen-sensitive organs and those important for steroidogenesis) in four species (dog, mouse, rabbit, rat).

Moreover, under the EDSP Program, the male and female pubertal assays were conducted to investigate a potential endocrine effect of glyphosate.
The female pubertal assay is relatively sensitive to alterations in estrogen function. During validation, the female pubertal assay was shown to detect numerous estrogenic compounds. The profile of effects for estrogen agonists included early vaginal opening, reduced body weight at vaginal opening, early first oestrus, decreased ovarian weight, increased uterine weight and altered ovarian/uterine histology. In the female pubertal assay, glyphosate had no effect on age or body weight at vaginal opening, pituitary, ovarian and uterine (wet or blotted) weights and uterine and ovarian histopathology. Mean age at first oestrus and mean oestrus cycle length were unaffected by glyphosate.
Experience with the male pubertal assay demonstrated that it is relatively sensitive to changes in androgen status. During validation, the male pubertal assay was shown to detect numerous estrogenic compounds. The general profile of effects for androgen antagonists included delayed preputial separation, decreased organ weights (i.e., prostate, seminal vesicle, levator ani-bulbocavernosus and epididymides), altered serum testosterone levels and altered testicular and epididymal histology. Mean dorsolateral prostate weight was significantly reduced with glyphosate at mid-dose group, 300 mg/kg bw/day, compared to control. However, this change was not noted at the high or low dose groups, so in the absence of a dose-response and coupled with none of the other reproductive organ weights were altered, this isolated finding is not considered to be endocrine-mediated. Taken together, the results from the pubertal assay with glyphosate does not fit the profile of an androgenic or anti-androgenic compound.

Potential EAS-related activity was investigated *in vivo* in the Uterotrophic and Hershberger Assay, which were both inactive. Glyphosate did neither induce uterine weight increases in the Uterotrophic assay nor induce significant increases in weights of two accessory sex tissues in the androgenic portion or significant decreases in the weights of two accessory sex tissues in the anti-androgenic portion of the Hershberger Assay. Furthermore, *in vivo* hormone levels were investigated in published studies and no relevant effects were observed. Therefore, EAS-related endocrine activity, including 5-alpha-reductase is not supported for glyphosate.

In conclusion, glyphosate does not induce EAS-mediated adversity and no EAS-related endocrine activity was observed *in silico, in vitro,* and *in vivo*.

Assessment and conclusion by RMS:
It is agreed with that glyphosate does not induce EAS-mediated adversity or EAS-mediated endocrine activity.

Initial analysis of the evidence and identification of relevant scenario for the ED assessment of EAS-modalities

Table 8: Selection of relevant scenario

Adversity based on EAS-mediated parameters	**Positive mechanistic OECD CF level 2/3 Test**	**Scenario**	**Next step of the assessment**	**Scenario selected**
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is not "**EAS-mediated**" adversity	**X**
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no **EAS-mediated endocrine activity** observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

MoA analysis for EAS-modalities

Not applicable (according to scenario 1a in Table 8, selected based on the available data on glyphosate, a MoA analysis is not required).

Assessment and conclusion by RMS:
It is agreed that a mode of action analysis is not required.

Conclusion of the assessment of EAS-modalities

Potential effects of glyphosate on the HPG axis were addressed in several repeated dose toxicity studies of subacute to chronic exposure also considering different life stages (level 4 and 5 studies of the OECD conceptual framework) where EAS-mediated parameters as well as "parameters sensitive to, but not diagnostic of EATS" ", and "*in vivo* mechanistic parameters" were analysed.

A review of the mammalian guideline studies as well as studies available in scientific literature in four species (dog, mouse, rabbit, rat), conducted with glyphosate for different exposure periods, including different life stages (in rat), did not show carcinogenicity or any other EAS-mediated adverse effects. Since a two-generation study, conducted according to the most recent OECD TG 416 (OECD, 2001), is also available, potential EAS-mediated adversity is considered sufficiently investigated based on the ECHA/EFSA ED Guidance.

For sufficient investigation of EAS-related activity, the ECHA/EFSA Guidance proposes the Uterotrophic and Hershberger Assay. Both assays have been conducted with glyphosate and shown negative results. Moreover, the available *in vitro* assays and *in silico* models do not provide any indication for EAS-related endocrine activity. Thus, EAS-related activity for glyphosate is not observed considering a sufficient dataset as requested by the ECHA/EFSA ED Guidance.

In conclusion, glyphosate does not induce EAS-mediated adversity and no EAS-related endocrine activity was observed *in silico*, *in vitro,* and *in vivo*. This conclusion is in concordance with the current

Peer review of the pesticide risk assessment of the potential endocrine disrupting properties of glyphosate (EFSA Journal 2017;15(9):4979) as well as with the conclusion of EPA on the Endocrine Screening Program (EDSP) Tier l (US EPA, 2015).

According to the ED criteria laid down in Regulation (EU) 2018/605, endocrine mediated adversity as well as activity and the biological link between those two must be apparent to identify a substance as an endocrine disruptor. Since glyphosate does neither induce EAS-mediated adversity *in vivo* nor EAS-related endocrine activity *in silico, in vitro,* and *in vivo*, it is concluded that the ED criteria with regard to EAS-modalities in mammalian species are not fulfilled for glyphosate (Scenario 1a, Table 8).

Assessment and conclusion by RMS:
It is agreed with overall conclusion of the applicant regarding the EAS-modalities. RMS considers the EAS-modalities to be sufficiently investigated and no adversity was observed. Additional *in silico* and *in vitro* data do not indicate EAS-mediated endocrine activity.
Based on the available data on glyphosate, the ED criteria for the EAS-modality are not met.

2.10.2.3 Overall conclusion on the ED assessment for humans

Potential effects of glyphosate on the HPT and HPG axis were addressed in several repeated dose toxicity studies of subacute to chronic exposure also considering different life stages (level 4 and 5 studies of the OECD conceptual framework) where EATS-mediated parameters, "parameters sensitive to, but not diagnostic of EATS", and "*in vivo* mechanistic parameters" were analysed. In addition, *in vitro* and *in silico* information are available and were considered for the ED assessment of glyphosate.

The general profile of effects for thyroid-active compounds include decreased T4, increased TSH, increased thyroid weight and/or altered thyroid histopathology (follicular cell hypertrophy/hyperplasia with decreased amounts of colloid). Within the repeated dose toxicity studies, relevant and consistent effects on thyroid weights and thyroid histopathology were not observed in four mammalian species (dog, mouse, rabbit, and rat). Moreover, there were no treatment-related effects on thyroid hormones (T4 and TSH) in the male pubertal assay in the absence of overt toxicity and no effects on thyroid hormones were observed in the female pubertal assay. In a published pilot study for an EOGRTS (study ID 93) an increase in TSH was observed in F1 males only sacrificed after 6 weeks of exposure post weaning. Since no effect on TSH was observed after 13 weeks of post-weaning exposure as well as in the pubertal assays, covering the same life stage as the 6 week period of the pilot study, the observed TSH increase is considered not biologically relevant. In addition, no indication for thyroid receptor binding is deduced from *in silico* modelling.

With regard to EAS modalities, a review of the available mammalian guideline studies as well as studies published in scientific literature in four species (dog, mouse, rabbit, rat), conducted with glyphosate over different exposure periods including different life stages (multi-generation studies in rat), did not show carcinogenicity or any other EAS-mediated adverse effects.

In addition, EAS-related activity was investigated *in vivo* in the Uterotrophic and Hershberger Assay showing negative results and the available *in vitro* OECD TG studies and *in silico* models do not provide any indication for EAS-related endocrine activity.
Thus, EAS-related activity for glyphosate is not observed, considering a sufficient dataset as requested by the ECHA/EFSA ED Guidance.

In conclusion, glyphosate does not induce EATS-mediated adversity and no EATS-related endocrine activity was observed *in silico, in vitro,* and *in vivo*. This conclusion is in concordance with the current Peer review of the pesticide risk assessment of the potential endocrine disrupting properties of glyphosate (EFSA Journal 2017;15(9):4979) as well as with the conclusion of EPA on the Endocrine Screening Program (EDSP) Tier l (US EPA, 2015).

According to the ED criteria laid down in Regulation (EU) 2018/605, endocrine mediated adversity as well as activity and the biological link between those two must be apparent to identify a substance as an endocrine disruptor. Since glyphosate does not induce EATS-mediated adversity, which is considered sufficiently investigated according to ECHA/EFSA ED Guidance, and EATS-related endocrine activity was not observed *in silico, in vitro,* and *in vivo*, it is concluded that the ED criteria with regard to EATS-modalities in mammalian species are not met for glyphosate.

Assessment and conclusion by RMS:
It is agreed with overall conclusion of the applicant regarding the EATS-modalities.
Based on the available data on glyphosate, the ED criteria are not met.

2.10.3 ED assessment for non-target organisms
Refer to overall Volume 1.

2.10.4 Overall conclusion on the ED assessment
Refer to overall Volume 1.

Appendix: Tables for endpoints 'sensitive to but not diagnostic of', systemic toxicity and target organ toxicity.

Changes, made by RMS are in *italic*.

Sensitive to, but not diagnostic of:

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
1	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	90 days	Oral	>20000	ppm	No effect		There were no effects observed on histopathology of adrenals in dogs, rabbits, rats, and mice. There are 4/25 studies indicating changes in adrenal weight of rats. However, no consistent weight change is apparent and without any histopathological correlate, weight changes are considered incidental. An increase in absolute and relative organ weight was observed in male dogs in 1/10 studies (study ID 5) only after sub-chronic exposure.	**Under consideration of all available studies in four species up to chronic exposure period, adversity based on "parameters sensitive to, but not diagnostic of EATS" is not observed.** **RMS:** Agreed	**N**
2	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	90 days	Oral	>50000	ppm	No effect				
3	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	90 days	Oral	>30000	ppm	No effect				
4	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Mouse	90 days	Oral	>50000	ppm	No effect				
5	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Dog	90 days	Oral	>1000	mg/kg bw/day	No effect				
6	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Dog	90 days	Oral	>10000	ppm	No effect				
7	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Dog	90 days	Oral	>40000	ppm	No effect				
8	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Dog	90 days	Oral	>50000	ppm	No effect				
9	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Dog	1 year	Oral	>500	mg/kg bw/day	No effect				
10	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Dog	1 year	Oral	>50000	ppm	No effect				
11	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Dog	1 year	Oral	>30000	ppm	No effect				
12	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	1 year	Oral	>20000	ppm	No effect				

13	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	2 years	Oral	>10000	ppm	No effect		However, without any histopathological correlate and no effect on weight in chronic studies at similar and higher doses in dog, the weight change is considered incidental. An effect on organ weight was not observed in rabbit and mouse. **In conclusion, glyphosate does not induce adverse effects on adrenals.** **RMS:** No treatment-related adverse effects on adrenal histopathology were seen in any of the studies in mouse, rat, rabbit and dog.		
14	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	2 years	Oral	>30000	ppm	No effect				
15	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	2 years	Oral	>20000	ppm	No effect				
16	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	2 years	Oral	>1000	mg/kg bw/day	No effect				
17	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	2 years	Oral	>20000	ppm	No effect				
18	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	2 years	Oral	>15000	ppm	No effect				
19	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Mouse	18 months	Oral	>10000	ppm	No effect				
20	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Mouse	18 months	Oral	>5000	ppm	No effect				
21	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Mouse	18 months	Oral	>40000	ppm	No effect				

22	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	10 weeks	Oral	15000	ppm	No effect				
23	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000	ppm	No effect				
49	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	28 days	Oral	>20000	ppm	No effect				
50	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	28 days	Oral	>2500	mg/kg bw/day	No effect				
52	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	90 days	Oral	>1000	mg/kg bw/day	No effect				
53	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	90 days	Oral	>20000	ppm	No effect				
54	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	90 days	Oral	>20000	ppm	No effect				
55	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	90 days	Oral	>20000	ppm	No effect				
56	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Mouse	90 days	Oral	>4500	mg/kg bw/day	No effect				
57	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Dog	6 months	Oral	>300	mg/kg bw/day	No effect				
58	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Dog	1 year	Oral	>500	mg/kg bw/day	No effect				
59	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Dog	1 year	Oral	>1000	mg/kg bw/day	No effect				
63	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rabbit	28 days	Dermal	>2000	mg/kg bw/day	No effect				
67	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Mouse	2 years	Oral	> 1000	mg/kg bw/day	No effect				
68	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Mouse	2 years	Oral	> 30000	ppm	No effect				
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Adrenals histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Adrenals histopathology*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				

73	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Mouse	90 days	Oral	>50000	ppm	No effect				
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Adrenals histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No treatment-related histopathological changes were observed in F1.*~~			
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Adrenals histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No treatment-related histopathological changes were observed in F2.*~~			
76	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	90-92 days	Oral	>7500	ppm	No effect				
78	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	90 days	Oral	>50000	ppm	No effect				
79	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Mouse	90 days	Oral	>50000	ppm	No effect				
93	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect	F0			
93	Sensitive to, but not diagnostic of, EATS	Adrenals histopathology	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect	Assessed for both F1 exposure groups.			
96	*Sensitive to, but not diagnostic of, EATS*	*Adrenals histopathology*	*Rat*	*90 days*	*Oral*	*>7500*	*ppm*	*No effect*				
1	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	90 days	Oral	>20000	ppm	No effect				
2	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	90 days	Oral	*>50000*	ppm	*No effect*				

3	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	90 days	Oral	>30000	ppm	No effect		**RMS:** In one 90-day study in dog, an increase in adrenal weight was seen in males without histopathological effects. In none of the other 90-day or 1-year dog studies, in which similar or even higher dose levels were tested, an effect on adrenal weight was found. In one 2-year study in the rat, a decrease in adrenal weight was found in females, which was within HCD and without histopathological effects. In the pubertal rat assay, a decrease in absolute adrenal weight was found, which was considered to be secondary to systemic toxicity. In a 90-day study in the rat, relative adrenal weight was decreased at the top dose, where		
4	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Mouse	90 days	Oral	>50000	ppm	No effect				
5	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Dog	90 days	Oral	300	mg/kg bw/day	**Increase**	Absolute and relative weight were increased in males at 300 mg/kg bw/day (+18 and +25%) and 1000 mg/kg bw/day (+21 and +70%). Statistical significance was reached for relative weight at 1000 mg/kg bw/day only. In absence of any histopathological changes and since the weight change was not reproducible in other chronic (study IDs 9-11, 57, 58, 59) as well as subchronic (study IDs 6, 7, 8) studies at similar doses, the observed increase is considered incidental and thus, not relevant for assessment of potential EATS-related adversity.			
6	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Dog	90 days	Oral	>10000	ppm	No effect				
7	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Dog	90 days	Oral	>40000	ppm	No effect				
8	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Dog	90 days	Oral	>50000	ppm	No effect				
9	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Dog	1 year	Oral	>500	mg/kg bw/day	No effect				
10	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Dog	1 year	Oral	>50000	ppm	No effect				
11	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Dog	1 year	Oral	>30000	ppm	No effect				
12	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	1 year	Oral	>20000	ppm	No effect				
13	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	2 years	Oral	>10000	ppm	No effect				
14	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	2 years	Oral	>30000	ppm	No effect				

15	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	2 years	Oral	6000	ppm	**Decrease**	Absolute and relative weights were decreased in females at ≥ 6000 ppm which was partly statistically significant but mainly within historical control data. Based on the fact that histopathological changes were not observed and no effects on organ weight were observed in further chronic studies in rat at similar or even higher doses (study IDs 13, 14, 16), the decreased organ weight is considered not toxicologically relevant.	also systemic toxicity was observed. Overall, some studies showed an effect on adrenal weight which was not consistent (decrease/increase), seen in the presence of systemic toxicity and without affecting adrenal histopathology. Overall, it is agreed that glyphosate does not cause adverse effects on the adrenals.		
16	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	2 years	Oral	>1000	mg/kg bw/day	No effect				
18	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	2 years	Oral	>15000	ppm	No effect				
19	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Mouse	18 months	Oral	>10000	ppm	No effect				
20	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Mouse	18 months	Oral	>5000	ppm	No effect				
21	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Mouse	18 months	Oral	>40000	ppm	No effect				
22	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	10 weeks	Oral	>15000	ppm	No effect				
23	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	10 days (pre-mating)	Oral	>10000	ppm	No effect				
24	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	10 weeks for pre-mating rearing 8 for subsequent breeding	Oral	>30000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect				
44	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	21 days (PND 22-42)	Oral	> 1000	mg/kg bw/day	No effect				

45	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	31 days (PND 23-53)	Oral	300	mg/kg bw/day	**Decrease**	Not statistically significantly lower mean absolute adrenal gland (9.2%, 8.6% for 1000 and 300 mg/kg bw/day, respectively) weight was observed. However, at the same dose, signs of general systemic toxicity such as decreased body weight gain and rales were observed. Since the relative organ weights were not affected, the non-significant decrease in absolute adrenal weights is considered to be an effect of general systemic toxicity and thus,s not considered relevant for EAS-mediated adversity.			
49	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	28 days	Oral	>20000	ppm	No effect				
50	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	28 days	Oral	>2500	mg/kg bw/day	No effect				
52	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	90 days	Oral	>1000	mg/kg bw/day	No effect				
53	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	90 days	Oral	20000	ppm	**Decrease**	Absolute organ weight was statistically significantly decreased in males only at 2000 and 20000 ppm but not at 6000 ppm. Since no dose-repsonse was observed, the toxicological relevance is questionable. Relative organ weight (to brain and body weight) was statistically significantly decreased in high dose group in males where also signs of general toxicity (diarrhea) were observed. Significant organ weight changes were not observed in further sub-chronic studies in rat at similar doses (study IDs 1, 3, 52, 54) and no histopathological changes were observed in the current study. Therefore, the decreased organ weight was considered not relevant for EATS-related effects.			
~~*54*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Adrenals weight*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~				
56	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Mouse	90 days	Oral	>4500	mg/kg bw/day	No effect				
57	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Dog	6 months	Oral	>300	mg/kg bw/day	No effect				

58	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Dog	1 year	Oral	>500	mg/kg bw/day	No effect				
59	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Dog	1 year	Oral	>1000	mg/kg bw/day	No effect				
61	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	21 days	Dermal	>1000	mg/kg bw/day	No effect				
62	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rabbit	21 days	Dermal	>5000	mg/kg bw/day	No effect				
63	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rabbit	28 days	Dermal	>2000	mg/kg bw/day	No effect				
67	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Mouse	2 years	Oral	> 1000	mg/kg bw/day	No effect				
68	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Mouse	2 years	Oral	> 30000	ppm	No effect				
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Adrenals weight*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Adrenals weight*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
76	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	90-92 days	Oral	>7500	ppm	No effect				
93	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect				
93	Sensitive to, but not diagnostic of, EATS	Adrenals weight	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and	Oral	>1.75	mg/kg bw/day	No effect				

				13 weeks cohorts, respectively								
96	*Sensitive to, but not diagnostic of, EATS*	*Adrenals weight*	*Rat*	*90 days*	*Oral*	*>7500*	*ppm*	*No effect*				
3	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	90 days	Oral	>30000	ppm	No effect		No toxicologically relevant effects on brain weight and histopathology were observed in four species in adult animals (dog, mouse, rabbit, rat). Increased brain weights were observed in 3/17 rat studies. In 14/17 rat studies including chronic exposure period, no effect was observed. Considering this as well as the lack of any histopathological correlate, intra- and inter-species consistency (no effects were observed in dog, mouse, and rabbit), brain weight changes are considered incidental and thus, not toxicologically relevant. In addition, no effects on brain were observed in two-, and three-generation studies in rat (study IDs 22, 26, 70, 74). **In conclusion,**		
13	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	2 years	Oral	>10000	ppm	No effect				
14	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	2 years	Oral	>30000	ppm	No effect				
15	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	2 years	Oral	>20000	ppm	No effect				
18	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	2 years	Oral	>15000	ppm	No effect				
20	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Mouse	18 months	Oral	>5000	ppm	No effect				
22	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	10 weeks	Oral	>15000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000	ppm	No effect				
49	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	28 days	Oral	>20000	ppm	No effect				
52	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	90 days	Oral	>1000	mg/kg bw/day	No effect				

~~*54*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Brain histopathology examination*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~		**glyphosate does not induce adverse effects on brain.** **RMS:** no effects on brain histopathology were observed in studies conducted in mouse, rat and dog.		
55	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	90 days	Oral	>20000	ppm	No effect				
57	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Dog	6 months	Oral	>300	mg/kg bw/day	No effect				
59	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Dog	1 year	Oral	>1000	mg/kg bw/day	No effect	The brain was sectioned at 3 levels (cerebral cortex, mid-brain and cerebellum with medulla) for histopathological examination.			
63	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rabbit	28 days	Dermal	>2000	mg/kg bw/day	No effect				
67	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Mouse	2 years	Oral	1000	mg/kg bw/day	No effect				
68	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Mouse	2 years	Oral	> 30000	ppm	No effect				
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Brain histopathology examination*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	~~*Investigated tissues were: two longitudinal sections of the brain, optic nerves, and Pineal gland (Pineal gland only in F2).*~~			
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Brain histopathology examination*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	~~*Tissues investigated: two longitudinal sections of the brain and optic nerves.*~~			
73	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Mouse	90 days	Oral	>50000	ppm	No effect				
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Brain histopathology examination*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27);*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No treatment-related histopathological changes were observed in F1.*~~			

				~~*F2 (M 20; F 27)*~~								
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Brain histopathology examination*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No treatment-related histopathological changes were observed in F2.*~~			
76	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	90-92 days	Oral	>7500	ppm	No effect				
78	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Rat	90 days	Oral		ppm	No effect	Three sections frontal cortex and basal ganglia, parietal cortex and thalamus, cerebellum and pons were examined.			
79	Sensitive to, but not diagnostic of, EATS	Brain histopathology examination	Mouse	90 days	Oral		ppm	No effect	Three sections frontal cortex and basal ganglia, parietal cortex and thalamus, cerebellum and pons were examined.			
96	*Sensitive to, but not diagnostic of, EATS*	*Brain histopathology examination*	*Rat*	*90 das*	*Oral*	*>7500*	*ppm*	*No effect*				
1	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	90 days	Oral	>20000	ppm	No effect				
2	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	90 days	Oral	*>50000*	*ppm*	*No effect*		**RMS:** In one 2-generation rat study, an increased relative brain weight was observed in F0 males at the high dose only. This was considered to be secondary to systemic toxicity. No effect on brain weight was seen in any of the other generational studies in rat. No		
3	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	90 days	Oral	*>30000*	*ppm*	*No effect*				
4	Sensitive to, but not diagnostic of, EATS	Brain weight	Mouse	90 days	Oral	>50000	ppm	No effect				
5	Sensitive to, but not diagnostic of, EATS	Brain weight	Dog	90 days	Oral	>1000	mg/kg bw/day	No effect				
7	Sensitive to, but not diagnostic of, EATS	Brain weight	Dog	90 days	Oral	>40000	ppm	No effect				
8	Sensitive to, but not diagnostic of, EATS	Brain weight	Dog	90 days	Oral	>50000	ppm	No effect				
9	Sensitive to, but not diagnostic of, EATS	Brain weight	Dog	1 year	Oral	>500	mg/kg bw/day	No effect				

10	Sensitive to, but not diagnostic of, EATS	Brain weight	Dog	1 year	Oral	>50000	ppm	No effect		effects on brain weight were found in any of the other studies in rat, or in studies in mouse or dog. Overall, it is concluded that glyphosate does not induce adverse effects on the brain.		
11	Sensitive to, but not diagnostic of, EATS	Brain weight	Dog	1 year	Oral	>30000	ppm	No effect				
12	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	1 year	Oral	>20000	ppm	No effect				
13	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	2 years	Oral	>10000	ppm	No effect				
14	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	2 years	Oral	>30000	ppm	No effect				
15	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	2 years	Oral	>20000	ppm	No effect				
16	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	2 years	Oral	>1000	mg/kg bw/day	No effect				
17	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	2 years	Oral	>20000	ppm	No effect				
18	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	2 years	Oral	>15000	ppm	No effect				
20	Sensitive to, but not diagnostic of, EATS	Brain weight	Mouse	18 months	Oral	>5000	ppm	No effect				
21	Sensitive to, but not diagnostic of, EATS	Brain weight	Mouse	18 months	Oral	>40000	ppm	No effect				
22	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	10 weeks (pre-mating)	Oral	>15000	ppm	No effect				
22	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	10 weeks	Oral	>15000	ppm	No effect	No effect was observed in offspring (F1 + F2).			
23	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
23	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect	No effect was observed in offspring (F1 + F2).			
24	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	30000	ppm	**Increase**	Relative brain weight was increased in F0 males at 30000 ppm. Since at this dose body weight change was decreased and absolute organ weight was not affected, the effect is not considered EATS-related but due to general systemic toxicity.			
26	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	10 weeks; prior to mating, continued	Oral	>10000	ppm	No effect				

				until termination								
52	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	90 days	Oral	>1000	mg/kg bw/day	No effect				
53	Sensitive to, but not diagnostic of, EATS	Brain weight	Rat	90 days	Oral	>20000	ppm	No effect				
56	Sensitive to, but not diagnostic of, EATS	Brain weight	Mouse	90 days	Oral	>4500	mg/kg bw/day	No effect				
57	Sensitive to, but not diagnostic of, EATS	Brain weight	Dog	6 months	Oral	>300	mg/kg bw/day	No effect				
58	Sensitive to, but not diagnostic of, EATS	Brain weight	Dog	1 year	Oral	>500	mg/kg bw/day	No effect				
59	Sensitive to, but not diagnostic of, EATS	Brain weight	Dog	1 year	Oral	>1000	mg/kg bw/day	No effect				
63	Sensitive to, but not diagnostic of, EATS	Brain weight	Rabbit	28 days	Dermal	>2000	mg/kg bw/day	No effect	Fresh brain weight was recorded.			
67	Sensitive to, but not diagnostic of, EATS	Brain weight	Mouse	2 years	Oral	> 1000	mg/kg bw/day	No effect				
68	Sensitive to, but not diagnostic of, EATS	Brain weight	Mouse	2 years	Oral	> 30000	ppm	No effect				
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Brain weight*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Brain weight*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
73	Sensitive to, but not diagnostic of, EATS	Brain weight	Mouse	90 days	Oral	>50000	ppm	No effect				
1	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	90 days	Oral	>20000	ppm	No effect		No toxicologically relevant effects on pituitary weight and histopathology were observed in four species in adult animals (dog, mouse, rabbit, rat).		
2	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	90 days	Oral	>50000	ppm	No effect				
4	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Mouse	90 days	Oral	>50000	ppm	No effect				
5	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Dog	90 days	Oral	>1000	mg/kg bw/day	No effect				

6	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Dog	90 days	Oral	>10000	ppm	No effect		Decreased pituitary weights were observed in single studies in rat (2/9) and dog (1/7) were also general systemic toxicity (decreased body weight gain) was evident. Since no histopathological correlate and no intra- and inter-species consistency was observed (no effect in mouse and rabbit), organ weight changes are considered isolated and incidental, not toxicologically relevant findings. Moreover, not effect on pituitary weight was observed in three two-generation studies (study IDs 22-24), thus showing no indication for an effect on different life stages. **In conclusion, glyphosate does not induce adverse effects on pituitary.** **RMS:** It is noted that RMS removed result on pituitary histopathology for two studies (ID 70, 74), as RMS considered these studies to be		
7	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Dog	90 days	Oral	>40000	ppm	No effect				
8	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Dog	90 days	Oral	>50000	ppm	No effect				
9	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Dog	1 year	Oral	>500	mg/kg bw/day	No effect				
10	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Dog	1 year	Oral	>50000	ppm	No effect				
11	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Dog	1 year	Oral	>30000	ppm	No effect				
12	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	1 year	Oral	>20000	ppm	No effect				
13	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	2 years	Oral	>10000	ppm	No effect				
14	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	2 years	Oral	>30000	ppm	No effect				
16	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	2 years	Oral	>1000	mg/kg bw/day	No effect				
17	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	2 years	Oral	>20000	ppm	No effect				
18	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	2 years	Oral	>15000	ppm	No effect				
19	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Mouse	18 months	Oral	>10000	ppm	No effect				
20	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Mouse	18 months	Oral	>5000	ppm	No effect				
21	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Mouse	18 months	Oral	>40000	ppm	No effect				

22	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	10 weeks	Oral	>15000	ppm	No effect		unacceptable. In addition, RMS added the results for one study (ID 96). No effects on pituitary histopathology were found in any of the studies conducted in mouse, rat and dog.		
23	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
24	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	10 weeks for pre-mating rearing 8 for subsequent breeding	Oral	>30000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000	ppm	No effect				
27	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	11 weeks; prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000	ppm	No effect				
49	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	28 days	Oral	>20000	ppm	No effect				
52	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	90 days	Oral	>1000	mg/kg bw/day	No effect				
53	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	90 days	Oral	>20000	ppm	No effect				
~~*54*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Pituitary histopathology*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~				
55	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	90 days	Oral	>20000	ppm	No effect				
56	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Mouse	90 days	Oral	>4500	mg/kg bw/day	No effect				
57	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Dog	6 months	Oral	>300	mg/kg bw/day	No effect				
58	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Dog	1 year	Oral	>500	mg/kg bw/day	No effect				
59	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Dog	1 year	Oral	>1000	mg/kg bw/day	No effect				
67	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Mouse	2 years	Oral	> 1000	mg/kg bw/day	No effect				
68	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Mouse	2 years	Oral	> 30000	ppm	No effect				

~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Pituitary histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Pituitary histopathology*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
73	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Mouse	90 days	Oral	>50000	ppm	No effect				
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Pituitary histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No treatment-related histopathological changes were observed in F1.*~~			
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Pituitary histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No treatment-related histopathological changes were observed in F2.*~~			
76	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Rat	90-92 days	Oral	>7500	ppm	No effect				
96	*Sensitive to, but not diagnostic of, EATS*	*Pituitary histopathology*	*Rat*	*90 days*	*Oral*	*>7500*	*ppm*	*No effect*				
2	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Rat	90 days	Oral	*>50000*	*ppm*	*No effect*				
5	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Dog	90 days	Oral	>1000	mg/kg bw/day	No effect				
7	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Dog	90 days	Oral	>40000	ppm	No effect				
9	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Dog	1 year	Oral	>500	mg/kg bw/day	No effect				
10	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Dog	1 year	Oral	>50000	ppm	No effect				
16	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Rat	2 years	Oral	>1000	mg/kg bw/day	No effect				
22	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Rat	10 weeks	Oral	>15000	ppm	No effect				
23	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
24	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Rat	10 weeks for pre-mating	Oral	>30000	ppm	No effect	**RMS:** In a pubertal rat assay (ID 45), a decrease			

				rearing 8 weeks for subsequent breeding						in absolute pituitary weight was seen, however, this was considered to be secondary to systemic toxicity. In one of the 1-year dog studies a decrease in pituitary weight was seen. No histopathological changes were seen in this study. Effects on pituitary weight were not seen in any of the dog studies, conducted at similar or higher dose levels. Therefore, this finding is considered to be incidental. Overall, it is concluded that glyphosate does not induce adverse effects on the pituitary.		
44	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Rat	21 days (PND 22-42)	Oral	> 1000	mg/kg bw/day	No effect				
45	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Rat	31 days (PND 23-53)	Oral	1000	mg/kg bw/day	**Decrease**	Statistically significantly lower mean absolute pituitary weight (15.6%) was observed. However, at the same dose, signs of general systemic toxicity such as (stat.sign.) decreased body weight gain and rales were observed. Thus, decreased organ weight is not considered not toxicologically relevant.			
52	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Rat	90 days	Oral	>1000	mg/kg bw/day	No effect				
56	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Mouse	90 days	Oral	>4500	mg/kg bw/day	No effect				
57	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Dog	6 months	Oral	>300	mg/kg bw/day	No effect				
58	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Dog	1 year	Oral	100	mg/kg bw/day	**Decrease**	Absolute and relative weight were decreased in males at 100 and 500 mg/kg bw/day. No histopathological changes were observed, neither in the current study nor in two similar studies in dog (study IDs 9, 59). Therefore, the organ weight change is considered not toxicologically relevant.			
59	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Dog	1 year	Oral	>1000	mg/kg bw/day	No effect				
62	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Rabbit	21 days	Dermal	>5000	mg/kg bw/day	No effect				
67	Sensitive to, but not diagnostic of, EATS	Pituitary weight	Mouse	2 years	Oral	> 1000	mg/kg bw/day	No effect				

~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Pituitary weight*~~	~~*Rat*~~	~~*21 days (PND0-21, exposure through milk)*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Pituitary weight*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
24	Sensitive to, but not diagnostic of, EATS	Dystocia	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000	ppm	No effect		Increased incidences of dystocia were not observed in reproductive toxicity studies. **In conclusion, glyphosate did not induce dystocia.** **RMS:** agreed		
25	Sensitive to, but not diagnostic of, EATS	Dystocia	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect				
22	Sensitive to, but not diagnostic of, EATS	Fertility (mammals)	Rat	10 weeks	Oral	>15000	ppm	No effect		No toxicologically relevant effects on fertility have been observed in rat. A non-significant decrease in gestation index (F1 only) was observed in 1/7		
23	Sensitive to, but not diagnostic of, EATS	Fertility (mammals)	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				

24	Sensitive to, but not diagnostic of, EATS	Fertility (mammals)	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	30000	ppm	**Decrease**	F0 males and females Reproductive performance of F0 parental animals was not adversely affected by test substance treatment, and no significant differences were observed in such parameters as percentage of females having normal oestrous cycle, mating index, fertility index, gestation index, duration of gestation, number of implantation sites, and number, motility and morphology of epididymal sperm between the control group and the treated groups. F1 females The gestation indices in the control, 1200, 6000 and 30000 ppm groups were 95.8 (23/24), 95.8 (23/24), 87.5 (21/24) and 79.2% (23/24), respectively, with somewhat low values in the 2 higher dose groups. However, these decreases were considered to be incidental because the differences between the control and treated groups were not statistically significant, and normal reproduction results were obtained in the F1 maternal animals, which had failed to produce offspring in this study, after remating with untreated animals (no Guideline-conform procedure). Moreover, no effects on sperm number and morphology have been observed for F0 and F1 males.	multi-generation studies. However, this was considered an incidental finding, since no effects were observed after re-mating. Moreover, no effects on fertility parameters were observed in six further multigeneration studies. Therefore, the reduction in gestation index in the F1 generation of one study only, is considered not toxicologically relevant. **In conclusion, glyphosate does not induce adverse effects on fertility.** **RMS:** agreed It is noted that RMS removed result for two studies (ID 70, 74), as RMS considered these studies to be unacceptable.		
25	Sensitive to, but not diagnostic of, EATS	Fertility (mammals)	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Fertility (mammals)	Rat	10 weeks; prior to	Oral	>10000	ppm	No effect				

				mating, continued until termination								
27	Sensitive to, but not diagnostic of, EATS	Fertility (mammals)	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000	ppm	No effect				
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Fertility (mammals)*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Fertility (mammals)*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*Pregnancy rate was not changed for F0 females.*~~			
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Fertility (mammals)*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*Pregnancy rate was not changed for F1 females.*~~			
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Fertility (mammals)*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*Pregnancy rate was not changed for F2 females.*~~			
22	Sensitive to, but not diagnostic of, EATS	Gestation length	Rat	10 weeks	Oral	>15000	ppm	No effect		No effect on gestation length in rat was observed in two- and three--generation studies (study IDs 22 – 27, 70, 74) as well as in a range finding study for an EOGRTS (study ID 93). **In conclusion, no EATS-related adversity with regards**		
23	Sensitive to, but not diagnostic of, EATS	Gestation length	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
24	Sensitive to, but not diagnostic of, EATS	Gestation length	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000	ppm	No effect				
25	Sensitive to, but not diagnostic of, EATS	Gestation length	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0	Oral	>10000	ppm	No effect				

				and continued for 2 successive generations up to weaning of F2						**togestation length is observed.** **RMS:** It is noted that RMS removed result from on gestation length for one study (ID 70), as RMS considered this study to be unacceptable. Agreed that there was no effect on gestation length.		
26	Sensitive to, but not diagnostic of, EATS	Gestation length	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000	ppm	No effect				
27	Sensitive to, but not diagnostic of, EATS	Gestation length	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000	ppm	No effect				
69	Sensitive to, but not diagnostic of, EATS	Gestation length	Rat	5.5 weeks (GD 3 till 21 days post partum)	Oral	>30000	ppm	No effect	The pregnancy rate was good, 90%, 100%, 100% and 90% in Groups 1 to 4 respectively. (Note, treatment started at GD 3.) The duration of pregnancy was similar in all groups and not adversely affected by treatment.			
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Gestation length*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
93	Sensitive to, but not diagnostic of, EATS	Gestation length	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect				

22	Sensitive to, but not diagnostic of, EATS	Number of ovarian follicles	Rat	10 weeks	Oral	>15000	ppm	No effect		**No EATS-related adversity was caused with regards to the number of ovarian follicles** **RMS:** glyphosate did not affect the number of ovarian follicles.		
23	Sensitive to, but not diagnostic of, EATS	Number of ovarian follicles	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
28	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect		No toxicologically relevant effects on embryonic and foetal viability were observed in rat and rabbit. 5/5 and 9/11 studies in rat and rabbit, respectively, showed no change. Isolated findings of abortions (2/11 studies) and late foetal deaths (1/11 studies) were observed only at doses of maternal toxicity and thus, are not considered EATS-related. **In conclusion no EATS-related adversity with regards to the number of embryonic or fetal deaths is observed.** RMS: It is noted that RMS removed results from one study (ID 75), as RMS considered this study to be unacceptable.		
29	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect				
30	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rabbit	13 days (GD 6-18)	Oral	>300	mg/kg bw/day	No effect				
31	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rabbit	13 days (GD 7-19)	Oral	200	mg/kg bw/day	**Increase**	Slight increase in late foetal deaths at 400 mg/kg bw/day leading to an increase of total foetal deaths. This effect is attributed to one animal with nine late deaths resulting in post-implantation loss of 69.2%, which is considered not treatment-related since it is based on the effect on a single animal. An increase in early foetal deaths leading to an increase in total foetal death at 200 mg/kg bw/day, was observed but not considered treatment-related according to the study report. Moreover, maternal toxicity was observed from 200 mg/kg bw/day (reduced body weight gain) and thus, a potential effect on foetal deaths would be related to maternal toxicity rather than to EATS-related adversity.			
32	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rabbit	13 days (GD 8-20)	Oral	300	mg/kg bw/day	No effect				

33	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rabbit	22 days (GD 6-27)	Oral	> 350	mg/kg bw/day	No effect		Agreed that glyphosate did not affect the numbers of embryonic or foetal deaths or the number of viable foetuses.		
34	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
34	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
35	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rabbit	13 days (GD 6-18)	Oral	500	mg/kg bw/day	**Increase**	Two animals of the high dose group aborted. This effect is attributed to maternal toxicity (decreased body weight gain *(-28 to -35% compared to control)* and food consumption).			
46	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rabbit	13 days (GD 7-19)	Oral	> 450	mg/kg bw/day	No effect				
47	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rabbit	13 days (GD 7-19)	Oral	> 625	mg/kg bw/day	No effect				
64	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rat	10 days (GD 6-15)	Oral	>3500	mg/kg bw/day	No effect				
65	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect				

66	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rabbit	22 days (GD 6-27)	Oral	*<350*	mg/kg bw/day	No effect	Non-viable fetuses were not present in any group and there were no biologically relevant or statistically significant differences in the mean numbers of early or late resorptions in any of the treatment groups when compared to the control group. A statistically significant, though not biologically relevant increase was noted in the mean number of viable fetuses in the 75 mg/kg/day dosage group which was considered incidental. There were no biologically relevant or statistically significant differences in the mean numbers of total implantations or corpora lutea in any of the treatment groups when compared to the control group. ABORTIONS: Two rabbits in the control group aborted and were sacrificed, both on gestation day 22. In the 175 mg/kg/day dosage group, one rabbit aborted and was sacrificed on gestation day 27. One rabbit in the 350 mg/kg/day dosage group aborted and was sacrificed on gestation day 23. Therefore, no treatment-related increase in the incidence of abortions was noted. RMS: Indeed no effect was seen. However, at the dose levels of 350 and 175 mg/kg bw/day high mortality of the dams occurred which limited the number of foetuses. RMS considers that it is not possible to exclude that the lower number of foetuses in treated animals could mask treatment-related effects. As a precautionary principle, RMS proposed to set the developmental NOAEL at 75 mg/kg bw/day.			
~~*75*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Numbers of embryonic or foetal deaths and viable foetuses*~~	~~*Rat*~~	~~*Males: 60 days prior to mating; females: 14 days prior to mating until end of lactation (PND 21) or until sacrifice GD 13*~~	~~*Oral*~~	~~*>10*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	~~*Number of early and late in utero deaths in females sacrificed at GD 13 were not affected.*~~			

77	Sensitive to, but not diagnostic of, EATS	Numbers of embryonic or foetal deaths and viable foetuses	Rabbit	22 days (GD 6-27)	Oral	250	mg/kg bw/day	No effect				
22	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rat	10 weeks	Oral	>15000	ppm	No effect		No toxicologically relevant effects on post-implantation loss were observed in rat (5/5) and rabbit (9/9) in reproduction and prenatal developmental toxicity (PDT) studies at non maternally toxic doses. Pre-implantation loss is reported for PDT studies, however, for potential substance-related effects only multi-generation studies are considered relevant since dosing in PDT studies starts after implantation. No effect on pre-implantation loss was observed in one two-generation study in rat. **In conclusion, glyphosate does not induce EATS-related pre- and post-implantation loss.** **RMS:** It is noted that RMS changed the conclusion on study ID 46 from no effect to an		
23	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
28	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect				
31	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rabbit	13 days (GD 7-19)	Oral	400	mg/kg bw/day	No effect	Increased at 400 mg/kg bw/day due to 1/18 females with nine late deaths (69.2%), not treatment-related since this is considered an isolated finding; increased at 200 mg/kg bw/day due to early fetal deaths, no dose relation, considered to be not treatment-related			
32	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rabbit	13 days (GD 8-20)	Oral	>300	mg/kg bw/day	No effect				
33	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rabbit	22 days (GD 6-27)	Oral	> 350	mg/kg bw/day	No effect				
34	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
35	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
46	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rabbit	13 days (GD 7-19)	Oral	*450*	*mg/kg bw/day*	***Increase***	An increase compared to concurrent control group was observed based on the increase of embryonic deaths. However, this effect was considered not treatment-related since the concurrent control group values were very low, no dose-response was observed, and incidence was only slightly above the historic control. RMS: increased post-implantation loss outside HCD was seen at the high dose and taken into account for setting the developmental NOAEL. However, it is noted that no dose-response was observed and that the value of the control group was below the HCD range.			
47	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rabbit	13 days (GD 7-19)	Oral	> 625	mg/kg bw/day	No effect				
64	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rat	10 days (GD 6-15)	Oral	>3500	mg/kg bw/day	No effect	No treatment-related effect on post-implantation loss.			

65	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect	The number of post-implantation loss was similar in both control and treatment groups.	increase, as an increased post-implantation loss outside HCD was seen at the top dose level tested. However, no dose response was observed and the value of the control group was below the HCD range. In a pilot range finding study in rabbit (ID 77) a slight increase in post-implantation loss was seen at 250 mg/kg bw/day. Higher dose levels in this study caused excessive maternal toxicity and could not be evaluated. Therefore, it is uncertain if this really is an effect or chance finding. In none of the other studies an effect on post- or pre-implantation loss was observed. Overall, it is agreed that glyphosate does not affect pre- or post-implantation loss.		
66	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rabbit	22 days (GD 6-27)	Oral	*<350*	mg/kg bw/day	No effect	There were no biologically relevant or statistically significant differences in the mean numbers of early or late resorptions in any of the treatment groups when compared to the control group. **RMS:** Indeed no effect was seen. However, at the dose levels of 350 and 175 mg/kg bw/day high mortality of the dams occurred which limited the number of foetuses. RMS considers that it is not possible to exclude that the lower number of foetuses in treated animals could mask treatment-related effects. As a precautionary principle, RMS proposed to set the developmental NOAEL at 75 mg/kg bw/day.			
77	Sensitive to, but not diagnostic of, EATS	Post implantation loss	Rabbit	22 days (GD 6-27)	Oral	250	mg/kg bw/day	**Increase**	A slight increase in post-implantation loss was observed in animals of the 250 mg/kg bw/d dose group. Higher doses cannot be evaluated due to excessive maternal toxicity. However, in further prenatal developmental toxicity studies in rabbit, no effect was observed (study IDs 32-35, 47, 66) and thus, the effect is not reproducible.			
22	Sensitive to, but not diagnostic of, EATS	Pre implantation loss	Rat	10 weeks	Oral	>15000	ppm	No effect				
28	Sensitive to, but not diagnostic of, EATS	Pre implantation loss	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect				
31	Sensitive to, but not diagnostic of, EATS	Pre implantation loss	Rabbit	13 days (GD 7-19)	Oral	> 400	mg/kg bw/day	No effect				
32	Sensitive to, but not diagnostic of, EATS	Pre implantation loss	Rabbit	13 days (GD 8-20)	Oral	>300	mg/kg bw/day	No effect				
34	Sensitive to, but not diagnostic of, EATS	Pre implantation loss	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
35	Sensitive to, but not diagnostic of, EATS	Pre implantation loss	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
46	Sensitive to, but not diagnostic of, EATS	Pre implantation loss	Rabbit	13 days (GD 7-19)	Oral	> 450	mg/kg bw/day	No effect	No effect on pre-implantation loss was observed. However, treatment was started after implantation.			
47	Sensitive to, but not diagnostic of, EATS	Pre implantation loss	Rabbit	13 days (GD 7-19)	Oral	> 625	mg/kg bw/day	No effect				

64	Sensitive to, but not diagnostic of, EATS	Pre implantation loss	Rat	10 days (GD 6-15)	Oral	3500	mg/kg bw/day	No effect	A significant increase in pre-implantation loss at 3500 mg/kg/day was observed. However, since treatment commences after implantation, this is not considered to be treatment-related.			
65	Sensitive to, but not diagnostic of, EATS	Pre implantation loss	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect				
22	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rat	10 weeks	Oral	>15000	ppm	No effect		Some anomalies and retarded ossification were observed in rat and rabbit. However, in most cases, this could be related to maternal toxicity. Moreover, no specific anomaly or malformation could be attributed to glyphosate treatment and thus, partially observed retarded development is attributed to general systemic toxicity not related to EATS. **In conclusion, no indication for EATS-related adversity was observed based on the presence of anomalies (external, visceral, skeletal) in foetuses.** **RMS:** agreed		
23	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
24	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	30000	ppm	**Increase**	Distention of the caecum in F1 and F2 weanlings at 30000 ppm was observed.			
25	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rat	10 weeks; prior to mating, continued until termination	Oral	>10000	ppm	No effect				
27	Sensitive to, but not diagnostic of, EATS	Presence of anomalies	Rat	11 weeks prior to mating for	Oral	>30000	ppm	No effect				

		(external, visceral, skeletal		F0, further generations for approx. 14 weeks until termination								
28	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect				
29	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect				
30	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rabbit	13 days (GD 6-18)	Oral	>300	mg/kg bw/day	No effect				

31	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rabbit	13 days (GD 7-19)	Oral	> 400	mg/kg bw/day	No effect				
32	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rabbit	13 days (GD 8-20)	Oral	>300	mg/kg bw/day	No effect				
33	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rabbit	22 days (GD 6-27)	Oral	> 350	mg/kg bw/day	No effect				
34	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rabbit	13 days (GD 6-18)	Oral	20	mg/kg bw/day	**Increase**	A significant increase in dilated heart was observed in all treatment groups while other incidences of visceral malformations were not considered treatment-related; no treatment and dose-related significant major skeletal malformations; no significant or dose-relationship of the incidences of external malformations			
35	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rabbit	13 days (GD 6-18)	Oral	500	mg/kg bw/day	**Increase**	In the high dose group, the incidences of external, visceral and skeletal malformations were higher than that in the control group. With regard to the heart malformations, 0, 1, 1, and 2 interventricular septal defects were observed in the 0, 125, 250, and 500 mg/kg bw/day dose groups. A similar pattern was seen in the variations observed externally, viscerally and skeletally; in the high dose group, the total number of observed variations was higher than those of the control, low or mid dose groups. The increase in malformations and variations observed in the high dose group occurred in the presence of maternal toxicity (reduced food consumption and body weight gains). Further, this was at a dose (500 mg/kg bw/day) that caused significant toxicity, including mortality, in another rabbit developmental study (study ID 34).			

46	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rabbit	13 days (GD 7-19)	Oral	*450*	*mg/kg bw/day*	***Increase***	Increases in fetuses with heart malformations (from 150 mg/kg bw/d) were not considered treatment-related when compared to historic control data of 13 studies performed the same year. Group mean incidences of anomalies and malformations showed no significant differences compared to the control group. RMS: At the high dose level of 450 mg/kg bw/day, an increase in cardiac malformations was seen outside the range of the historical control data. At this dose level also increased post-implantation loss and late embryonic death were observed.			
47	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rabbit	13 days (GD 7-19)	Oral	> 625	mg/kg bw/day	No effect				
64	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rat	10 days (GD 6-15)	Oral	3500	mg/kg bw/day	**Increase**	Skeletal change: The incidence of rib distortion (wavy ribs) was markedly increased at 3500 mg/kg bw/day. The marginally higher incidence at 1000 mg/kg bw/day was of uncertain relationship to treatment. No increase in incidence of malformed foetuses was observed (a total of 1, 2, 1 and 3 foetuses in control to high dose groups, respectively were malformed). Increased incidence of reduced ossification was observed in all treated groups compared to the concurrent control. However, compared to historical control data, the incidence of these skeletal changes at 3500 mg/kg bw/day was only slightly outside the range. Since no clear dosage-response was apparent, reduced ossification was not considered treatment-related. The incidence of foetuses with visceral anomalies was low and did not indicate any adverse treatment-related effects. Moreover, reduced maternal body weight change was observed in the high dose group, which could lead to retarded development of fetuses.			

65	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rat	10 days (GD 6-15)	Oral	1000	mg/kg bw/day	**Increase**	The intergroup comparison of litter data regarding "number of abnormal, dead and live fetuses" between control group and treatment group has not shown any statistically significant (p=0.5) difference. EXTERNAL MALFORMATIONS: No incidence of major external malformations was seen in either of the study groups. VISCERAL MALFORMATION: There was no incidence of major visceral malformations. SKELETAL MALFORMATIONS: Incidence of minor and major skeletal malformations, did not show any statistically significant intergroup difference. delayed ossification: The incidence of delayed ossification of caudal vertebral arch, forelimb-proximal phalange and hindlimb-distal phalange was significantly higher in the treatment group than in control. The incidence of incomplete to partial ossification of parietal and interparietal of the skull was less in the treatment group.			
66	Sensitive to, but not diagnostic of, EATS	Presence of anomalies (external, visceral, skeletal	Rabbit	22 days (GD 6-27)	Oral	*<350*	mg/kg bw/day	No effect	All fetuses were individually weighed and examined for external malformations and variations, including the palate and eyes. Each fetus was dissected, internally sexed and examined for visceral malformations and variations, including the brain by a mid-coronal slice. There were no statistically significant or biologically meaningful differences in the number of litters with malformations in any of the treatment groups when compared to the control group. Malformations were noted only in the treatment groups, however, this was not considered to be treatment-related as they did not occur in a dose-related pattern, were not similar in nature and the frequency did not exceed that of the historical control. RMS: At the dose levels of 350 and 175 mg/kg bw/day high mortality of the dams occurred which limited the number of foetuses. RMS considers that it is not possible to exclude that the lower number of			

									foetuses in treated animals could mask treatment-related effects. As a precautionary principle, RMS proposed to set the developmental NOAEL at 75 mg/kg bw/day.			
~~70~~	~~Sensitive to, but not diagnostic of, EATS~~	~~Presence of anomalies (external, visceral, skeletal~~	~~Rat~~	~~life-time, all three generations~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~				
~~70~~	~~Sensitive to, but not diagnostic of, EATS~~	~~Presence of anomalies (external, visceral, skeletal~~	~~Rat~~	~~life-time, all three generations~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~				
22	Sensitive to, but not diagnostic of, EATS	Reproduction	Rat	10 weeks	Oral	>15000	ppm	No effect		**No EATS-related adversity on reproduction was observed in rats** **RMS:** agreed		
25	Sensitive to, but not diagnostic of, EATS	Reproduction	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Reproduction	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect				
22	Sensitive to, but not diagnostic of, EATS	Time to mating	Rat	10 weeks	Oral	>15000	ppm	No effect		**No EATS-related adversity on time to mating was observed in rats.**		
23	Sensitive to, but not diagnostic of, EATS	Time to mating	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
25	Sensitive to, but not diagnostic of, EATS	Time to mating	Rat	10 weeks for pre-mating	Oral	>10000	ppm	No effect				

				in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2						**RMS:** agreed		
26	Sensitive to, but not diagnostic of, EATS	Time to mating	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect				
27	Sensitive to, but not diagnostic of, EATS	Time to mating	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000	ppm	No effect				
28	Sensitive to, but not diagnostic of, EATS	Fetal development	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect		**No EATS-related adversity on fetal development was observed in rats** **RMS:** agreed. It is noted that RMS removed the results from one rat study (ID 75), as RMS considers this study to be unacceptable.		
30	Sensitive to, but not diagnostic of, EATS	Fetal development	Rabbit	13 days (GD 6-18)	Oral	>300	mg/kg bw/day	No effect				
31	Sensitive to, but not diagnostic of, EATS	Fetal development	Rabbit	13 days (GD 7-19)	Oral	> 400	mg/kg bw/day	No effect				
~~*75*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Fetal development*~~	~~*Rat*~~	~~*Males: 60 days prior to mating; females: 14 days prior to mating until end of lactation (PND 21) or until sacrifice GD 13*~~	~~*Oral*~~	~~*>10*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	~~*Growth rate of pups was not affected.*~~			
22	Sensitive to, but not diagnostic of, EATS	Litter size	Rat	10 weeks	Oral	>15000	ppm	No effect		Overall, no effects on litter size were		

23	Sensitive to, but not diagnostic of, EATS	Litter size	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect		observed in rabbit (4/4 studies) and rat (13/15 studies). Slightly reduced litter size (not statistically significant) in F1 pups and F2a pups at 30000 ppm but not in F2b pups (re-mating of F1) was observed in 1/6 two-generation studies. Thus, treatment-relation was considered equivocal within the study. However, since body weights were reduced in parental animals (F0) which might affect the litter size and since no effects were observed in 5/6 two-generation studies (study IDs 22-26) and thus intra-species consistency is lacking, this effect was considered secondary to parental toxicity. **In conclusion, no EATS-related adversity on litter size was observed in rats and rabbits.** **RMS:** Agreed. It is noted that RMS removed the results from three studies (ID 70, 74, 75), as RMS		
24	Sensitive to, but not diagnostic of, EATS	Litter size	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000	ppm	No effect				
25	Sensitive to, but not diagnostic of, EATS	Litter size	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Litter size	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect				
27	Sensitive to, but not diagnostic of, EATS	Litter size	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	30000	ppm	**Decrease**	Slightly reduced (not statistically significant) in F1 pups and F2a pups at 30000 ppm, not reproduced in F2b pups (re-mating of F1), treatment relation equivocal. Body weights were reduced in parental animals (F0) which might affect the litter size. As findings of litter size in F2a and F2b animals were inconsistent, this effect was considered secondary to parental toxicity. In addition, the reduced litter size was not reproduced in the most recent two-generation studies (study IDs 22, 23) and not toxicologically relevantly affected in older two-generation studies (study IDs 24-26) and thus not consistent.			

31	Sensitive to, but not diagnostic of, EATS	Litter size	Rabbit	13 days (GD 7-19)	Oral	>400	mg/kg bw/day	No effect		considers these studies to be unacceptable.		
34	Sensitive to, but not diagnostic of, EATS	Litter size	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
35	Sensitive to, but not diagnostic of, EATS	Litter size	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
47	Sensitive to, but not diagnostic of, EATS	Litter size	Rabbit	13 days (GD 7-19)	Oral	> 625	mg/kg bw/day	No effect				
64	Sensitive to, but not diagnostic of, EATS	Litter size	Rat	10 days (GD 6-15)	Oral	>3500	mg/kg bw/day	No effect				
65	Sensitive to, but not diagnostic of, EATS	Litter size	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect				
69	Sensitive to, but not diagnostic of, EATS	Litter size	Rat	5.5 days (GD 3 till 21 days post partum)	Oral	>30000	ppm	No effect	The implantation rates in all treated groups were higher than the controls. Since pup losses, both pre-birth and from birth to weaning, were generally similar among the groups, litter size of all treated groups was, as a consequence, generally greater than controls throughout weaning. These findings are not, however, considered to be an adverse effect of treatment.			
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Litter size*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Litter size*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effect observed in F1 offspring.*~~			

~~74~~	~~Sensitive to, but not diagnostic of, EATS~~	~~Litter size~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effect observed in F2 offspring.~~			
~~74~~	~~Sensitive to, but not diagnostic of, EATS~~	~~Litter size~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effect observed in F3 offspring.~~			
~~75~~	~~Sensitive to, but not diagnostic of, EATS~~	~~Litter size~~	~~Rat~~	~~Males: 60 days prior to mating; females: 14 days prior to mating until end of lactation (PND 21) or until sacrifice GD 13~~	~~Oral~~	~~>10~~	~~mg/kg bw/day~~	~~No effect~~	-			
93	Sensitive to, but not diagnostic of, EATS	Litter size	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect				
95	Sensitive to, but not diagnostic of, EATS	Litter size	Mouse	Dams were exposed during gestation. Offspring samples were collected on GD 19, PND 7, and PND 21	Oral	5000	mg/L water	No effect				
22	Sensitive to, but not diagnostic of, EATS	Litter viability	Rat	10 weeks	Oral	>15000	ppm	No effect		**No EATS-related adversity on litter**		

23	Sensitive to, but not diagnostic of, EATS	Litter viability	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect		**viability was observed in rats (10/10 studies).** **RMS:** Agreed It is noted that RMS removed the results from two rat studies (ID 70 and 74), as RMS considers this studies to be unacceptable.		
24	Sensitive to, but not diagnostic of, EATS	Litter viability	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000	ppm	No effect				
25	Sensitive to, but not diagnostic of, EATS	Litter viability	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Litter viability	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect				
27	Sensitive to, but not diagnostic of, EATS	Litter viability	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000	ppm	No effect				
69	Sensitive to, but not diagnostic of, EATS	Litter viability	Rat	only secondary exposure through milk from PND 0-21	Oral	>30000	ppm	No effect				

~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Litter viability*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Litter viability*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effect observed in F1 offspring.*~~			
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Litter viability*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effect observed in F2 offspring.*~~			
~~*74*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Litter viability*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effect observed in F3 offspring.*~~			
93	Sensitive to, but not diagnostic of, EATS	Litter viability	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect				
22	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rat	10 weeks	Oral	>15000	ppm	No effect		Litter/pup weight was investigated in		

23	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rat	10 weeks (pre-mating)	Oral	10000	ppm	**Decrease**	Decreased in F1 pups of the 10000 ppm group from day 8 to day 29 in males and from day 5 to day 29 in females. Other litter parameters such as litter size and litter viability were not affected by treatment. F2 pup weights were not affected. In addition, this effect was not reproduced in the most recent two-generation study (study ID 22) at a higher dose. Therefore, the observed decrease is considered not consistent and EATS-related.	17 rat, one mouse and 9 rabbit studies. Decreased litter/pup weight was observed in 5/17 rat and 2/9 rabbit studies. However, maternal toxicity, manifested in clinical signs and/or decreased body weights, was accompanying the decreased litter/pup weight and thus, the effect was considered secondary to maternal toxicity. **Therefore, no EATS-related adversity is observed with regard to litter/pup weight.** **RMS:** Agreed It is noted that RMS removed the results from three studies (ID 70, 74, 75), as RMS considers these studies to be unacceptable.		
24	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	30000	ppm	**Decrease**	F1 pups of both sexes in the 30000 ppm group, showed significantly higher mean body weights on lactation day 0 than the controls. However, mean body weights on days 14 and 21 were significantly decreased when compared controls. In F2 pups in the 30000 ppm group, mean body weights of both sexes on day 21 of lactation were significantly lower than those in the control group. Parental toxicity was observed at the high dose (> 2000 mg/kg bw/day) as well and consisted of loose stool (F0/F1, m/f), reduced body weight (F0/F1, m) caecum distension (F0/F1, m/f), increased liver and kidney weights (F0/F1, m/f). Therefore, decreased pup weight is considered a secondary effect due to systemic toxicity.			
25	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect				

26	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect				
27	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	30000	ppm	**Decrease**	Reduced (> -10%) by lactation Day 21 at 30000 ppm in F1. In F2 pups the effect appeared to occur earlier (Day 14 of lactctation), consumption of prepared diet was considered responsible for bw effect. (Not treatment-related: slightly reduced at weaning in the 10000 ppm group, transient, not consistent for both sexes in all generations, toxicological relevance questionable) Body weight loss correlated with body weight loss of parental animals at the same dose group. Furthermore, clinical signs were evident in the same animals. Based on this, the effect on litter weight was considered to be secondary to systemic toxicity.			
28	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect				
29	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect				
30	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rabbit	13 days (GD 6-18)	Oral	>300	mg/kg bw/day	No effect				
31	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rabbit	13 days (GD 7-19)	Oral	> 400	mg/kg bw/day	No effect				
32	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rabbit	13 days (GD 8-20)	Oral	300	mg/kg bw/day	**Decrease**	Mean fetal weight was reduced, which was attributed to 2 litters with particularly low fetal weight. Body weights of maternal animals were reduced at the same dose (from 175 mg/kg bw/day) group and below. Futhermore, clinical signs such as diarrhea occurred in maternal animals during the study. Therefore, litter weight decrease was considered to be secondary to systemic toxicity.			

33	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rabbit	22 days (GD 6-27)	Oral	> 350	mg/kg bw/day	No effect				
34	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rabbit	13 days (GD 6-18)	Oral	20	mg/kg bw/day	**Increase**	Litter weight was statistically significant higher in the low and mid dose group, but not in the high dose group. As there was no dose-response and clinical signs occurred in maternal animals, this effect was considered to be secondary to systemic toxicity. In addition, this effect was not reproducible in further pre-natal developmental studies.			
35	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
46	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rabbit	13 days (GD 7-19)	Oral	> 450	mg/kg bw/day	No effect				
47	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rabbit	13 days (GD 7-19)	Oral	> 625	mg/kg bw/day	No effect				
64	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rat	10 days (GD 6-15)	Oral	3500	mg/kg bw/day	**Decrease**	At 3500 mg/kg, both litter and mean fetal weights were reduced compared to control (statistically significant for mean fetal weight). Maternal body weight was significantly reduced during the first days of gestation but returned to normal levels thereafter. This might have affected fetal weights and therefore, fetal weight reduction is considered to be secondary to systemic toxicity. **RMS:** at 3500 mg/kg bw/day maternal body weight gain was reduced by 84% compared to controls during GD6-8; and reduced by 19% considering GD6-20.			
65	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect				

66	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rabbit	22 days (GD 6-27)	Oral	<350	mg/kg bw/day	No effect	There were no biologically relevant or statistically significant differences in mean fetal body weight in any of the treatment groups when compared to the control group. A slight decrease was noted in mean fetal body weight in all treated groups when compared to the control group, however, the parameter was comparable to the historical control. RMS: Indeed no effect on pup body weight was seen. However, at the dose levels of 350 and 175 mg/kg bw/day high mortality of the dams occurred which limited the number of foetuses. RMS considers that it is not possible to exclude that the lower number of foetuses in treated animals could mask treatment-related effects. As a precautionary principle, RMS proposed to set the developmental NOAEL at 75 mg/kg bw/day.			

69	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Rat	only secondary exposure through milk from PND 0-21	Oral	30000	ppm	**Decrease**	At birth, (total) litter weight of all treatment groups was increased compared to control - this is due to the increased litter sizes seen in the treatment groups. At 30000 ppm litter weight converged towards control values to Day 8; thereafter litter weight became reduced and by Day 21 (78% of the concurrent control value). Mean pup weight was reduced at birth through to Day 21 (62% of the controls). At 3000 and 10000 ppm litter weight through to weaning was comparable with the controls even though litter size was increased. As a consequence mean pup weight diverged below control values to an extent that on Day 21 post partum mean pup weight at 3000 and 10000 ppm was 91% and 87% lower than the corresponding control value. These differences, however, can probably be attributed to the pivotal association between litter size, litter weight and mean pup weight and, at this stage, no conclusive treatment-related effects can be established. In all dose groups litter sizes were increased and consequently mean pup weight was decreased. In addition, maternal toxicity was observed during gestation manifested in reduced body weights at 30000 ppm. Further, systemic toxicity in maternal animals was observed such as soft stool also at the highest dose group. Taken together, the reduced pup weight is considered to be secondary to maternal toxicity and the increased litter size and not directly related to the treatment.			

~~70~~	~~Sensitive to, but not diagnostic of, EATS~~	~~Litter/pup weight~~	~~Rat~~	~~life-time, all three generations~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~				
~~74~~	~~Sensitive to, but not diagnostic of, EATS~~	~~Litter/pup weight~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effect observed in F1 offspring.~~			
~~74~~	~~Sensitive to, but not diagnostic of, EATS~~	~~Litter/pup weight~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effect observed in F2 offspring.~~			
~~74~~	~~Sensitive to, but not diagnostic of, EATS~~	~~Litter/pup weight~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effect observed in F3 offspring.~~			
~~75~~	~~Sensitive to, but not diagnostic of, EATS~~	~~Litter/pup weight~~	~~Rat~~	~~Males: 60 days prior to mating; females: 14 days prior to mating until end of lactation (PND 21) or until sacrifice GD 13~~	~~Oral~~	~~>10~~	~~mg/kg bw/day~~	~~No effect~~	~~Group mean pup weight was not affected.~~			
95	Sensitive to, but not diagnostic of, EATS	Litter/pup weight	Mouse	Dams were exposed during gestation. Offspring samples were collected on GD 19, PND 7, and PND 21	Oral	5000	mg/L water	No effect				

22	Sensitive to, but not diagnostic of, EATS	Number of live births	Rat	10 weeks	Oral	>15000	ppm	No effect		The number of live births was not affected by glyphosate. **Consequently, no EATS-related adversity was observed.** **RMS:** Agreed It is noted that RMS removed the results from two studies (ID 70 and 75), as RMS considers these studies to be unacceptable.		
23	Sensitive to, but not diagnostic of, EATS	Number of live births	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
24	Sensitive to, but not diagnostic of, EATS	Number of live births	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000	ppm	No effect				
25	Sensitive to, but not diagnostic of, EATS	Number of live births	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Number of live births	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect				
27	Sensitive to, but not diagnostic of, EATS	Number of live births	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000	ppm	No effect				
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Number of live births*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
~~*75*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Number of live births*~~	~~*Rat*~~	~~*Males: 60 days prior to*~~	~~*Oral*~~	~~*>10*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	-			

				~~*mating; females: 14 days prior to mating until end of lactation (PND 21) or until sacrifice GD 13*~~								
22	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rat	10 weeks	Oral	>15000	ppm	No effect		The number of implantations and corpora lutea was not affected by glyphosate. **Consequently, no EATS-related adversity was observed.** **RMS:** Agreed It is noted that RMS removed the results from one study (ID 75), as RMS considers this study to be unacceptable.		
23	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
24	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000	ppm	No effect				
25	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect				
28	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect				
29	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect				

30	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rabbit	13 days (GD 6-18)	Oral	>300	mg/kg bw/day	No effect				
31	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rabbit	13 days (GD 7-19)	Oral	> 400	mg/kg bw/day	No effect				
32	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rabbit	13 days (GD 8-20)	Oral	>300	mg/kg bw/day	No effect				
33	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rabbit	22 days (GD 6-27)	Oral	> 350	mg/kg bw/day	No effect				
34	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
35	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
46	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rabbit	13 days (GD 7-19)	Oral	> 450	mg/kg bw/day	No effect				
47	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rabbit	13 days (GD 7-19)	Oral	> 625	mg/kg bw/day	No effect				
64	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rat	10 days (GD 6-15)	Oral	>3500	mg/kg bw/day	No effect				
65	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect				
66	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rabbit	22 days (GD 6-27)	Oral	*<350*	mg/kg bw/day	No effect	There were no biologically meaningful or statistically significant differences in the mean numbers of total implantations or corpora lutea in any of the treatment groups when compared to the control group. RMS: Indeed no effect on number of implantations/corpora lutea was seen. However, at the dose levels of 350 and 175 mg/kg bw/day high mortality of the dams occurred which limited the number of foetuses. RMS considers that it is not possible to exclude that the lower number of foetuses in treated animals could mask treatment-related effects. As a			

									precautionary principle, RMS proposed to set the developmental NOAEL at 75 mg/kg bw/day.			
69	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rat	5.5 weeks (GD 3 till 21 days post partum)	Oral	>30000	ppm	No effect	The implantation rates in all treated groups were higher than the controls. Since pup losses, both pre-birth and from birth to weaning, were generally similar among the groups, litter size of all treated groups was, as a consequence, generally greater than controls throughout weaning. These findings are not, however, considered to be an adverse effect of treatment.			
~~*75*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Number of implantations, corpora lutea*~~	~~*Rat*~~	~~*Males: 60 days prior to mating; females: 14 days prior to mating until end of lactation (PND 21) or until sacrifice GD 13*~~	~~*Oral*~~	~~*>10*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	~~*Number of corpora lutea and total implants in females killed at GD 13 were not affected.*~~			
77	Sensitive to, but not diagnostic of, EATS	Number of implantations, corpora lutea	Rabbit	22 days (GD 6-27)	Oral	>250	mg/kg bw/day	No effect				
22	Sensitive to, but not diagnostic of, EATS	Pup development	Rat	10 weeks	Oral	>15000	ppm	No effect		**No EATS-related adversity was observed on pup development in rat.** **RMS:** Agreed		
25	Sensitive to, but not diagnostic of, EATS	Pup development	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to	Oral	1000	ppm	No effect				

				weaning of F2								
26	Sensitive to, but not diagnostic of, EATS	Pup development	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect				
27	Sensitive to, but not diagnostic of, EATS	Pup development	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000	ppm	No effect				
24	Sensitive to, but not diagnostic of, EATS	Pup survival index	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000	ppm	No effect		**No EATS-related adverse was observed on pup survival in rat in 7/7 studies.** **RMS:** Agreed It is noted that RMS removed the results from two studies (ID 70, 75), as RMS considers these studies to be unacceptable.		
25	Sensitive to, but not diagnostic of, EATS	Pup survival index	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Pup survival index	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect				
27	Sensitive to, but not diagnostic of, EATS	Pup survival index	Rat	11 weeks prior to mating for	Oral	>30000	ppm	No effect				

				F0, further generations for approx. 14 weeks until termination								
~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Pup survival index*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
~~*75*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Pup survival index*~~	~~*Rat*~~	~~*Males: 60 days prior to mating; females: 14 days prior to mating until end of lactation (PND 21) or until sacrifice GD 13*~~	~~*Oral*~~	~~*>10*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
93	Sensitive to, but not diagnostic of, EATS	Pup survival index	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect	Survival index was calculated on PND 1, 4, 7, 10, 13, 16, 19, 21, 25.			
22	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rat	10 weeks	Oral	>15000	ppm	No effect		**No EATS-related adversity was observed on sex ratio in prenatal developmental toxicity studies in rabbit (8/8 studies) and rat (5/5 studies) as well as in multi-generation reproductive toxicity studies in rat (6/6 studies).**		
23	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect				
24	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000	ppm	No effect				
26	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect				

28	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect		**RMS:** Agreed It is noted that RMS removed the results from one study (ID 70), as RMS considers this study to be unacceptable.		
29	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect				
30	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rabbit	13 days (GD 6-18)	Oral	>300	mg/kg bw/day	No effect				
31	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rabbit	13 days (GD 7-19)	Oral	> 400	mg/kg bw/day	No effect				
32	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rabbit	13 days (GD 8-20)	Oral	>300	mg/kg bw/day	No effect				
33	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rabbit	22 days (GD 6-27)	Oral	> 350	mg/kg bw/day	No effect				
34	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect				
46	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rabbit	13 days (GD 7-19)	Oral	> 450	mg/kg bw/day	No effect				
47	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rabbit	13 days (GD 7-19)	Oral	> 625	mg/kg bw/day	No effect				
64	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rat	10 days (GD 6-15)	Oral	>3500	mg/kg bw/day	No effect				
65	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect				
66	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rabbit	22 days (GD 6-27)	Oral	*<350*	mg/kg bw/day	No effect	There were no biologically meaningful or statistically significant differences in the mean numbers of fetal sex distribution in any of the treatment groups when compared to the control group. RMS: Indeed no effect on sex ration was seen. However, at the dose levels of 350 and 175 mg/kg bw/day high mortality of the dams occurred which limited the number of foetuses. RMS considers that it is not possible to exclude that the lower number of foetuses in treated animals could mask treatment-related effects. As a precautionary principle, RMS proposed to set the developmental NOAEL at 75 mg/kg bw/day.			
69	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rat	only secondary exposure through milk from PND 0-21	Oral	>30000	ppm	No effect	Glyphosate did not selectively affect pups of one sex since, in all groups, sex ratios at birth and weaning were similar.			

~~*70*~~	~~*Sensitive to, but not diagnostic of, EATS*~~	~~*Sex ratio*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~				
93	Sensitive to, but not diagnostic of, EATS	Sex ratio	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect				
22	Sensitive to, but not diagnostic of, EATS	Functional observation battery	Rat	10 weeks	Oral	>15000	ppm	No effect		**No EATS-related adversity was observed on functional observation battery in rat in a two-generation study.** **RMS:** Agreed		

Systemic toxicity:

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Route of administra-tion	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
1	Systemic toxicity	Body weight	Rat	90 days	Oral	20000	ppm	**Decrease**	Decreased in males at 20000 ppm over the whole study period, -8% in final bw (no effect in females).	Body weight (gain) decreases were observed frequently at high doses in dog, mouse, rabbit, and rat after oral exposure. RMS: Agreed It is noted that RMS included the result on body weight from an additional study (ID 96). RMS has deleted the results from three studies (ID 70, 74, 75) as RMS considered these studies to be unacceptable.	Not applicable.	
2	Systemic toxicity	Body weight	Rat	90 days	Oral	50000	ppm	**Decrease**	Reduced body weight gain in males and females at 50000 ppm during the fist 4 weeks, effects partially reversible in males and fully reversible in females.			
3	Systemic toxicity	Body weight	Rat	90 days	Oral	30000	ppm	**Decrease**	Decreased bw (5--10%) in both sexes at 30000 ppm.			
4	Systemic toxicity	Body weight	Mouse	90 days	Oral	50000	ppm	**Decrease**	Decreased body weight (-9% at week 13) in males at 50000 ppm, occasionally statistically significant.			
5	Systemic toxicity	Body weight	Dog	90 days	Oral	1000	mg/kg bw/day	**Decrease**	Reduced mean body weight (-28%) and lower weight gain in males (+4% vs +31% in controls) and body weight loss in females (-7% vs. +14% in controls) at 1000 mg/kg bw/day (males: study week 4-11, females: study week 1-11.			
6	Systemic toxicity	Body weight	Dog	90 days	Oral	>10000	ppm	No effect				
7	Systemic toxicity	Body weight	Dog	90 days	Oral	>40000	ppm	No effect				
8	Systemic toxicity	Body weight	Dog	90 days	Oral	50000	ppm	**Decrease**	Depressed in males (not statistically significant) and females (occasionally statistically significant) at 50000 ppm.			
9	Systemic toxicity	Body weight	Dog	1 year	Oral	*500*	mg/kg bw/day	***Decrease***	Decreased body weight in males at 500 mg/kg bw/day, within historical control data, sporadic body weight changes in single dogs among all dose groups, not treatment-related RMS: as the decrease was >10% compared to control, it is considered adverse.			
10	Systemic toxicity	Body weight	Dog	1 year	Oral	50000	ppm	**Decrease**	Retarded body weight gain in both sexes at 50000 ppm (terminated bw were -6% in males, -11% in females			

									when compared to controls, not statistically significant).
11	Systemic toxicity	Body weight	Dog	1 year	Oral	30000	ppm	**Decrease**	Reduced body weight (-11%) in females at 30000 ppm during the second half of the study, reflects a palatability effect
12	Systemic toxicity	Body weight	Rat	1 year	Oral	8000	ppm	**Decrease**	Reduced body weight at ≥ 8000 ppm in both sexes.
13	Systemic toxicity	Body weight	Rat	2 years	Oral	>10000	ppm	No effect	
14	Systemic toxicity	Body weight	Rat	2 years	Oral	10000	ppm	**Decrease**	Decreased body weight gain in males at ≥ 10000 ppm and in females at 30000 ppm (terminal bw: 93-95% of control) during the treatment period, which is in line with reduced food consumption and low food efficiency.
15	Systemic toxicity	Body weight	Rat	2 years	Oral	20000	ppm	**Decrease**	Decreased in males (-5%) and females (-8%) at 20000 ppm throughout the study.
16	Systemic toxicity	Body weight	Rat	2 years	Oral	1000	mg/kg bw/day	**Decrease**	Reduced body weight gain in both sexes at 1000 mg/kg bw/day in week 52 and 104 (m: -14-32%; f: -11-17%) (not treatment-related findings: reduced at interim kill at 100 and 300 mg/kg bw/day, not reproduced at terminal kill, occasional fluctuations among all groups, no dose-relation).
17	Systemic toxicity	Body weight	Rat	2 years	Oral	20000	ppm	**Decrease**	Statistically significantly decreased in females only at 20000 ppm from study Day 51 until month 20 (bw 86% of control after 20 month, -23% bw gain after 20 month).
18	Systemic toxicity	Body weight	Rat	2 years	Oral	>15000	ppm	No effect	
19	Systemic toxicity	Body weight	Mouse	18 months	Oral	>10000	ppm	No effect	

20	Systemic toxicity	Body weight	Mouse	18 months	Oral	>5000	ppm	No effect	
21	Systemic toxicity	Body weight	Mouse	18 months	Oral	8000	ppm	**Decrease**	Occasional decreases among groups at 8000 and 40000 ppm throughout the treatment in both sexes, reduction in females at 8000 during weeks 6, 9 and 24 were considered to be treatment-related, body weight gain was comparable to those of controls at study termination
22	Systemic toxicity	Body weight	Rat	10 weeks	Oral	*>15000*	*ppm*	*No effect*	~~No adverse effect of bodyweight change was evident for treated animals in comparison to controls throughout the treatment period for both the F0 and F1 generations except for post-partum females treated with 15000 ppm. During the final week of lactation, both the F0 and F1 generations showed statistically significant less bodyweight loss in comparison to controls.~~
23	Systemic toxicity	Body weight	Rat	10 weeks (pre-mating)	Oral	10000	ppm	**Decrease**	Decreased body weight in F1 males at 10000 ppm during week 1, decreased body weight gain in F1 males at 10000 ppm from weeks 2 to 8, (there were no effects in females during maturation, gestation and lactation)
24	Systemic toxicity	Body weight	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	30000	ppm	**Decrease**	Decreased in F0 and F1 males at 30000 ppm from treatment week 1 until necropsy (non treatment-related findings in females, increased mean body weight in F1 females at 30000 ppm on lactation day 0)

25	Systemic toxicity	Body weight	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect		
26	Systemic toxicity	Body weight	Rat	10 weeks prior to mating, continued until termination	Oral	*>10000*	*ppm*	***No effect***	~~Absolute weight reduced in F1 males at 10000 ppm apparent at selection, overall weight gain was comparable to control, (no clear adverse effects on bw gain during pregnancy and lactation, during the first mate of each generation bw gains during the initial stages of pregnancy were slightly lower than control at all dosage groups, no consistent dose-response)~~	
27	Systemic toxicity	Body weight	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	30000	ppm	**Decrease**	Reduced in both sexes (F0+F1) at 30000 ppm throughout the study, (F0: -8% and F1 -10% during pre-mating) (Not treatment-related findings: during gestation and lactation maternal bw at 30000 ppm tended to be lower than controls although bw gain was comparable to those of controls)	
28	Systemic toxicity	Body weight	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect		
29	Systemic toxicity	Body weight	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect		
30	Systemic toxicity	Body weight	Rabbit	13 days (GD 6-18)	Oral	300	mg/kg bw/day	**Decrease**	Decreased bw at 300 mg/kg bw/day on gestation days 16-24, not statistically significant; decreased bw gain at 300 mg/kg bw/day during gestation days 0-16 and 0-24	
31	Systemic toxicity	Body weight	Rabbit	13 days (GD 7-19)	Oral	200	mg/kg bw/day	**Decrease**	Reduced bw gain at ≥ 200 mg/kg bw/day from days 9-29 of gestation. Statistical significance was	

									observed for body weight gain in the high dose group only from Days 13-29 post coitum.
32	Systemic toxicity	Body weight	Rabbit	13 days (GD 8-20)	Oral	175	mg/kg bw/day	**Decrease**	Body weight decrease statistically significant; all animals except one showed recovery in the post dosing period
33	Systemic toxicity	Body weight	Rabbit	22 days (GD 6-27)	Oral	> 350	mg/kg bw/day	No effect	
34	Systemic toxicity	Body weight	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect	
35	Systemic toxicity	Body weight	Rabbit	13 days (GD 6-18)	Oral	500	mg/kg bw/day	**Decrease**	Reduced body weight was observed in the high dose group.
36	Systemic toxicity	Body weight	Mouse	28 days	Oral	> 5000	ppm	No effect	
42	Systemic toxicity	Body weight	Rat	3 days	Oral	> 1000	mg/kg bw/day	No effect	
43	Systemic toxicity	Body weight	Rat	10 days	Oral	> 1000	mg/kg bw/day	No effect	
44	Systemic toxicity	Body weight	Rat	21 days (PND 22-42)	Oral	> 1000	mg/kg bw/day	No effect	
45	Systemic toxicity	Body weight	Rat	31 days (PND 23-53)	Oral	300	mg/kg bw/day	**Decrease**	Mean body weight gains for the 300 and 1000 mg/kg/day groups were decreased (7.5% and 12.4%, respectively) when the overall treatment period (PND 23-53) was evaluated, reaching statistical significance for the high dose group. Mean body weights for the 300 mg/kg/day group were 5.07% - 8.08% lower than the control group towards the end of the treatment period (PND 44-53), whereas mean body weights for the 1000 mg/kg/day group were 5.09% - 11.06% lower generally throughout the entire treatment period (PND 24-53). Final body weight was statistically significantly decreased by 12.4% and 7.5% for high and mid dose, respectively.

46	Systemic toxicity	Body weight	Rabbit	13 days (GD 7-19)	Oral	150	mg/kg bw/day	**Decrease**	Body weight gain was slightly reduced from 150 mg/kg bw (GD11-19)
47	Systemic toxicity	Body weight	Rabbit	13 days (GD 7-19)	Oral	100	mg/kg bw/day	**Decrease**	Transient body weight gain reductions were observed in the low and mid dose group and throughout the treatment period for the high dose group.
48	Systemic toxicity	Body weight	Rabbit	7 days (high dose) -13 (mid and low dose)	Oral	750	mg/kg bw/day	**Decrease**	Marked weight loss was observed from 750 mg/kg bw/day.
49	Systemic toxicity	Body weight	Rat	28 days	Oral	>20000	ppm	No effect	
50	Systemic toxicity	Body weight	Rat	28 days	Oral	2500	mg/kg bw/day	No effect	
51	Systemic toxicity	Body weight	Dog	Study part A: 21 days Study Part B: 14 days	Oral	>1000	mg/kg bw/day	No effect	
52	Systemic toxicity	Body weight	Rat	90 days	Oral	>1000	mg/kg bw/day	No effect	
53	Systemic toxicity	Body weight	Rat	90 days	Oral	20000	ppm	**Decrease**	RMS: The total mean body weight gain was similar for all groups. However, decreased bwg at week 50 and 85 in both sexes Statistically sign. increased mean body weight gains in males on Day 43 at 6000 and 20000 ppm were attributed to decreased weight gain in the control group. Statistically significantly. decreased body weight at 20000 ppm in both sexes on Day 50 and in males on Day 85.
~~*54*~~	~~*Systemic toxicity*~~	~~*Body weight*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*20000*~~	~~*ppm*~~	~~**Decrease**~~	~~*Reduced body weight gain in females at 20000 ppm during study weeks 3-6 and thereafter, statistically signif. reduced body weight throughout the treatment period. Findings were restricted to females and were not evident in the high dose recovery group during the exposure period.*~~

55	Systemic toxicity	Body weight	Rat	90 days	Oral	>20000	ppm	No effect	
56	Systemic toxicity	Body weight	Mouse	90 days	Oral	>4500	mg/kg bw/day	No effect	
57	Systemic toxicity	Body weight	Dog	6 months	Oral	>300	mg/kg bw/day	No effect	
58	Systemic toxicity	Body weight	Dog	1 year	Oral	>500	mg/kg bw/day	No effect	
59	Systemic toxicity	Body weight	Dog	1 year	Oral	*1000*	mg/kg bw/day	**Decrease**	Reduced mean body weight gain in males at 30 (-17%), 300 (-25%) and 1000 mg/kg bw/day (-25%) and in females at 1000 mg/kg bw/day (-19%), statistically not significant, treatment-relation not clear. RMS: treatment related and adverse effect in males and females at 1000 mg/kg bw/day
60	Systemic toxicity	Body weight	Rat	21 days	Dermal	>1000	mg/kg bw/day	No effect	
61	Systemic toxicity	Body weight	Rat	21 days	Dermal	>1000	mg/kg bw/day	No effect	
62	Systemic toxicity	Body weight	Rabbit	21 days	Dermal	>5000	mg/kg bw/day	No effect	
63	Systemic toxicity	Body weight	Rabbit	28 days	Dermal	>2000	mg/kg bw/day	No effect	
64	Systemic toxicity	Body weight	Rat	10 days (GD 6-15)	Oral	3500	mg/kg bw/day	**Decrease**	At 3500 mg/kg/day, the rate of body weight gain was markedly reduced during the first two days of treatment when compared to the concurrent control values. Thereafter, apart from a slight reduction in the rate of body weight gain during Days 12 to 14 of pregnancy, the rate of body weight gain was comparable with the controls, although absolute parity with the control group was not

									attained by Day 20. At 1000 mg/kg/day, there was a marginal reduction in the rate of body weight gain during the first two days of treatment when compared with the concurrent control group. Thereafter, the pattern of bodyweight change was similar to the controls.	
65	Systemic toxicity	Body weight	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect		
66	Systemic toxicity	Body weight	Rabbit	22 days (GD 6-27)	Oral	>350	mg/kg bw/day	No effect		
67	Systemic toxicity	Body weight	Mouse	2 years	Oral	> 1000	mg/kg bw/day	No effect		
68	Systemic toxicity	Body weight	Mouse	2 years	Oral	30000	ppm	**Decrease**	Mean body weights for the high-dose males were generally lower than control (-11% at Week 102) and were (mostly) statistically significant. Mean body weights for the high-dose females and the males and females at the low- and mid-dose levels were not affected. Mean fasted body weight at termination of the study was statistically significantly reduced for male high dose animals. Moreover, no effect on body weight gain was observed for all dose groups.	

69	Systemic toxicity	Body weight	Rat	5.5 weeks (GD 3 till 21 days post partum)	Oral	30000	ppm	**Decrease**	At 30000 ppm, the rate of bodyweight gain following the initiation of treatment was reduced to Day 14 of pregnancy: thereafter, the rate of bodyweight gain to Day 20 of pregnancy was similar to controls, however, absolute parity with controls at Day 20 was not achieved. At both 3000 and 10000 ppm the pattern of bodyweight gain during pregnancy was essentially similar to controls throughout, although by Day 14 of pregnancy, bodyweights were slightly lower than controls. During the first week of lactation the pattern of bodyweight change in all groups was comparable. Thereafter, slight differences in the pattern of change were apparent to weaning at 10000 and 30000 ppm in so much as more weight loss occurred than in the control group. There were no further effects at 3000 ppm.	
69	Systemic toxicity	Body weight	Rat	3 weeks (PND 21-42)	Oral	30000	ppm	**Decrease**	From weaning to termination (PND 21 - 42), males at 30000 ppm had a reduced rate of weight change. At lower dosages, and at all dosages among females, the rate of weight change was comparable with controls, however, differences inherent at weaning were still present by Week 6.	

~~*70*~~	~~*Systemic toxicity*~~	~~*Body weight*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	
71	Systemic toxicity	Body weight	Rat	28 days	Oral	30000	ppm	**Decrease**	Cumulative body weight change treated vs. control: M 40000= -53%* (day 1 - 8); M 40000=-40%* (day 1-16); M 50000=-100%* (day 1-8); M 50000=-50%* (day 1-16); M 50000=-44%* (day 1-23); M50000=-44%* (day 1-28); F 50000=-64%* (day 1-8); F 50000=-46%* (day 1-16); F 50000=-47%* (day 1-23); F 50000=-46%* (day 1-28); F 30000= -38%* (day 1-23); F 50000=-33%* (day 1-28) Body weight reduction are considered secondary to gastrointestinal effects.
72	Systemic toxicity	Body weight	Mouse	28 days	Oral	*>800*	mg/kg bw/day	No effect	
73	Systemic toxicity	Body weight	Mouse	90 days	Oral	50000	ppm	**Decrease**	Statistically significant decrease of body weights in males and females at 50000 ppm throughout the study period leading to final body weight reduction of -11%* in M at 50000 ppm and -8%* in F at 50000 ppm (compared to control). Incidences

									of statistically significant lower body weights were observed in males at 10000 ppm and females at 5000 and 10000 ppm.
~~*74*~~	~~*Systemic toxicity*~~	~~*Body weight*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*Body weight was not affected in F0 adults.*~~
~~*74*~~	~~*Systemic toxicity*~~	~~*Body weight*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*Body weight was not affected in F1 adults.*~~
~~*74*~~	~~*Systemic toxicity*~~	~~*Body weight*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*Body weight was not affected in F2 adults.*~~
~~*75*~~	~~*Systemic toxicity*~~	~~*Body weight*~~	~~*Rat*~~	~~*Males: 60 days prior to mating; females: 14 days prior to mating until end of lactation (PND 21) or until sacrifice GD 13*~~	~~*Oral*~~	~~*>10*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	
76	Systemic toxicity	Body weight	Rat	90-92 days	Oral	>7500	ppm	No effect	
77	Systemic toxicity	Body weight	Rabbit	22 days (GD 6-27)	Oral	500	mg/kg bw/day	**Decrease**	Severe body weight loss at 500 mg/kg bw (-9%* on GD 24 compared to GD 0) was observed.
78	Systemic toxicity	Body weight	Rat	90 days	Oral	25000	ppm	**Decrease**	Reduced weight gain in M at 25000 and 50000 ppm. Terminal body weight M 50000 ppm= -18% (in comparison to control) Terminal body weight F 50000 ppm= -5% (in comparison to control)
79	Systemic toxicity	Body weight	Mouse	90 days	Oral	25000	ppm	**Decrease**	Decreased body weight gains in M and F at 25000 ppm and 50000 ppm

80	Systemic toxicity	Body weight	Rat	5 weeks	Oral	50	mg/kg bw/day	**Decrease**	Although not statistically significant there was a dose-dependent decrease in daily weight gain. Mean terminal body weight was not statistically significantly changed. However, there was a ~10% reduction of mean body weights at 50 and 500 mg/kg bw groups providing an indication that the MTD was reached or exceeded.		
92	Systemic toxicity	Body weight	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect			
92	Systemic toxicity	Body weight	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect			
95	Mouse	Body weight	Mouse	Dams were exposed during gestation. Offspring samples were collected on GD 19, PND 7, and PND 21	Oral	5000	mg/L water	No effect			
96	*Systemic toxicity*	*Body weight*	*Rat*	*90 days*	*Oral*	*>7500*	*ppm*	*No effect*			

1	Systemic toxicity	Clinical chemistry and haematology	Rat	90 days	Oral	20000	ppm	**Change**	Haematology: reduced platelet count in both sexes at ≥ 5000 ppm, marginal increase in prothrombin time in males at all doses, both considered to be not tox. relevant Clinical chemistry: ALT↑ and ALP ↑in both sexes at 20000 ppm throughout the study (non-treatment related findings: AST ↑ in females at 20000 ppm at week 4, ALT in males+females ocassionally increased at 5000 ppm, ALP in males at 1000 and 5000 ppm marginally increased, ALP↑ in each one females at control group and 1000 ppm in week 13, no dose-response relationship; ↓plasma urea (both sexes), plasma glucose (males) and triglyceride levels (males) at 20000 ppm) Urinalysis: lower pH in both sexes at 20000 ppm and higher values at 1000 and 5000 ppm for females, marginal changes within historical control data	Changes in clinical chemistry parameters were observed and included: In rats: Increased ALT (2500 ppm in females and 8000 ppm in males or 250 mg/kg bw/day in males) and ALP (250 mg/kg bw/day in males, 100 mg/kg bw/day in females or 2000 ppm in females and 8000 ppm in males). These changes were observed in the long-time studies and are indicative for liver damage. Other changes included but were not limited to decreased creatinine, proteine, albumine and calcium. These changes were however rare or not consistently observed among the studies. In dog: Increased ALT, ALP and GGT were
2	Systemic toxicity	Clinical chemistry and haematology	Rat	90 days	Oral	10000	ppm	**Change**	Haematology: MCHC ↑ in females at 50000 ppm within historical control data, Neutrophils ↑ in males at 1000 and 50000 ppm, no dose-relation, findings incidental Clinical chemistry: Ca ↓ and ALP ↑ in both sexes at ≥ 10000 ppm, P↑ and Creat↓ in both sexes at 50000 ppm, total plama protein and albumin ↓ in females at 50000 ppm, treatment-related (non-treatment-related findings: plasma urea↓ and Na ↓ in both sexes at 50000, within historical control data) Urinalysis: haemoglobin in urine ↑ in both sexes at 50000 ppm, particulate matter in sediment in males at 50000 ppm, findings may	

									be attributed to faecal contamination	observed in males and females from 1000 mg/kg bw/day or 10000 ppm. In mouse: Increased calcium and decreased albumin were observed at 50000 ppm in females which is consistent with the findings in dogs, this change might be a consequence of effects on the kidney, however no correlating histopathological changes were observed. No effects on clinical chemistry were observed in rabbits. Hematology paramteres were not affected in rats. Dogs and mice however showed the same effects: Decreased hematocrit, hemoglobin and red blood cells.
3	Systemic toxicity	Clinical chemistry and haematology	Rat	90 days	Oral	30000	ppm	**Change**	Haematology: no abnormalities observed Clinical chemistry: ALP ↑ in females at 30000 ppm, treatment-related (findings without toxicological relevance: Alb ↓ in females at 30000 ppm) Urinalysis: lower pH in males at ≥ 10000 ppm and in females at 30000 ppm, attributed to the acidic nature of the test substance (findings without toxicological significante: decreased urine protein in males at ≥ 10000 ppm and in females at 30000 ppm, not treatment-related findings: increased urine volume in females at 30000 ppm)	
4	Systemic toxicity	Clinical chemistry and haematology	Mouse	90 days	Oral	50000	ppm	**Change**	Haematology: ↓ Ht, ↓ Hb and ↓ RBC and anemia in females at 50000 ppm, treatment-related; no changes in males Clinical chemistry: ↑ALP in both sexes at 50000 ppm, ↑ P in females at 50000 ppm, treatment-related (not treatment-related findings: ↓GPT in females at 50000 ppm, ↑ Creat.phosphokinase in females at 5000 and 50000 ppm, ↑BUN in females at 10000 ppm) Urinalysis: reduced pH in males of all treatment-groups, attributed to the acidic nature of the test substance	

5	Systemic toxicity	Clinical chemistry and haematology	Dog	90 days	Oral	1000	mg/kg bw/day	**Change**	Haematology: no treatment-related findings (occassional changes in Hb, Ht in females at 1000 mg/kg bw/day, reduced RBC in males at 30 and 300 mg/kg bw/day and reduced leucocytes in females at 30 mg/kg bw/day were without dose relation) Clinical chemistry: ALT ↑ in 2/3 males and 1/3 females at 1000 mg/kg bw, ALP↓ in 3/3 females at 1000 mg/kg bw/day, T.Prot and Alb ↓ in 3/3 females at 1000 mg/kg bw/day, treatment-related (not treatment-related findings: ocassionally Na↓, Creat↓ and urea ↓ in males at 1000 mg/kg bw, P↑ in females at 30 mg/kg bw/day, Gluc↓ in both sexes at 1000 mg/kg bw/day, findings not consistent throughout the study or not dose-related) Urinalysis: ↓ mean specific gravity in 1/3 males and 3/3 females at 1000 mg/kg bw/day, ↑ mean urinary volume and less marked colour in 3/3 females at 1000 mg/kg bw/day, treatment-related	**RMS:** It is noted that the result from one additional study were added (ID 96). RMS changed the conclusion for two studies: in a 2yr rat study (ID 17) a change was seen (increase alkaline phosphatase at 20000 ppm) and in a 90 d rat study (ID 54) (increased ALP at 20000 ppm).
6	Systemic toxicity	Clinical chemistry and haematology	Dog	90 days	Oral	>10000	ppm	**Change**	Haematology: after 45 days of treatment: dose-related increase in clotting time in both sexes at all dose, treatment-related but fully reversible (non-treatment-related findings: MCH ↑ in females at 10000 ppm, but within normal range); after 90 days of treatment: Neutrophils↓ in males at 2000 ppm, WBC↑ in females at 200 ppm, and Hct, MCV and MCH↑in females at 10000 ppm, within HCD); all effects were considered non-adverse Clinical chemistry: after 45 days of treatment: ALP↑ and GGT ↑ in	

									males at 10000 ppm, GGT ↑ in females at 10000 ppm (non-treatment-related findings: T.Bilirubin ↑ in females at ≥ 2000 ppm and Ca ↑ in females at 10000 ppm, but within normal range); after 90 days of treatment: T.Bilirubin ↑ in both sexes at 10000 ppm, treatment- and dose-related; all effects were considered non-adverse Urinalysis: no adverse effects observed
7	Systemic toxicity	Clinical chemistry and haematology	Dog	90 days	Oral	>40000	ppm	No effect	
8	Systemic toxicity	Clinical chemistry and haematology	Dog	90 days	Oral	50000	ppm	**Change**	Haematology: no treatment-related findings Clinical chemistry: at 50000 ppm Alb ↓, Ca ↓and T.Protein ↓ in males , treatment-related, and ALP ↑ in females Urinalysis: no treatment-related findings
9	Systemic toxicity	Clinical chemistry and haematology	Dog	52 weeks	Oral	>500	mg/kg bw/day	No effect	

10	Systemic toxicity	Clinical chemistry and haematology	Dog	1 year	Oral	50000	ppm	**Change**	Haematology: Ht↓, Hb↓and RBC↓ in females at 50000 ppm, anemic condition may be caused by malnutrition, treatment-related (no abnormalities in males) Clinical chemistry: Cl↑ (week 26), Alb↓ and Pi↓ (both week 52) in females at 50000 ppm, treatment-related (not treatment-related: Ca↓ in females at 1600 and 50000 ppm at week 52, CPK↓ in males at 8000 ppm in week 52, no dose-relation) Urinalysis: reduced pH in both sexes at 50000 ppm, attributed to the acidic nature of the test item		
11	Systemic toxicity	Clinical chemistry and haematology	Dog	1 year	Oral	>30000	ppm	No effect			
12	Systemic toxicity	Clinical chemistry and haematology	Rat	1 year	Oral	2000	ppm	**Change**	Haematology: no treatment-related findings (changes on several parameters were found but there was no dose-relation and differences were small + inconsistent) Clinical chemistry: ALP↑ in females at ≥ 2000 and in males at ≥ 8000 ppm, treatment-related but toxicologically not significant as no pathological change was found; Creat↓ in males at ≥ 2000 ppm, no dose-relation; T.Chol↓ and TG↓ in males at ≥ 8000 ppm at weeks 14+27; ALT↑ in both sexes at ≥8000 ppm; Creat. Kinase↑ in both sexes at 20000 ppm, treatment-related Urinalysis: reduced volume in males at ≥ 8000 ppm in week 13+26		

									and in 2000 ppm at week 26, treatment-related		
13	Systemic toxicity	Clinical chemistry and haematology	Rat	2 years	Oral	10000	ppm	**Change**	Haematology: no treatment-related findings (not treatment-related findings: surviving rats: occasional fluctuations of several parameters were all witihn historical control data, no dose-relation; Ht↑ (after 6 months) and Eosinophils↑ (after 18 months) in females at 10000 ppm were slightly outside historical control data, not consistent/ moribund rats: lymphocyte count↓ and neutrophil count↑ in both sexes among all treatment and control groups) Clinical chemistry: Alb↓ and ALP↑ in females at 10000 after 6 months, treatment-related, GGT↓ in males at 10000 ppm after 12 months, treatment-related (not treatment-related findings, occasional fluctuations were all within historical control range, not consistent or without dose relation) Urinalysis: Protein↑ in females at 10000 ppm, treatment-related (non treatment-related findings: occasional fluctuations of other parameters were not consistent throughout the study and/or not dose-related)		

14	Systemic toxicity	Clinical chemistry and haematology	Rat	2 years	Oral	10000	ppm	**Change**	Haematology: Ht↑ and PT↓ in males at 30000 ppm in week 104, attributed to altered values of the control animals which had callosities in the hind paw and anemia due to haemorrhage from the ulcered surfaces of the callosities Clinical chemistry: Gluc↓ and Glob↓ in females at 30000 ppm, considered secondary to the decreased body weight gain , Creat↓ (week 26) in females at ≥ 10000 ppm, GPT↓ in males (week 52) at 30000 ppm, treatment-related but considered not to be of toxicological significance, ALP↑(week 52) in females at 30000 ppm, treatment-relation unclear (not treatment-related findings: ALP↑ in males at 3000 ppm in week 78, Alb↓ in females at 3000 ppm in week 26, A/G↓ in females at 3000 ppm in week 26 and in males at 30000 ppm in week 104, attributed to the presence of callosities in control animals, T.Bil↓ in females at 3000 ppm in week 26, Cl↓ in males at 3000 and 10000 ppm in week 104, no dose-relation) Urinalysis: low pH in both sexes at ≥ 10000 ppm throughout the treatment period, attributed to the metabolic features of the test item; reduced protein in males at 30000 ppm at study week 26, treatment-related but toxicologically not significant as no blood chemistry or histopathological findings were noted (not treatment-related findings: dark coloured urine in females at ≥ 3000 ppm at study week 104, increased volume in			

									males at 3000 ppm at week 104, no dose-relation)
15	Systemic toxicity	Clinical chemistry and haematology	Rat	2 years	Oral	20000	ppm	**Change**	Haematology: no treatment-related findings (Hb↑ and PT↓ in all females at the interim kill, no dose-relation) Clinical chemistry: ALP↑ (weeks 1-79) in both sexes at 20000 ppm, ALT↑ in males (weeks 1-79) and occasionally in females at 20000 ppm, T.Bil↑ (throughout the study) and AST↑ (at interim kill) in males at 20000 ppm, findings in males in line with increased liver weight, hepatitis and proliferative cholangitis, treatment-related (not treatment-related/ no tox. relevance: occasionally reduced TG and Chol. in males at 20000 ppm, ALP↑ during the first study year and variations in ALT at 6000 ppm, considered to be without toxicological significance as no

									histopathological abnormalities were found, Creat↓ in females at 6000 ppm in week 27 and at 20000 ppm in week 14) Urinalysis: pH↓ in males at 20000 ppm, attributed to the acidic nature of the test material; blood/RBC↑ in both sexes at 20000 ppm, treatment-related		
16	Systemic toxicity	Clinical chemistry and haematology	Rat	2 years	Oral	100	mg/kg bw/day	**Change**	Haematology: Ht and MCH were occasionally increased at 100 and 1000 mg/kg bw/day in males, Hb occasionally increased in males at ≥ 100 mg/kg bw/day and in females at 1000 mg/kg bw/day, MCH occasionally increased in females at 1000 mg/kg bw/day, not treatment-related as changes were of small magnitude and inconsistent during the study, Eosinophils↓, Lymphocytes↓ and WBC↓ in females, effect not dose-related and not consistent throughout the study, high degree of individual variation, not reproducible Clinical chemistry: ALP↑ in males at 1000 mg/kg bw/day and in females at 100 mg/kg bw/day, treatment-related but without histopathological abnormalities (not treatment-related findings: T.Bil↑ in females, effect not consistent, high degree of individual variation, not reproducible, T.Chol↓ in males at 100 and 1000 mg/kg bw/day, no dose relationship, reproducibility		

									questionable, occasional variations in BUN, Glc and Ca, ALT and AST, Alb, T.Chol in males, no dose-relation, incidental, occasional variations of Creat and P in females, no dose-relation and/or inconsistent effect) Urinalysis: pH↓ in males at 1000 mg/kg bw/day, toxicological significance unknown		
17	Systemic toxicity	Clinical chemistry and haematology	Rat	2 years	Oral	*20000*	ppm	***Change***	RMS: Alkaline phosphatase was statistically increased in high dose females.		

18	Systemic toxicity	Clinical chemistry and haematology	Rat	2 years	Oral	15000	ppm	**Change**	Haematology: no treatment-related findings (not treatment-related findings: APTT↑ in males at ≥ 1500 ppm at 6 months, APTT↑ and leucocytes↓ in females at ≥ 1500 ppm at 18 months, PT↑ in females at 15000 ppm after 6 months, neutrophils↑ in males at 15000 ppm and in females at 5000 ppm after 18 months, Hb↓ in females at ≥ 5000 ppm after 12 months, Hb↑ and Ht↑ in males at 1500 ppm after 6 months, lymphocytes↓ in females at 15000 ppm after 18 months, monocytes↑ in females at 1500 ppm after 24 months, MCHC↓ in males at ≥ 5000 ppm at 6 months) Clinical chemistry: ALP↑ in males at 15000 ppm 6, 12 and 18 months, marginal, considered to be a minor adaptive change to test substance intake; increase in plasma electrolytes in both sexes at 15000 ppm, treatment-related, considered minor and adaptive responses (further findings without toxicological relevance: changes in plasma electrocytes in all groups (Na↑ and Cl↑ in both sexes and K↑ in males at ≥ 1500 ppm and Ca↓ in females at 15000 ppm after 18 months, Na↓ in satellite females at 15000 ppm after 12 months, P↓ in both sexes at 1500 ppm after 18 months and P↑ in males at 15000 ppm after 24 months) no dose relation, toxicological significance unclear; TBil↑ in males at ≥ 1500 ppm after 18 months, A/G ratio↓ in females at ≥ 1500 ppm after 24 months, ALT↑ in satellite males at 150000 ppm after 6 months, in females after 12 months and in males after 18 months, TG↑ in		

									females at 150000 ppm after 12 months, ALP↑ in satellite males at 5000 ppm after 12 months, urea↑ in females at 1500 ppm after 6 months, all findings without dose-relation and/or inconsistency throughout the study) Urinalysis: no treatment-related findings		
19	Systemic toxicity	Clinical chemistry and haematology	Mouse	18 months	Oral	>10000	ppm	No effect	Clinical chemistry and urinalysis: not performed		
20	Systemic toxicity	Clinical chemistry and haematology	Mouse	18 months	Oral	>5000	ppm	No effect	Clinical chemistry and urinalysis: not performed		

21	Systemic toxicity	Clinical chemistry and haematology	Mouse	18 months	Oral	8000	ppm	**Change**	Haematology (differential white blood cell count only): no treatment-related findings (increased lymphocytes in males and decreased neutrophils in males killed in extremis at 40000 ppm and increased lymphocytes in females at week 78, findings were attributed to skin lesions of high grade in moribund animals of the control group, which had high values of leukocytes and reduced values of lymphocytes, considered to be of sporadic nature) Clinical Chemistry: not performed Urinalysis: decreased pH in males at ≥ 8000 ppm, treatment-related, no histopathological correlates		
44	Systemic toxicity	Clinical chemistry and haematology	Rat	21 days (PND 22-42)	Oral	> 1000	mg/kg bw/day	No effect			
45	Systemic toxicity	Clinical chemistry and haematology	Rat	31 days (PND 23-53)	Oral	> 1000	mg/kg bw/day	No effect			
49	Systemic toxicity	Clinical chemistry and haematology	Rat	28 days	Oral	*>20000*	ppm	*No effect*	~~Haematology: No treatment-related findings. (Statistically significant decrease in haemoglobin in the high dose recovery animals; as the animals of the main group were not affected the effect was considered to be incidental.) Clinical chemistry: Statistically significant increase in GPT and BUN at 20000 ppm in both sexes, which is reversible after 14 days of recovery (Non-treatment-related findings: statistically significant~~		

									~~increase in BUN at 200 ppm, considered to be incidental due to the lack of a dose relationship NOEAL for changes in BUN and GPT is 2000 mg/kg bw/d equivalent to 100 mg/kg bw; incidental decrease in Ca2+ at 200 ppm, increase in Ca2+ in 20000 ppm recovery group but not in the main group)~~		
50	Systemic toxicity	Clinical chemistry and haematology	Rat	28 days	Oral	250	mg/kg bw/day	**Change**	Haematology: No treatment-related findings (statistically significantly decreased MCHC (-2%) in males at 50 mg/kg bw/day was considered to be incidental) Clinical chemistry: statistically significantly increased ALT in males at ≥ 250 mg/kg bw/day and in females at 2500 mg/kg bw/day, increased ALP in males at ≥ 250 mg/kg bw/day (statistically significant at 250 and 2500 mg/kg bw/day) and in females at ≥ 1000 mg/kg bw/day (not significant) and bilirubin were regarded as normal responses to increased liver activity; increased phosphate levels in males at ≥ 1000 mg/kg bw/day, treatment-related (slightly increased Na in females at 50, 1000 and 2500 mg/kg bw/day and slighly decreased Cl in females at 50 mg/kg bw/day were considered to be incidental)		

51	Systemic toxicity	Clinical chemistry and haematology	Dog	Study part A: 21 days Study Part B: 14 days	Oral	1000	mg/kg bw/day	**Change**	Haematology: Study part A (21 days treatment): the male dog showed a reduced Hb and a mild increase in reticulocytes on Day 22 (treatment period 1000 mg/kg bw/day), not treatment-related, attributed to repeated blood sampling Study part B (14 days treatment): no treatment-related findings Clinical chemistry: Study part A (21 days treatment): mild increase in ALT in the male dog and reduced cholesterol in the male and the female dog over the whole treatment period, considered to be not treatment-related Study part B (14 days treatment): mild increase in ALT in the male dog, considered to be not treatment-related Urinalysis (available for study part B only, 14 days treatment): no adverse effects observed Faecal occult blood: no adverse effects observed		
52	Systemic toxicity	Clinical chemistry and haematology	Rat	90 days	Oral	1000	mg/kg bw/day	**Change**	Haematology: statistically significant increase in eosinophils in males at 300 mg/kg bw/day, no dose relation, considered to be incidental Clinical chemistry: statistically significantly increased glucose (11%), total protein (9%), albumin (9%) and creatinine (8%) in females at 1000 mg/kg bw/day, treatment-related (statistically significantly increased ALP in males (28%) at 300 mg/kg bw/day was considered to be incidental as it was not observed at the higher dose) Urinalysis: reduced pH in males at 1000 mg/kg bw/day, treatment-related		

53	Systemic toxicity	Clinical chemistry and haematology	Rat	90 days	Oral	*>20000*	ppm	*No effect*	~~Haematology: No changes in haematological parameters observed.~~ ~~Clinical chemistry: No treatment-related effects observed. (K was statistically signif. reduced in males at 2000 ppm, which was considered to be incidental because a dose-response relationship was lacking. Reduced ALT and increased bilirubin in males at 20000 ppm were considered to be without toxicological significance)~~ ~~Urinalysis: Treatment-related increase in RBC and detection of blood in females at ≥ 6000 ppm and in all treatment groups in males. Findings in males were not unequivocally attributed to treatment, as a mild elevation of RBC is commonly observed in male rats~~			
~~*54*~~	~~*Systemic toxicity*~~	~~*Clinical chemistry and haematology*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*20000*~~	~~*ppm*~~	~~***Change***~~	~~*RMS: Clinical chemistry: statistically significant. increase in ALP in males at 20000 ppm which remained high (not statistically significant) and increased glucose levels in females at 20000 ppm treatment related*~~		

55	Systemic toxicity	Clinical chemistry and haematology	Rat	90 days	Oral	>5000	ppm	**Change**	Haematology: No adverse effects observed. Clinical chemistry: No treatment-related findings. (Statistically significant increases in lymphocytes in males at 1000 and 5000 ppm and increased WBC in males at 5000 ppm were not dose-related and therefore not attributed to treatment; statistically signif. increased P and K in both sexes in all test item-treated groups and statistically signif. increased glucose levels in males at 5000 and 20000 ppm showed no dose-relation and/or where within or close to the upper levels of normal values and therefore considered to be without toxicological significance; increased BUN and AP (not siginificant) was attributed to extreme values of one rat) Urinalysis: Statistically signif. changes in specific gravity and pH at 5000 ppm in males were not considered to be related to treatment		
56	Systemic toxicity	Clinical chemistry and haematology	Mouse	90 days	Oral	>4500	mg/kg bw/day	No effect	Haematology: No toxicologically relevant finding was observed. (Prothrombin time statist. signif. increased in females at 200 mg/kg bw/day, no dose-relation, considered to be incidental) Clinical chemistry: No toxicologically relevant finding was observed. (Dose-related increase in glucose levels in males over all test item treated groups, statistically not signifant; increase in plasma cholinesterase and AP and decrease of K in males over all dose groups, not dose-related, toxicological significance of this finding is unclear; slightly increased glucose		

									and AP levels in females in all test item treated groups, statistically not significant, no dose-response relationship) Urinalysis: Not performed		
57	Systemic toxicity	Clinical chemistry and haematology	Dog	6 months	Oral	300	mg/kg bw/day	**Change**	Haematology: Statistically significantly increased MCHC in both sexes at different sampling time points, no dose-relation, within normal range, not related to treatment Clinical chemistry: A dose-related increase in alkaline phosphatase activity was observed in males and females at all doses (statistically significant in high-dose males (month 5) only) and total lactic dehydrogenase levels statist. signif. decreased in males at 60 and 300 mg/kg bw/day after 4 months of treatment until study termination. As no gross or microscopic liver lesions were observed, biological relevance equivocal Urinalysis: No treatment-related effects observed.		

58	Systemic toxicity	Clinical chemistry and haematology	Dog	1 year	Oral	>500	mg/kg bw/day	No effect	
59	Systemic toxicity	Clinical chemistry and haematology	Dog	1 year	Oral	>1000	mg/kg bw/day	No effect	
60	Systemic toxicity	Clinical chemistry and haematology	Rat	21 days	Dermal	1000	mg/kg bw/day	**Change**	Haematology: statistically significant increase in MCH (4%) and MCV (4%) in females, reduced number of neutrophils (31%) in females. There was a decrease in monocytes (44%, P<0.05) and large unstained cells (62%, P<0.05) in the high dose males compared to controls. These findings have not been seen in previous studies and the decrease in monocytes may partly be due to higher values in concurrent control animals. Clinical chemistry: no adverse effects observed Urinalysis: not performed

61	Systemic toxicity	Clinical chemistry and haematology	Rat	21 days	Dermal	1000	mg/kg bw/day	**Change**	Haematology: statistically significant increase in Hb in females at 1000 mg/kg bw/day, treatment-related; statist. signif. decrease in RBC in females at 250 and 1000 mg/kg bw/day, considered not to be of tox. significance since no effect on the red cell parameters were observed Clinical chemistry: statistically significant increase in plasma urea but not urea levels in females at 1000 mg/kg bw/day, considered to be not of tox significance; stat. signif. decrease in triglycerides in males at 500 mg/kg bw/day, no dose relation, considered to be not treatment-related Urinalysis: not performed		
62	Systemic toxicity	Clinical chemistry and haematology	Rabbit	21 days	Dermal	>5000	mg/kg bw/day	No effect	Urinalysis: not performed		
63	Systemic toxicity	Clinical chemistry and haematology	Rabbit	28 days	Dermal	>2000	mg/kg bw/day	No effect	Urinalysis: not performed		
67	Systemic toxicity	Clinical chemistry and haematology	Mouse	2 years	Oral	> 1000	mg/kg bw/day	No effect			

68	Systemic toxicity	Clinical chemistry and haematology	Mouse	2 years	Oral	> 30000	ppm	No effect	
76	Systemic toxicity	Clinical chemistry and haematology	Rat	90-92 days	Oral	*7500*	ppm	**Change**	Hematology: RBC in F 2000 ppm=+13.6%* and M 7500 ppm=-1.4%* (males within normal range of historical controls); HCT in F 2000 ppm=+13.2%* and M 7500 ppm=-1.4%*; All values were close to the historical controls. Slight change in monocytes in males and females at 2000 ppm however not considered treatment-related Clinical chemistry: Ca in M 5000 ppm increase; Na in M changed ; Cl in M 7500 ppm increase (none of the clinical chemistry parameters is considered treatment-related)
78	Systemic toxicity	Clinical chemistry and haematology	Rat	90 days	Oral	12500	ppm	**Change**	Hematology: mild increase in hct and RBC in M at 12500 ppm; 25000 ppm; 50000 ppm; mild increase in hgb in M at 25000 ppm; 50000 ppm; mild increase in plts in M at 50000 ppm minimal but significant increase in lymphocyte and plts counts, WBC, MCH, MCV in F Clinical chemistry: Changes in: ALP in M and F at all time points (except 90 days), total bile acids in M (days 23 and 90) and F (day 23), total protein in F at all time points; sporadic increases in urea nitrogen and albumin

96	*Systemic toxicity*	*Clinical chemistry and haematology*	*Rat*	*90 days*	*Oral*	*>7500*	*ppm*	*No effect*		
1	Systemic toxicity	Clinical signs	Rat	90 days	Oral	>20000	ppm	No effect		The most common finding were related to distrubances of the gastrointestinal tract such as soft/loose feces, diarrhea or reduced fecal output. In some studies rales were observed in rat and rabbit. No effects were observed in mice. RMS: It is noted that RMS removed the results from two studies (ID 70 and 74), as RMS considered these studies to be unacceptable. RMS has included an
2	Systemic toxicity	Clinical signs	Rat	90 days	Oral	50000	ppm	**Increase**	Soft faeces and diarrhea in 10/10 males and 10/10 females at 50000 ppm from Day 4 until termination.	
3	Systemic toxicity	Clinical signs	Rat	13 weeks	Oral	>30000	ppm	No effect		
4	Systemic toxicity	Clinical signs	Mouse	90 days	Oral	>50000	ppm	No effect		
5	Systemic toxicity	Clinical signs	Dog	90 days	Oral	1000	mg/kg bw/day	**Increase**	At 1000 mg/kg bw/day: liquid/soft feces in 3/3 males and 3/3 females, vomiting in 2/3 females, thin appearance in 1/3 males and 3/3 females, dehydration in 1/3 males and 2/3 females, pallor of ears and mouth in 1/3 females.	
6	Systemic toxicity	Clinical signs	Dog	90 days	Oral	>10000	ppm	No effect		
7	Systemic toxicity	Clinical signs	Dog	90 days	Oral	>40000	ppm	No effect		
8	Systemic toxicity	Clinical signs	Dog	90 days	Oral	>50000	ppm	No effect		
9	Systemic toxicity	Clinical signs	Dog	1 year	Oral	>500	mg/kg bw/day	No effect		
10	Systemic toxicity	Clinical signs	Dog	1 year	Oral	50000	ppm	**Increase**	Loose stool in 3/4 males and 4/4 females at 50000 ppm	

11	Systemic toxicity	Clinical signs	Dog	1 year	Oral	>30000	ppm	No effect		additional study (ID 96).	
12	Systemic toxicity	Clinical signs	Rat	1 year	Oral	20000	ppm	**Increase**	Slight increase in urinary staining (wet and dry) at 20000 ppm in both sexes		
13	Systemic toxicity	Clinical signs	Rat	2 years	Oral	>10000	ppm	No effect			
14	Systemic toxicity	Clinical signs	Rat	2 years	Oral	30000	ppm	**Increase**	Loose stool and soiled and/or wetted fur in perianal/genital region in both sexes at 30000 ppm, bradypnea and integument mass (tail) in males at 30000 ppm (non treatment-related findings: decreased spontaneous motor activity and bradypnea in males at 3000 ppm, ptosis in females at 3000 ppm, reduced tactile hairloss in males at ≥ 3000 ppm and in females at 3000 and 10000 ppm, reduced integument wounds and hairloss in males at 30000 ppm)		
15	Systemic toxicity	Clinical signs	Rat	2 years	Oral	20000	ppm	**Increase**	Clinical signs: red-brown staining of tray papers, particularly in males at 20000 ppm (not treatment-related findings: red/brown colored urine in 3/52 males and 1/52 females at 20000 ppm) Functional observational battery: decreased landing foot splay in females at 20000 ppm, not treatment-related		

16	Systemic toxicity	Clinical signs	Rat	2 years	Oral	300	mg/kg bw/day	**Increase**	Pale faeces in males and females at ≥ 300 mg/kg bw/day from weeks 16-104, treatment-related, considered to be not toxicologically significant
17	Systemic toxicity	Clinical signs	Rat	2 years	Oral	20000	ppm	**Increase**	**No signs of clinical toxicity Ophthalmology (examined by 3 independent experts): increased incidences of degenerative lens changes in males at 20000 ppm, within historical control range, treatment-related as histopathological abnormalities were exacerbated by treatment**
18	Systemic toxicity	Clinical signs	Rat	2 years	Oral	>15000	ppm	No effect	
19	Systemic toxicity	Clinical signs	Mouse	18 months	Oral	>10000	ppm	No effect	
20	Systemic toxicity	Clinical signs	Mouse	18 months	Oral	>5000	ppm	No effect	
21	Systemic toxicity	Clinical signs	Mouse	18 months	Oral	>40000	ppm	No effect	

22	Systemic toxicity	Clinical signs	Rat	10 weeks	Oral	>15000	ppm	No effect	
22	Systemic toxicity	Clinical signs	Rat	10 weeks	Oral	>15000	ppm	No effect	
23	Systemic toxicity	Clinical signs	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect	
23	Systemic toxicity	Clinical signs	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect	
24	Systemic toxicity	Clinical signs	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	30000	ppm	**Increase**	Loose stool in F1 males during pre-mating and in F0 + F1 females during pre-mating and lactation at 30000 ppm, treatment-related (not treatment-related findings: hairloss in F0 males at ≥ 1200 ppm, considered to be incidental, malocclusion of the incisors, respiratory wheezing and red sebum in 1/24 F0 control males, 1/24 F0 control females and 1/24 F0 males at 6000 ppm and in 1/24 F1 males at 1200 ppm; distention of the abdomen in 1/24 F0 males at 6000 ppm)
24	Systemic toxicity	Clinical signs	Rat	10 weeks for pre-mating rearing 8 weeks for	Oral	>30000	ppm	No effect	

				subsequent breeding					
25	Systemic toxicity	Clinical signs	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect	
25	Systemic toxicity	Clinical signs	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect	
26	Systemic toxicity	Clinical signs	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect	
27	Systemic toxicity	Clinical signs	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	30000	ppm	**Increase**	Soft stool at 30000 ppm in F0 and F1 animals of both sexes, treatment-related (not treatment-related findings: red ocular discharge, result of overgrown / maloccluded teeth in both sexes, no dose-relation)
27	Systemic toxicity	Clinical signs	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000	ppm	No effect	

28	Systemic toxicity	Clinical signs	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect	
29	Systemic toxicity	Clinical signs	Rat	10 days (GD 6-15)	Oral	1000	mg/kg bw/day	**Increase**	Loose stool in 20/22 pregnant females at 1000 mg/kg bw/day during the dosing period and in 9/20 females one day after treatment (gestation day 16) (not treatment-related findings: hair loss or scabs in maternal rats at 30 and 300 mg/kg bw/day during the dosing period, within historical control data, hairloss in 1-2 maternal rats per group in each treated group)
30	Systemic toxicity	Clinical signs	Rabbit	13 days (GD 6-18)	Oral	300	mg/kg bw/day	**Increase**	Loose stool in 4/17 females during the dosing period at 300 mg/kg bw/day and soiled fur in the perianal region in 2 of them, loose stool remained in 2/4 affected females of this group after dosing, one of the affected does aborted on gestation day 26 and the other one prematurely delivered on gestation day 27, treatment-related (not treatment-related findings: hair loss in 1/17 and 1/16 females at 10 and 100 mg/kg bw/day during dosing and in 1/17 and 1/16 females at 10 and 100 mg/kg bw/day post-dosing, loose stool and red material on the tray in 2/18 control females after dosing, loose stool in 1/17 females at 10 mg/kg bw/day post-dosing)
31	Systemic toxicity	Clinical signs	Rabbit	13 days (GD 7-19)	Oral	400	mg/kg bw/day	**Increase**	Scours (16/18 does), reduced faecal output (6/18 does) and diarrhoea (10/18 does) at 400 mg/kg bw/day, treatment-related (lethargy, ptosis, hunched posture, hypothermia and blood on tray in 1/18 females at 400 mg/kg bw/day killed in extremis) (not treatment-related: vaginal bleeding in 1/18 females at 200 mg/kg bw/day, no dose-relation, not evaluated as toxicological effect,

									scours in 5/18, 10/18 and 7/18 females at 0, 50 and 200 mg/kg bw/day)
32	Systemic toxicity	Clinical signs	Rabbit	13 days (GD 8-20)	Oral	175	mg/kg bw/day	**Increase**	Sings of diarrhoea; reduction in faecal output; staining in the genital area (300 mg/kg bw/day group); not significant for all groups
33	Systemic toxicity	Clinical signs	Rabbit	22 days (GD 6-27)	Oral	175	mg/kg bw/day	**Increase**	Increase in soft stool and diarrhea (from 175 mg/kg bw/d); nasal discharge (350 mg/kg bw/day group only)
34	Systemic toxicity	Clinical signs	Rabbit	13 days (GD 6-18)	Oral	500	mg/kg bw/day	**Increase**	Toxic symptoms of the respiratory and the gastrointestinal tract (rales, dyspnoea, diarrhea/soft stool and weakness)
35	Systemic toxicity	Clinical signs	Rabbit	13 days (GD 6-18)	Oral	> 500	mg/kg bw/day	No effect	
36	Systemic toxicity	Clinical signs	Mouse	28 days	Oral	> 5000	ppm	No effect	
42	Systemic toxicity	Clinical signs	Rat	3 days	Oral	> 1000	mg/kg bw/day	No effect	
43	Systemic toxicity	Clinical signs	Rat	10 days	Oral	> 1000	mg/kg bw/day	No effect	
44	Systemic toxicity	Clinical signs	Rat	21 days (PND 22-42)	Oral	300	mg/kg bw/day	**Increase**	Dose dependent rales were noted in 4/15 animals in the 300 mg/kg bw/day group and 13/15 animals in the 1000 mg/kg bw/day group.
45	Systemic toxicity	Clinical signs	Rat	31 days (PND 23-53)	Oral	300	mg/kg bw/day	**Increase**	Rales were noted in 9/15 animals in the 300 mg/kg bw/day group and 14/14 animals in the 1000 mg/kg bw/day group throughout the treatment period approximately 4 hours following dose administration.
46	Systemic toxicity	Clinical signs	Rabbit	13 days (GD 7-19)	Oral	50	mg/kg bw/day	**Increase**	Light increase in females with gastro-intestinal disturbances (from 50 mg/kg bw/day), dose-related increase in the incidence of females showing soft/liquid faeces; sings of

									inappetence (150 mg/kg bw/day group and higher dose groups)
47	Systemic toxicity	Clinical signs	Rabbit	13 days (GD 7-19)	Oral	100	mg/kg bw/day	**Increase**	Signs of gastro-intestinal disturbances and inappetence were observed in all dose groups.
48	Systemic toxicity	Clinical signs	Rabbit	7 days (high dose) -13 (mid and low dose)	Oral	500	mg/kg bw/day	**Increase**	Soft feces (from 500 mg/kg bw/day); gastro-intestinal disturbances (from 750 mg/kg bw/day); haemorrhagic depressions of the stomach and damp/stained fur of the tail (1000 mg/kg bw/day).
49	Systemic toxicity	Clinical signs	Rat	28 days	Oral	>20000	ppm	No effect	
50	Systemic toxicity	Clinical signs	Rat	28 days	Oral	2500	mg/kg bw/day	**Increase**	Soft faeces in 3/5 males at 2500 mg/kg bw/day during weeks 3 and 4.
51	Systemic toxicity	Clinical signs	Dog	Study part A: 21 days Study Part B: 14 days	Oral	>1000	mg/kg bw/day	No effect	
52	Systemic toxicity	Clinical signs	Rat	90 days	Oral	>1000	mg/kg bw/day	No effect	
53	Systemic toxicity	Clinical signs	Rat	90 days	Oral	20000	ppm	**Increase**	Diarrhea in 10/10 males and 9/10 females at 20000 ppm Ophthalmic examinations: persistent pupillary membrane in the right eye of 1/10 control males and numerous corneal deposits in the right eye of 1/10 males at 20000 ppm, not treatment-related
~~*54*~~	~~*Systemic toxicity*~~	~~*Clinical signs*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~	~~Higher incidences of respiratory affections (nasal discharge, snuffling) in both sexes in all test item treated groups, persistent in males after recovery period.~~
55	Systemic toxicity	Clinical signs	Rat	90 days	Oral	>20000	ppm	No effect	

56	Systemic toxicity	Clinical signs	Mouse	90 days	Oral	>4500	mg/kg bw/day	No effect	
57	Systemic toxicity	Clinical signs	Dog	6 months	Oral	>300	mg/kg bw/day	No effect	
58	Systemic toxicity	Clinical signs	Dog	1 year	Oral	20	mg/kg bw/day	**Increase**	Increased incidences of abnormal excrement (bloody stool, yellow mucoid stool, diarrhea, emesis) were observed in a few females at 20 and 500 mg/kg bw/day; most observations were attributed to 1 female of each group (1/6), no findings at 100 mg/kg bw/day females or in males (all dose groups), considered to be not dose-related and of questionable biological significance; skin redness with slight alopecia in 1/6 females at 100 and in 1/6 females at 500 mg/kg bw/day. Ophthalmoscopy: no treatment-related findings
59	Systemic toxicity	Clinical signs	Dog	1 year	Oral	1000	mg/kg bw/day	**Increase**	Increased incidences of changes in faecal consistency (soft, loose, liquid) were recorded more frequently at 1000 mg/kg bw/day, treatment-related (not treatment-related observations: vomiting, salivation, minor wound bites and conjunctivitis were infrequently observed, no dose or treatment relation) Ophthalmoscopy: no treatment-related findings
60	Systemic toxicity	Clinical signs	Rat	21 days	Dermal	1000	mg/kg bw/day	**Increase**	Clinical signs of systemic toxicity: no adverse effects observed Local skin reactions: 2/5 males and 3/5 females showed very slight erythema during Week 2, which remained apparent in 1/5 females in Week 3 at 1000 mg/kg bw/day, moderate to severe desquamation in 3/5 males and mild to severe desquamation in 5/5 females at

									1000 mg/kg bw/day during Week 2 and in 1/5 males and 1/5 females at 1000 mg/kg bw/day in Week 3.	
61	Systemic toxicity	Clinical signs	Rat	21 days	Dermal	>1000	mg/kg bw/day	No effect		
62	Systemic toxicity	Clinical signs	Rabbit	21 days	Dermal	>5000	mg/kg bw/day	No effect		
63	Systemic toxicity	Clinical signs	Rabbit	28 days	Dermal	>2000	mg/kg bw/day	No effect		
64	Systemic toxicity	Clinical signs	Rat	10 days (GD 6-15)	Oral	1000	mg/kg bw/day	**Change**	3500 mg/kg: respiratory distress (noisy respiration/gasping (15/25)), post-dose salivation (22/22), wet coats (13/22), loose faeces from GD7-GD16 (22/22). 1000 mg/kg: noisy respiration on one occasion (2/25). Hair loss/scabbing in occasional animals, including controls, not treatment related.	
65	Systemic toxicity	Clinical signs	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect		

66	Systemic toxicity	Clinical signs	Rabbit	22 days (GD 6-27)	Oral	175	mg/kg bw/day	**Change**	Soft stool and diarrhea were noted in all groups during the treatment period. A slight increase was noted, however, in the 175 mg/kg/day dosage group when compared to the control group and either soft stool, diarrhea or both were noted in each animal at least once during the treatment period in the 350 mg/kg/day dosage group. A definite increase in nasal discharge was also noted in the 350 mg/kg/day dosage group when compared to the control group.
67	Systemic toxicity	Clinical signs	Mouse	2 years	Oral	> 1000	mg/kg bw/day	No effect	
68	Systemic toxicity	Clinical signs	Mouse	2 years	Oral	> 30000	ppm	No effect	
69	Systemic toxicity	Clinical signs	Rat	5.5 weeks (GD 3 till 21 days post partum)	Oral	10000	ppm	**Change**	Clinical signs included soft faeces and yellow stained sawdust (considered to be caused by the urine) in both cages of animals at 10000 and 30000 ppm. Onset of these signs was earlier at 30000 ppm than at 10000 ppm (soft faeces occurred immediately dietary administration commenced at 30000 ppm but not until the third week post partum at 10000 ppm; yellow staining of the sawdust occurred on Day 26 post coitum at 30000 ppm but not until Day 28 post coitum at 10000 ppm), with signs still apparent in both groups at termination. There were no clinical signs at 3000 ppm considered to be attributable to treatment.
69	Systemic toxicity	Clinical signs	Rat	3 weeks (PND 21-42)	Oral	30000	ppm	**Change**	Soft faeces were observed for all animals at 30000 ppm from Week 4 through to sacrifice at Week 6. No other clinical signs were observed at this or lower dosages.

~~*70*~~	~~*Systemic toxicity*~~	~~*Clinical signs*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	
71	Systemic toxicity	Clinical signs	Rat	28 days	Oral	30000	ppm	**Increase**	Significant incidences of soft stools and/or diarrhea were noted for both sexes at all three exposure levels with the highest dose group most affected (M/F 30000= Soft stool, diarrhea; M/F 40000= soft stool/diarrhea; M/F 50000=marked diarrhea).
72	Systemic toxicity	Clinical signs	Mouse	28 days	Oral	>*800*	mg/kg bw/day	No effect	
73	Systemic toxicity	Clinical signs	Mouse	90 days	Oral	>50000	ppm	No effect	
~~*74*~~	~~*Systemic toxicity*~~	~~*Clinical signs*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	
~~*74*~~	~~*Systemic toxicity*~~	~~*Clinical signs*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	
~~*74*~~	~~*Systemic toxicity*~~	~~*Clinical signs*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	
76	Systemic toxicity	Clinical signs	Rat	90-92 days	Oral	>7500	ppm	No effect	
77	Systemic toxicity	Clinical signs	Rabbit	22 days (GD 6-27)	Oral	>2500	mg/kg bw/day	No effect	
78	Systemic toxicity	Clinical signs	Rat	90 days	Oral	50000	ppm	**Increase**	F and M at 50000 ppm = diarrhea during first 50 days was observed (normal thereafter).
92	Systemic toxicity	Clinical signs	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks	Oral	>1.75	mg/kg bw/day	No effect	There was no clinical evidence of alterations in activity or behavior, reflexes, eyes or skin, respiratory, gastrointestinal, genito-urinary and cardiovascular systems.

				cohorts, respectively						
96	*Systemic toxicity*	*Clinical signs*	*Rat*	*90 days*	*Oral*	*>7500*	*ppm*	*No effect*		
1	Systemic toxicity	Food consumption	Rat	90 days	Oral	*>20000*	*ppm*	*No effect*		Food consumption was decreased in most studies at high doses. In rats: From 1000 ppm in males and 7500 ppm in females or 1000 mg/kg bw/day in females. In dogs: From 1000 mg/kg bw/day or 10000 ppm in males and females. In rabbits: From 100 mg/kg bw/day in females. In mice: From 40000 ppm in males and females. There was one study in mice with increased food consumption in males and females from 5000 ppm although incidents of body weight loss were observed in this dose group.
2	Systemic toxicity	Food consumption	Rat	90 days	Oral	50000	ppm	**Decrease**	Food consumption/efficiency: reduced in males and females at 50000 ppm during the first 4 weeks, effects partially reversible in males and fully reversible in females, effects in line with reduced bw development, treatment-related	
3	Systemic toxicity	Food consumption	Rat	90 days	Oral	30000	ppm	**Decrease**	Food consumption: statistically significantly decreased in both sexes at 30000 ppm during the first week, in line with reduced body weight, treatment-related (not treatment-related findings: decreased food consumption in both sexes at 3000 ppm) food efficiency: statistically significantly decreased (-5-6 %) in both sexes at 30000 ppm during the first week, in line with reduced body weight, treatment-related	
4	Systemic toxicity	Food consumption	Mouse	90 days	Oral	50000	ppm	**Decrease**	Food consumption: decreased (-6%) in males at 50000 ppm during the treatment period, treatment-related food efficiency: decreased (m:-21%; f: -12%) in both sexes at 50000 ppm during the treatment period, treatment-related	
5	Systemic toxicity	Food consumption	Dog	90 days	Oral	1000	mg/kg bw/day	**Decrease**	Food consumption: reduced food consumption, varying from 25-75% of the amount given, was observed on many occasions in both sexes at 1000 mg/kg bw (males: study week	

									4-11, females: study week 1-11), treatment-related	RMS: It is noted that RMS removed the results from three studies (ID 70, 74, 75), as RMS considered these studies to be unacceptable. In addition, RMS has added an additional study (ID 96).	
6	Systemic toxicity	Food consumption	Dog	90 days	Oral	10000	ppm	**Decrease**	Food consumption: decreased in both sexes at 10000 ppm during study week 2, fully reversible food efficiency: no adverse effects observed		
7	Systemic toxicity	Food consumption	Dog	90 days	Oral	>40000	ppm	No effect			
8	Systemic toxicity	Food consumption	Dog	90 days	Oral	>50000	ppm	No effect			
9	Systemic toxicity	Food consumption	Dog	1 year	Oral	>500	mg/kg bw/day	No effect			
10	Systemic toxicity	Food consumption	Dog	1 year	Oral	>50000	ppm	No effect			
11	Systemic toxicity	Food consumption	Dog	1 year	Oral	>30000	ppm	No effect			
12	Systemic toxicity	Food consumption	Rat	1 year	Oral	8000	ppm	**Decrease**	Food consumption: reduced in both sexes at ≥ 8000 ppm, treatment-related (20000 ppm: reduced during the first 12 weeks of the study, 8000 ppm: occasionally reduced at the end of the study) food efficiency: reduced in both sexes at 20000 ppm, treatment-related (reduced during the first 4 weeks of the study)		
13	Systemic toxicity	Food consumption	Rat	2 years	Oral	>10000	ppm	No effect			
14	Systemic toxicity	Food consumption	Rat	2 years	Oral	30000	ppm	**Decrease**	Food consumption: decreased in males at 30000 ppm during the first weeks of treatment, treatment-related (not treatment-related findings: increased in females at 3000 ppm during study week 48) food efficiency: decreased in both		

									sexes at 30000 ppm during the first 13 weeks of treatment (not treatment-related findings: reduced in males at 10000 ppm during the first 6 weeks)	
15	Systemic toxicity	Food consumption	Rat	2 years	Oral	20000	ppm	**Decrease**	Food consumption: statistically significantly reduced in males (-6%) and females (-5%) at 20000 ppm during the first study year, treatment-related food efficiency: statistically significantly reduced in both sexes at 20000 ppm during study weeks 1-4, reduced in males at 20000 ppm in weeks 1-12, treatment-related (not treatment-related: slightly increased in females at 20000 ppm during weels 9-12)	
16	Systemic toxicity	Food consumption	Rat	2 years	Oral	>1000	mg/kg bw/day	No effect		
17	Systemic toxicity	Food consumption	Rat	2 years	Oral	>20000	ppm	No effect		
18	Systemic toxicity	Food consumption	Rat	2 years	Oral	>15000	ppm	No effect		
19	Systemic toxicity	Food consumption	Mouse	18 months	Oral	>10000	ppm	No effect		
20	Systemic toxicity	Food consumption	Mouse	18 months	Oral	>5000	ppm	No effect		

21	Systemic toxicity	Food consumption	Mouse	18 months	Oral	8000	ppm	**Decrease**	Food consumption: statistically significantly depressed (-6% overall) in males at 40000 ppm at weeks 1 and 68 and in females (-7% overall) at 40000 ppm at weeks 1, 4, 8, 12, 20, 28, 40, 48 and 68, treatment-related Food efficiency: decreased in both sexes at 40000 ppm (-9% and -24% in males and femeles, respectively) and in females at 8000 ppm throughout the study period (-16% overall), treatment-related	
22	Systemic toxicity	Food consumption	Rat	10 weeks	Oral	>15000	ppm	No effect		
23	Systemic toxicity	Food consumption	Rat	10 weeks (pre-mating)	Oral	10000	ppm	**Decrease**	Food consumption: decreased in F1 males at 10000 ppm during pre-mating, treatment-related Food efficiency: increased in F1 males at 10000 ppm during weeks 5-8, treatment-related	
24	Systemic toxicity	Food consumption	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000	ppm	No effect		
25	Systemic toxicity	Food consumption	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	10000	ppm	**Change**	Decreased in F1 males at ≥ 1000 ppm during weeks 0-2; increased in F1 females at 10000 ppm during gestation (not treatment-related findings: decreased in F0 females at 100 and 1000 ppm and in F1 females at 100 ppm during lactation; increased in F0 females at 10000 ppm during lactation)	

26	Systemic toxicity	Food consumption	Rat	10 weeks prior to mating, continued until termination	Oral	*>10000*	ppm	*No effect*	~~Food consumption: slightly increased in F1 females at 10000 ppm during the latter stage of the first pre-mating period, not statistically significant Food efficiency: no clear consistent adverse effects observed across both generations Water consumption: slightly increased in F1 females at 10000 ppm with statistical significance in week 16~~
27	Systemic toxicity	Food consumption	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000	ppm	No effect	
28	Systemic toxicity	Food consumption	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect	
29	Systemic toxicity	Food consumption	Rat	10 days (GD 6-15)	Oral	1000	mg/kg bw/day	**Decrease**	Decreased at 1000 mg/kg bw/day on gestation days 6-9, treatment-related (increase at 1000 mg/kg bw/day on gestation days 15-20 was considered to be due to the rebound effect against the reduced food consumption during the dosing period)
30	Systemic toxicity	Food consumption	Rabbit	13 days (GD 6-18)	Oral	>300	mg/kg bw/day	No effect	
31	Systemic toxicity	Food consumption	Rabbit	13 days (GD 7-19)	Oral	400	mg/kg bw/day	**Decrease**	Food consumption: Reduced at 400 mg/kg bw/day during the dosing period, treatment-related
32	Systemic toxicity	Food consumption	Rabbit	13 days (GD 8-20)	Oral	175	mg/kg bw/day	**Decrease**	Food consumption was statistically significantly decreased.
34	Systemic toxicity	Food consumption	Rabbit	13 days (GD 6-18)	Oral	*500*	*mg/kg bw/day*	***Decrease***	RMS: Feed intake was decreased during the dosing period
35	Systemic toxicity	Food consumption	Rabbit	13 days (GD 6-18)	Oral	500	mg/kg bw/day	**Decrease**	
36	Systemic toxicity	Food consumption	Mouse	28 days	Oral	> 5000	ppm	No effect	

46	Systemic toxicity	Food consumption	Rabbit	13 days (GD 7-19)	Oral	150	mg/kg bw/day	**Decrease**	Food consumption was decreased throughout the treatment period.
47	Systemic toxicity	Food consumption	Rabbit	13 days(GD 7-19)	Oral	100	mg/kg bw/day	**Decrease**	A marked reduction was observed in the high dose group and slight or transient reductions in the low and mid-dose group.
48	Systemic toxicity	Food consumption	Rabbit	7 days (high dose) -13 (mid and low dose)	Oral	*450*	mg/kg bw/day	**Decrease**	RMS: food consumption was reduced by 6-17% throughout the treatment period.
49	Systemic toxicity	Food consumption	Rat	28 days	Oral	>20000	ppm	No effect	
50	Systemic toxicity	Food consumption	Rat	28 days	Oral	>2500	mg/kg bw/day	No effect	
51	Systemic toxicity	Food consumption	Dog	Study part A: 21 days Study Part B: 14 days	Oral	>1000	mg/kg bw/day	No effect	
52	Systemic toxicity	Food consumption	Rat	90 days	Oral	>1000	mg/kg bw/day	No effect	
53	Systemic toxicity	Food consumption	Rat	90 days	Oral	>20000	ppm	No effect	
~~*54*~~	~~*Systemic toxicity*~~	~~*Food consumption*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~	
55	Systemic toxicity	Food consumption	Rat	90 days	Oral	>20000	ppm	No effect	
56	Systemic toxicity	Food consumption	Mouse	90 days	Oral	>4500	mg/kg bw/day	No effect	
57	Systemic toxicity	Food consumption	Dog	6 months	Oral	>300	mg/kg bw/day	No effect	
58	Systemic toxicity	Food consumption	Dog	1 year	Oral	>500	mg/kg bw/day	No effect	
59	Systemic toxicity	Food consumption	Dog	1 year	Oral	>1000	mg/kg bw/day	No effect	
60	Systemic toxicity	Food consumption	Rat	21 days	Dermal	1000	mg/kg bw/day	No effect	
61	Systemic toxicity	Food consumption	Rat	21 days	Dermal	>1000	mg/kg bw/day	No effect	
62	Systemic toxicity	Food consumption	Rabbit	21 days	Dermal	>5000	mg/kg bw/day	No effect	

63	Systemic toxicity	Food consumption	Rabbit	28 days	Dermal	>2000	mg/kg bw/day	No effect	
64	Systemic toxicity	Food consumption	Rat	10 days (GD 6-15)	Oral	3500	mg/kg bw/day	**Change**	Food: 3500 mg/kg: Food consumption was decreased throughout the treatment period, thereafter, food intake was comparable with controls to termination. At lower dosages, food consumption was comparable with controls throughout. Water: 3500 mg/kg: Water consumption was increased following the start of treatment and continued to increase throughout the remainder of the treatment period. Thereafter, intake decreased, but was still slightly greater than controls at termination. At lower dosages, the pattern of water consumption did not indicate any clear effects, although at 1000 mg/kg/day, there was a suggestion of increased intake from Days 14 - 15 to termination, although at this stage no clear association with treatment can be made.
65	Systemic toxicity	Food consumption	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect	
67	Systemic toxicity	Food consumption	Mouse	2 years	Oral	> 1000	mg/kg bw/day	No effect	
68	Systemic toxicity	Food consumption	Mouse	2 years	Oral	> 30000	ppm	No effect	
69	Systemic toxicity	Food consumption	Rat	5.5 weeks (GD 3 till 21 days post partum)	Oral	>30000	ppm	No effect	

69	Systemic toxicity	Food consumption	Rat	3 weeks (PND 21-42)	Oral	30000	ppm	**Decrease**	Food consumption at 30000 ppm was lower than controls during Weeks 5 and 6 (males only). There were no other effects considered attributable to treatment for males or females at any dosage. The food conversion ratio for males at 30000 ppm was slightly greater when compared to controls (Week 6 only), indicating a slightly lower efficiency of food utilisatian into bodyweight gain. There were no other effects on food conversion ratios.
~~*70*~~	~~*Systemic toxicity*~~	~~*Food consumption*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	
71	Systemic toxicity	Food consumption	Rat	28 days	Oral	>50000	ppm	No effect	
72	Systemic toxicity	Food consumption	Mouse	28 days	Oral	*>800*	mg/kg bw/day	No effect	
73	Systemic toxicity	Food consumption	Mouse	90 days	Oral	>50000	ppm	**Increase**	Incidents of statistically significant increased food consumption in M at 5000; 10000; 50000 ppm and in F at 5000; 50000 ppm.
~~*74*~~	~~*Systemic toxicity*~~	~~*Food consumption*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*Food consumption of F0 adults was not affected.*~~
~~*74*~~	~~*Systemic toxicity*~~	~~*Food consumption*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*Food consumption of F1 adults was not affected.*~~
~~*74*~~	~~*Systemic toxicity*~~	~~*Food consumption*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*Food consumption of F2 adults was not affected.*~~
~~*75*~~	~~*Systemic toxicity*~~	~~*Food consumption*~~	~~*Rat*~~	~~*Males: 60 days prior to mating; females: 14*~~	~~*Oral*~~	~~*>10*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	

				~~*days prior to mating until end of lactation (PND 21) or until sacrifice GD 13*~~							
76	Systemic toxicity	Food consumption	Rat	90-92 days	Oral	7500	ppm	**Decrease**	Indication for slight decrease in males and females at 7500 ppm		
78	Systemic toxicity	Food consumption	Rat	90 days	Oral	>50000	ppm	No effect			
79	Systemic toxicity	Food consumption	Mouse	90 days	Oral	>50000	ppm	No effect			
80	Systemic toxicity	Food consumption	Rat	5 weeks		>500	mg/kg bw/day	No effect			
92	Systemic toxicity	Food consumption	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect			
92	Systemic toxicity	Food consumption	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6 and 13 weeks cohorts, respectively	Oral	>1.75	mg/kg bw/day	No effect			
95	Systemic toxicity	Food consumption	Mouse	Dams were exposed during gestation. Offspring samples were collected on GD 19, PND 7, and PND 21	Oral	5000	mg/L water	No effect			
96	*Systemic toxicity*	*Food consumption*	*Rat*	*90 days*	*Oral*	*>7500*	*ppm*	*No effect*			

1	Systemic toxicity	Mortality	Rat	90 days	Oral	>20000	ppm	No effect		Mortalities were observed in some studies in rat and rabbit at high doses. RMS: It is noted that RMS removed the results from one study (ID 70), as RMS considered this study to be unacceptable. RMS has added results from an additional study (ID 96). Furthermore, it is noted that increased mortality was also observed in one long-term study with mice (study ID 19).	
2	Systemic toxicity	Mortality	Rat	90 days	Oral	>50000	ppm	No effect			
3	Systemic toxicity	Mortality	Rat	90 days	Oral	>30000	ppm	No effect			
4	Systemic toxicity	Mortality	Mouse	90 days	Oral	>50000	ppm	No effect			
5	Systemic toxicity	Mortality	Dog	90 days	Oral	1000	mg/kg bw/day	**Change**	Each 1/4 males and 1/4 females were sacrificed for human reasons on Days 61 and 72, associated with clinical signs and histopathological findings.		
6	Systemic toxicity	Mortality	Dog	90 days	Oral	>10000	ppm	No effect			
7	Systemic toxicity	Mortality	Dog	90 days	Oral	>40000	ppm	No effect			
8	Systemic toxicity	Mortality	Dog	90 days	Oral	>50000	ppm	No effect			
9	Systemic toxicity	Mortality	Dog	1 year	Oral	>500	mg/kg bw/day	No effect			
10	Systemic toxicity	Mortality	Dog	1 year	Oral	>50000	ppm	No effect			
11	Systemic toxicity	Mortality	Dog	1 year	Oral	>30000	ppm	No effect			
12	Systemic toxicity	Mortality	Rat	1 year	Oral	>20000	ppm	No effect			
13	Systemic toxicity	Mortality	Rat	2 years	Oral	>10000	ppm	No effect			
14	Systemic toxicity	Mortality	Rat	2 years	Oral	>30000	ppm	No effect			

15	Systemic toxicity	Mortality	Rat	2 years	Oral	20000	ppm	**Increase**	**Statistically increased in males at 20000 ppm, attributed to the overall decreased severity of glomerula nephropathy occuring as a consequence of lower food consumption and body weight gain in this group; no effect in females**		
16	Systemic toxicity	Mortality	Rat	2 years	Oral	>1000	mg/kg bw/day	No effect			
17	Systemic toxicity	Mortality	Rat	2 years	Oral	>20000	ppm	No effect			
18	Systemic toxicity	Mortality	Rat	2 years	Oral	>15000	ppm	No effect			
19	Systemic toxicity	Mortality	Mouse	18 months	Oral	10000	ppm	**Increase**	Increased mortality at 10000 ppm (survival was 56, 60, 56 and 46% in males and 62, 64, 58 and 53% in females at 0, 100, 1000 and 10000 ppm); mortality rates at study termination were 44, 40, 44 and 54% at 0, 100, 1000 and 10000 ppm, life expectancy was not affected in any treated group		
20	Systemic toxicity	Mortality	Mouse	18 months	Oral	>5000	ppm	No effect			
21	Systemic toxicity	Mortality	Mouse	18 months	Oral	>40000	ppm	No effect			
22	Systemic toxicity	Mortality	Rat	10 weeks	Oral	>15000	ppm	No effect			
23	Systemic toxicity	Mortality	Rat	10 weeks (pre-mating)	Oral	>10000	ppm	No effect			
24	Systemic toxicity	Mortality	Rat	10 weeks for pre-mating rearing 8 weeks for subsequent breeding	Oral	>30000	ppm	No effect			

25	Systemic toxicity	Mortality	Rat	10 weeks for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Oral	>10000	ppm	No effect			
26	Systemic toxicity	Mortality	Rat	10 weeks prior to mating, continued until termination	Oral	>10000	ppm	No effect			
27	Systemic toxicity	Mortality	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000	ppm	No effect			
27	Systemic toxicity	Mortality	Rat	11 weeks prior to mating for F0, further generations for approx. 14 weeks until termination	Oral	>30000	ppm	No effect			
28	Systemic toxicity	Mortality	Rat	10 days (GD 7-16)	Oral	>1000	mg/kg bw/day	No effect			
29	Systemic toxicity	Mortality	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect			
30	Systemic toxicity	Mortality	Rabbit	13 days (GD 6-18)	Oral	300	mg/kg bw/day	**Increase**	1/18 females died at 300 mg/kg bw/day, histopathology revealed pale color in the liver and ascites in the abdomnial cavity, treatment relation could not be entirely denied (not treatment-related findings: 1/18 females at 10 mg/kg bw/day		

									died, necropsy revealed no abnormalities)		
31	Systemic toxicity	Mortality	Rabbit	13 days (GD 7-19)	Oral	400	mg/kg bw/day	**Increase**	Intercurrent deaths in 2/18 females at 400 mg/kg bw/day (one died on gestation day 19, one was sacrificed in extremis on day 20, histopathological findings of the stomach and intestine in the animal found dead, treatment-related (further mortalities, not treatment-related: each 1/18 females at 0 and 200 mg/kg bw/day, mal-dosing)		
32	Systemic toxicity	Mortality	Rabbit	13 days (GD 8-20)	Oral	> 300	mg/kg bw/day	No effect			
33	Systemic toxicity	Mortality	Rabbit	22 days (GD 6-27)	Oral	350	mg/kg bw/day	**Increase**	11/16 animals died in the high dose group; 2/16, 1/16 and 3/16 animals died in the control, 75 and 175 mg/kg bw/day group, respectively. Reasons for mortality were: pneumonia, gastroenteritis, enteritis, respiratory disease, gastroenteritis and caecal ulcerations		
34	Systemic toxicity	Mortality	Rabbit	13 days (GD 6-18)	Oral	*100*	mg/kg bw/day	**Increase**	4/16 and 8/15 animals died in the 100 and 500 mg/kg bw/day group, respectively.		
36	Systemic toxicity	Mortality	Mouse	28 days	Oral	> 5000	ppm	No effect			
42	Systemic toxicity	Mortality	Rat	3 days	Oral	> 1000	mg/kg bw/day	No effect			
43	Systemic toxicity	Mortality	Rat	10 days	Oral	> 1000	mg/kg bw/day	No effect			
44	Systemic toxicity	Mortality	Rat	21 days (PND 22-42)	Oral	> 1000	mg/kg bw/day	No effect			
45	Systemic toxicity	Mortality	Rat	31 days (PND 23-53)	Oral	1000	mg/kg bw/day	**Increase**	One male in the 1000 mg/kg/day group was found dead prior to dose administration on PND 24.		

46	Systemic toxicity	Mortality	Rabbit	13 days (GD 7-19)	Oral	450	mg/kg bw/day	**Increase**	1/20 animals of the high dose group died after abortion: gastro-intestinal disturbances; heart and kidneys pale; a few haemorrhagic depressions in the stomach (concurrent severe reduction in food intake; body weight loss)		
47	Systemic toxicity	Mortality	Rabbit	13 days (GD 7-19)	Oral	625	mg/kg bw/day	**Increase**	2/6 animals died in the high dose group (following marked body weight loss, inappetence, complete litter loss).		
49	Systemic toxicity	Mortality	Rat	28 day	Oral	>20000	ppm	No effect			
50	Systemic toxicity	Mortality	Rat	28 days	Oral	>2500	mg/kg bw/day	No effect			
51	Systemic toxicity	Mortality	Dog	Study part A: 21 days Study Part B: 14 days	Oral	>1000	mg/kg bw/day	No effect			
52	Systemic toxicity	Mortality	Rat	90 days	Oral	>1000	mg/kg bw/day	No effect			
53	Systemic toxicity	Mortality	Rat	90 days	Oral	>20000	ppm	No effect			
~~*54*~~	~~*Systemic toxicity*~~	~~*Mortality*~~	~~*Rat*~~	~~*90 days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~			
55	Systemic toxicity	Mortality	Rat	90 days	Oral	>20000	ppm	No effect			
56	Systemic toxicity	Mortality	Mouse	90 days	Oral	>4500	mg/kg bw/day	No effect			
57	Systemic toxicity	Mortality	Dog	6 months	Oral	>300	mg/kg bw/day	No effect			
58	Systemic toxicity	Mortality	Dog	1 year	Oral	>500	mg/kg bw/day	No effect			
59	Systemic toxicity	Mortality	Dog	1 year	Oral	>1000	mg/kg bw/day	No effect			
60	Systemic toxicity	Mortality	Rat	21 days	Dermal	>1000	mg/kg bw/day	No effect			
61	Systemic toxicity	Mortality	Rat	21 days	Dermal	>1000	mg/kg bw/day	No effect			
62	Systemic toxicity	Mortality	Rabbit	21 days	Dermal	>5000	mg/kg bw/day	No effect			

63	Systemic toxicity	Mortality	Rabbit	28 days	Dermal	>2000	mg/kg bw/day	No effect			
64	Systemic toxicity	Mortality	Rat	10 days (GD 6-15)	Oral	3500	mg/kg bw/day	**Increase**	One female was sacrificed on GD10 immediately after dosing following a probable intubation error (white fluid was found in the thoracic cavity). A further two females were sacrificed on GD7 and GD13 respectively following signs of respiratory distress (noisy respiration/gasping). Post mortem observation did not reveal the cause of distress but the marked signs were a continuation of the signs representative for this group and these two deaths are considered to be related to treatment. There were no further deaths.		
65	Systemic toxicity	Mortality	Rat	10 days (GD 6-15)	Oral	>1000	mg/kg bw/day	No effect			
66	Systemic toxicity	Mortality	Rabbit	22 days (GD 6-27)	Oral	*175*	mg/kg bw/day	**Increase**	Two rabbits in the control group aborted and were sacrificed (GD 22). One rabbit in the 75 mg/kg/day dosage group died on gestation day 26. In the 175 mg/kg/day dosage group, one rabbit aborted and was sacrificed on gestation day 27 and two rabbits died, one each on gestation days 22 and 25. One rabbit in the 350 mg/kg/day dosage group aborted and was sacrificed on gestation day 23 and 10 died by gestation day 21. One rabbit in this group died on gestation day 3. On the same day, a replacement female was selected and artificially inseminated.		
67	Systemic toxicity	Mortality	Mouse	2 years	Oral	> 1000	mg/kg bw/day	No effect			
68	Systemic toxicity	Mortality	Mouse	2 years	Oral	> 30000	ppm	No effect			

69	Systemic toxicity	Mortality	Rat	5.5 weeks (GD 3 till 21 days post partum)	Oral	>30000	ppm	No effect	There were two mortalities. One at 3000 ppm was sacrificed Day 22 of pregnancy due to poor condition. Post mortem examination did not reveal any reason for the apparent dystocia. Since no similar mortalities were seen at higher levels, this death is not considered to be attributed to treatment. A second animal at 30000 ppm was found dead Day 21 post partum (Day 43 of study). Post mortem examination or signs prior to sacrifice did not reveal the cause of death; it is difficult to relate this death to treatment or not.
69	Systemic toxicity	Mortality	Rat	3 weeks (PND 21-42)	Oral	>30000	ppm	No effect	
~~*70*~~	~~*Systemic toxicity*~~	~~*Mortality*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	
71	Systemic toxicity	Mortality	Rat	28 days	Oral	>50000	ppm	No effect	
72	Systemic toxicity	Mortality	Mouse	28 days	Oral	*>800*	mg/kg bw/day	No effect	
73	Systemic toxicity	Mortality	Mouse	90 days	Oral	>50000	ppm	No effect	
76	Systemic toxicity	Mortality	Rat	90-92 days	Oral	>7500	ppm	No effect	
77	Systemic toxicity	Mortality	Rabbit	22 days (GD 6-27)	Oral	500	mg/kg bw/day	**Increase**	4/5 at 500 mg/kg bw died between GD 15 and 22; 5/5 at 1250 mg/kg bw died on GD 10 and 11; 5/5 at 2500 mg/kg bw die on GD 9 and 10
78	Systemic toxicity	Mortality	Rat	90 days	Oral	>50000	ppm	No effect	
79	Systemic toxicity	Mortality	Mouse	90 days	Oral	>50000	ppm	No effect	
92	Systemic toxicity	Mortality	Rat	F0 from GD 6 and offspring up to PND 73±2 and PND 125±2 for the 6	Oral	>1.75	mg/kg bw/day	No effect	

				and 13 weeks cohorts, respectively							
96	*Systemic toxicity*	*Mortality*	*Rat*	*90 days*	*Oral*	*>7500*	*ppm*	*No effect*			

Target organ toxicity:

Study ID Matrix	Effect classification	Effect target	Species	Duration of exposure	Duration unit	Route of administration	Lowest Effect dose	Dose unit	Effect direction	Observed effect (positive and negative)	Assessment of each line of evidence	Assessment on the integrated line of evidence	Modality
5	Target organ toxicity	Bone histopathology	Dog	90	Days	Oral	1000	mg/kg bw/day	**Change**	Sternum: increased number of adipocytes in 2/3 males and 3/3 females at 1000 mg/kg bw/day.	Consistent effects on bone and bone marrow histopathology were not observed in three species up to a chronic exposure period. RMS: Agreed RMS: It is noted that RMS removed the result from one study (ID 70) as RMS considered this study to be unacceptable.	Not applicable.	
14	Target organ toxicity	Bone histopathology	Rat	2	Years	Oral	>30000	ppm	No effect				
18	Target organ toxicity	Bone histopathology	Rat	2	Years	Oral	>15000	ppm	No effect				

19	Target organ toxicity	Bone histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect			
20	Target organ toxicity	Bone histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
67	Target organ toxicity	Bone histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect			
68	Target organ toxicity	Bone histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect			
78	Target organ toxicity	Bone histopathology	Rat	90	Days	Oral	>50000	ppm	No effect			
79	Target organ toxicity	Bone histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect	Femur and epiphysis was examined.		
18	Target organ toxicity	Bone marrow histopathology	Rat	2	Years	Oral	15000	ppm	**Change**	Histopathology, non-neoplastic: increased incidence of severe adipose infiltration in males at 15000 ppm at terminal kill, which were attributed to myeloid hyperplasia, no abnormalities in high dose females (not treatment-related: increased incidence of severe adipose infiltration in premature dead animals at 1500 and 5000 ppm) histopathology, neoplastic: myeloid hyperplasia was noted in a few rats of either		

										sex, no dose relation, no treatment relation, no primary neoplastic lesions were seen		
20	Target organ toxicity	Bone marrow histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
21	Target organ toxicity	Bone marrow histopathology	Mouse	18	Months	Oral	>40000	ppm	No effect			
55	Target organ toxicity	Bone marrow histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	Histopathology was performed for control and high dose group animals including bone and bone marrow.		
68	Target organ toxicity	Bone marrow histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect	Bone marrow histopathology was performed of the costochondral junction.		

~~*70*~~	~~*Target organ toxicity*~~	~~*Bone marrow histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Bone marrow histopathology*~~	~~*Rat*~~	~~*21 (PND0 21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
73	Target organ toxicity	Bone marrow histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect			
78	Target organ toxicity	Bone marrow histopathology	Rat	90	Days	Oral	>50000	ppm	No effect			
79	Target organ toxicity	Bone marrow histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect			
13	Target organ toxicity	Eyes histopathology	Rat	2	Years	Oral	*10000*	ppm	*Change*	No relevant treatment-related histopathological changes were observed. (Interim kill: no abnormal findings; terminal kill: cateract in 4/44, 4/46, 6/51 and 10/50 and corneal opacity in 4/44, 2/46, 5/51 and 3/50 rats at 0, 100, 1000 and 10000 ppm, not treatment-related) RMS: An increase in cataract was seen in males of the high dose group of 10000 ppm (all animals: 6, 8, 4 and 14% with increasing doses).	No effects on the histopathology of eyes were observed in rat and mouse up to a chronic exposure period. RMS: In one 2-year rat study (ID 13), RMS considered the finding of cataract in male rats to be adverse. No effects on eyes were seen in any of the other studies. It is noted that RMS removed the results for two studies (ID 70, 74),	

18	Target organ toxicity	Eyes histopathology	Rat	2	Years	Oral	>15000	ppm	No effect		as RMS considered these studies to be unacceptable.	
20	Target organ toxicity	Eyes histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
21	Target organ toxicity	Eyes histopathology	Mouse	18	Months	Oral	>40000	ppm	No effect			
49	Target organ toxicity	Eyes histopathology	Rat	28	Days	Oral	>20000	ppm	No effect			
68	Target organ toxicity	Eyes histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect	Eyes were examined including the optic nerve and contiguous Harderian glands.		
~~*70*~~	~~*Target organ toxicity*~~	~~*Eyes histopathology*~~	~~*Rat*~~	~~*life time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Eyes histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			

~~74~~	~~Target organ toxicity~~	~~Eyes histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Weeks~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effects in F1 observed.~~		
~~74~~	~~Target organ toxicity~~	~~Eyes histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Weeks~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effects in F2 observed.~~		
78	Target organ toxicity	Eyes histopathology	Rat	90	Days	Oral	>50000	ppm	No effect			
79	Target organ toxicity	Eyes histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect			
20	Target organ toxicity	Aorta histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect		Organ specific toxicity of glyphosate was not observed for aorta and heart in three species up to a chronic exposure period. Weight changes observed in some studies are attributed to effects on body weight. This conclusion is substantiated by the absence of histopathological changes. RMS: agreed It is noted that RMS removed the results for two studies (ID 70, 74), as RMS considered these studies to be unacceptable.	
68	Target organ toxicity	Aorta histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect			
~~70~~	~~Target organ toxicity~~	~~Aorta histopathology~~	~~Rat~~	~~life time, all three generations~~	~~Weeks~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~			
~~74~~	~~Target organ toxicity~~	~~Aorta histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Weeks~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effects in F1 observed.~~		
~~74~~	~~Target organ toxicity~~	~~Aorta histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Weeks~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effects in F2 observed.~~		
13	Target organ toxicity	Heart histopathology	Rat	2	Years	Oral	>10000	ppm	No effect			

14	Target organ toxicity	Heart histopathology	Rat	2	Years	Oral	>30000	ppm	No effect		
18	Target organ toxicity	Heart histopathology	Rat	2	Years	Oral	>15000	ppm	No effect		
19	Target organ toxicity	Heart histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect		
20	Target organ toxicity	Heart histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect		
49	Target organ toxicity	Heart histopathology	Rat	28	Days	Oral	>20000	ppm	No effect		
50	Target organ toxicity	Heart histopathology	Rat	28	Days	Oral	>2500	mg/kg bw/day	No effect		
52	Target organ toxicity	Heart histopathology	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect		
53	Target organ toxicity	Heart histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	Heart and aorta were subject to histopathology.	
55	Target organ toxicity	Heart histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	Heart and aorta were subject to histopathology.	
57	Target organ toxicity	Heart histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect	Heart and aorta were subject to histopathology.	
58	Target organ toxicity	Heart histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect	Heart and aorta were subject to histopathology.	

59	Target organ toxicity	Heart histopathology	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect	Heart and aorta were subject to histopathology.		
67	Target organ toxicity	Heart histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	Heart and aorta were subject to histopathology.		
68	Target organ toxicity	Heart histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect			
~~*70*~~	~~*Target organ toxicity*~~	~~*Heart histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Heart histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*74*~~	~~*Target organ toxicity*~~	~~*Heart histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F1 observed.*~~		
~~*74*~~	~~*Target organ toxicity*~~	~~*Heart histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F2 observed.*~~		
1	Target organ toxicity	Heart weight	Rat	90	Days	Oral	20000	ppm	**Decrease**	Absolute weight in males was reduced at 20000 ppm which was attributed to reduced body weight (-8%) at this dose.		
2	Target organ toxicity	Heart weight	Rat	90	Days	Oral	*>50000*	ppm	*No effect*	~~Absolute weight was reduced in both sexes and relative weight was increased in males at 50000 ppm. This effect was attributed to reduced body weight and thus, not considered toxicologically relevant or organ specific.~~		

16	Target organ toxicity	Heart weight	Rat	2	Years	Oral	>1000	mg/kg bw/day	No effect			
51	Target organ toxicity	Heart weight	Dog	Study part A: 21 Study Part B: 14	Days	Oral	>1000	mg/kg bw/day	No effect			
52	Target organ toxicity	Heart weight	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect			
56	Target organ toxicity	Heart weight	Mouse	90	Days	Oral	>4500	mg/kg bw/day	No effect			
57	Target organ toxicity	Heart weight	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect			
58	Target organ toxicity	Heart weight	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect			
59	Target organ toxicity	Heart weight	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect			
67	Target organ toxicity	Heart weight	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect			
68	Target organ toxicity	Heart weight	Mouse	2	Years	Oral	> 30000	ppm	No effect			
~~70~~	~~Target organ toxicity~~	~~Heart weight~~	~~Rat~~	~~21 (PND0-21, exposure through milk)~~	~~Days~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~			
~~70~~	~~Target organ toxicity~~	~~Heart weight~~	~~Rat~~	~~life-time, all three generations~~	~~Weeks~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~			
73	Target organ toxicity	Heart weight	Mouse	90	Days	Oral	>50000	ppm	No effect			
78	Target organ toxicity	Heart weight	Rat	90	Days	Oral	>50000	ppm	No effect			
79	Target organ toxicity	Heart weight	Mouse	90	Days	Oral	12500	ppm	**Increase**	Relative organ weight was increased in males (M at 12500 ppm; 25000 ppm;		

										50000 ppm; F no treatment-related effects), which was attributed to decreased body weight.		
1	Target organ toxicity	Kidney histopathology	Rat	90	Days	Oral	>20000	ppm	No effect		Organ specific toxicity of glyphosate was not observed in kidney in four species up to a chronic exposure period. Histopathological changes such as renal necrosis and mineralisation were observed in isolated rat studies. However, these changes were not consistent within rat or in mouse, dog and rabbit. RMS: It is noted that RMS removed the results from two studies (ID 70, 74), as RMS considered these studies to be unacceptable. RMS has added results from an additional study (ID 96).	
2	Target organ toxicity	Kidney histopathology	Rat	90	Days	Oral	>50000	ppm	No effect			
3	Target organ toxicity	Kidney histopathology	Rat	90	Days	Oral	>30000	ppm	No effect			
4	Target organ toxicity	Kidney histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect			
5	Target organ toxicity	Kidney histopathology	Dog	90	Days	Oral	>1000	mg/kg bw/day	No effect			
6	Target organ toxicity	Kidney histopathology	Dog	90	Days	Oral	>10000	ppm	No effect			
7	Target organ toxicity	Kidney histopathology	Dog	90	Days	Oral	>40000	ppm	No effect			
8	Target organ toxicity	Kidney histopathology	Dog	90	Days	Oral	>50000	ppm	No effect			
9	Target organ toxicity	Kidney histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect			
10	Target organ toxicity	Kidney histopathology	Dog	1	Year	Oral	>50000	ppm	No effect			
11	Target organ toxicity	Kidney histopathology	Dog	1	Year	Oral	>30000	ppm	No effect			
12	Target organ toxicity	Kidney histopathology	Rat	1	Year	Oral	>20000	ppm	No effect			

13	Target organ toxicity	Kidney histopathology	Rat	2	Years	Oral	>10000	ppm	No effect			
14	Target organ toxicity	Kidney histopathology	Rat	2	Years	Oral	>30000	ppm	No effect			
15	Target organ toxicity	Kidney histopathology	Rat	2	Years	Oral	6000	ppm	**Change**	Gross necropsy: Enlarged organ in males at 6000 ppm and 20000 ppm Histopathology, non-neoplastic: Papillary necrosis with varying degrees of mineralisation of the papilla and/or transitional cell hyperplasia in both sexes but particularly in males at 20000 ppm, papillary haemorrhage in 2 males and 2 females at 20000 ppm, hydronephrosis in males at ≥ 6000 ppm, within historical control data) Histopathology, neoplastic findings: no treatment-related findings		
16	Target organ toxicity	Kidney histopathology	Rat	2	Years	Oral	>1000	mg/kg bw/day	No effect			
17	Target organ toxicity	Kidney histopathology	Rat	2	Years	Oral	>20000	ppm	No effect			

18	Target organ toxicity	Kidney histopathology	Rat	2	Years	Oral	15000	ppm	**Change**	Histopathology, non-neoplastic: Renal mineralisation, reduced pelvic mineralisation and increased corticomedullary mineralisation in premature death and terminal kill females at 15000 ppm, reduced incidences of hyperplasia in the renal pelvic/papillary epithelium in females at 15000 ppm, reduced pelvic mineralisation in males at 15000 ppm, treatment-related (not treatment-related findings: progressive glomerulonephropathy in rats of both sexes with greater prevalence in males, age-related, pyelitis in males at 5000 ppm, tubular necrosis in premature dead control females, renal tubular hyperplasia in 1/51 females at 1500 ppm and in 1/51 males and 1/51 females at 15000 ppm, occasional findings without dose relation included papillary necrosis, pyeliti, hydronephrosis, cortical cyst formation, tubular dilatation, generalised tubular basophilia, tubular mineralisation, cortical scarring, hypertrophy of the collecting duct epithelium, congestion)		

										histopathology, neoplastic findings: no treatment-related findings (renal tumors (lipoma, tubular carcinoma, clear cell carcinoma) in 1/51 and 1/51 males at 0 and 15000 ppm and in 1/51 females at 5000 ppm)		
19	Target organ toxicity	Kidney histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect			
20	Target organ toxicity	Kidney histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
21	Target organ toxicity	Kidney histopathology	Mouse	18	Months	Oral	>40000	ppm	No effect			
22	Target organ toxicity	Kidney histopathology	Rat	10	Weeks	Oral	>15000	ppm	No effect			
23	Target organ toxicity	Kidney histopathology	Rat	10 (pre-mating)	Weeks	Oral	>10000	ppm	No effect			
24	Target organ toxicity	Kidney histopathology	Rat	10 for pre-mating rearing 8 for subsequent breeding	Weeks	Oral	>30000	ppm	No effect			

25	Target organ toxicity	Kidney histopathology	Rat	10 for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Weeks	Oral	>10000	ppm	No effect			
27	Target organ toxicity	Kidney histopathology	Rat	11 prior to mating for F0, further generations for approx. 14 weeks until termination	Weeks	Oral	>30000	ppm	No effect			
44	Target organ toxicity	Kidney histopathology	Rat	21 (PND 22-42)	Days	Oral	> 1000	mg/kg bw/day	No effect			
45	Target organ toxicity	Kidney histopathology	Rat	31 (PND 23-53)	Days	Oral	> 1000	mg/kg bw/day	No effect			
49	Target organ toxicity	Kidney histopathology	Rat	28	Days	Oral	>20000	ppm	No effect			
50	Target organ toxicity	Kidney histopathology	Rat	28	Days	Oral	250	mg/kg bw/day	**Change**	Nephrocalcinosis (mineral deposition) in 2/5, 2/5 and 4/5 females was observed at 250, 1000 and 2500 mg/kg bw/day.		
52	Target organ toxicity	Kidney histopathology	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect			
53	Target organ toxicity	Kidney histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	Urinary bladder histopathology was performed as well.		

~~*54*~~	~~*Target organ toxicity*~~	~~*Kidney histopathology*~~	~~*Rat*~~	~~*90*~~	~~*Days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~		
55	Target organ toxicity	Kidney histopathology	Rat	90	Days	Oral	>20000	ppm	No effect		
56	Target organ toxicity	Kidney histopathology	Mouse	90	Days	Oral	>4500	mg/kg bw/day	No effect		
57	Target organ toxicity	Kidney histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect	Urinary bladder was examined as well.	
58	Target organ toxicity	Kidney histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect	Kidney, ureter and urinary bladder were examined.	
59	Target organ toxicity	Kidney histopathology	Dog	1	Years	Oral	>1000	mg/kg bw/day	No effect		
60	Target organ toxicity	Kidney histopathology	Rat	21	Days	Dermal	1000	mg/kg bw/day	No effect		
61	Target organ toxicity	Kidney histopathology	Rat	21	Days	Dermal	>1000	mg/kg bw/day	No effect		
62	Target organ toxicity	Kidney histopathology	Rabbit	21	Days	Dermal	>5000	mg/kg bw/day	No effect		
63	Target organ toxicity	Kidney histopathology	Rabbit	28	Days	Dermal	>2000	mg/kg bw/day	No effect		
67	Target organ toxicity	Kidney histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect		
68	Target organ toxicity	Kidney histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect		
~~*70*~~	~~*Target organ toxicity*~~	~~*Kidney histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~		
~~*70*~~	~~*Target organ toxicity*~~	~~*Kidney histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~		
71	Target organ toxicity	Kidney histopathology	Rat	28	Days	Oral	>50000	ppm	No effect		

73	Target organ toxicity	Kidney histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect			
~~*74*~~	~~*Target organ toxicity*~~	~~*Kidney histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F1 observed.*~~		
~~*74*~~	~~*Target organ toxicity*~~	~~*Kidney histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F2 observed.*~~		
76	Target organ toxicity	Kidney histopathology	Rat	90-92	Days	Oral	>7500	ppm	No effect	Kidney and urinary bladder were examined.		
96	*Target organ toxicity*	*Kidney histopathology*	*Rat*	*90*	*Days*	*Oral*	*>7500*	*ppm*	*No effect*			
1	Target organ toxicity	Kidney weight	Rat	90	Days	Oral	20000	ppm	No effect			
2	Target organ toxicity	Kidney weight	Rat	90	Days	Oral	50000	ppm	**Increase**			
3	Target organ toxicity	Kidney weight	Rat	90	Days	Oral	30000	ppm	No effect			
4	Target organ toxicity	Kidney weight	Mouse	90	Days	Oral	>50000	ppm	No effect			
5	Target organ toxicity	Kidney weight	Dog	90	Days	Oral	>1000	mg/kg bw/day	No effect			
6	Target organ toxicity	Kidney weight	Dog	90	Days	Oral	>10000	ppm	No effect			
7	Target organ toxicity	Kidney weight	Dog	90	Days	Oral	>40000	ppm	No effect			
8	Target organ toxicity	Kidney weight	Dog	90	Days	Oral	10000	ppm	**Increase**			
9	Target organ toxicity	Kidney weight	Dog	1	Years	Oral	>500	mg/kg bw/day	No effect			
10	Target organ toxicity	Kidney weight	Dog	1	Years	Oral	>50000	ppm	No effect			

11	Target organ toxicity	Kidney weight	Dog	1	Years	Oral	>30000	ppm	No effect			
12	Target organ toxicity	Kidney weight	Rat	1	Years	Oral	>20000	ppm	No effect			
13	Target organ toxicity	Kidney weight	Rat	24	Months	Oral	>10000	ppm	No effect			
14	Target organ toxicity	Kidney weight	Rat	24	Months	Oral	>30000	ppm	No effect			
15	Target organ toxicity	Kidney weight	Rat	2	Years	Oral	>20000	ppm	No effect			
16	Target organ toxicity	Kidney weight	Rat	2	Years	Oral	100	mg/kg bw/day	No effect			
17	Target organ toxicity	Kidney weight	Rat	24	Months	Oral	20000	ppm	No effect			
18	Target organ toxicity	Kidney weight	Rat	2	Years	Oral	>15000	ppm	No effect			
19	Target organ toxicity	Kidney weight	Mouse	18	Months	Oral	>10000	ppm	No effect			
20	Target organ toxicity	Kidney weight	Mouse	18	Months	Oral	>5000	ppm	No effect			
21	Target organ toxicity	Kidney weight	Mouse	18	Months	Oral	40000	ppm	**Increase**	Relative weight was statistically significantly increased in females at 40000 ppm. However, no relevant treatment-related histopathological changes were observed. And body weight reductions were also observed at this dose level.		
22	Target organ toxicity	Kidney weight	Rat	10	Weeks	Oral	*15000*	*ppm*	***Increase***	Abs.+rel. weight increased in F0 females at 15000 ppm, abs. weight increased in F1 females at 5000 ppm, no histopathological findings, considered to be adaptive in nature and		

										non-adverse, no effect in males RMS: the increased kidney weight in F0 females at 15000 ppm is considered adverse.		
23	Target organ toxicity	Kidney weight	Rat	10 (pre-mating)	Weeks	Oral	>10000	ppm	No effect			
24	Target organ toxicity	Kidney weight	Rat	10 for pre-mating rearing 8 for subsequent breeding	Weeks	Oral	30000	ppm	**Increase**	Relative organ weight was increased in F0+F1 males and females at 30000 ppm, where also reductions in body weight were observed for males.		
44	Target organ toxicity	Kidney weight	Rat	21 (PND 22-42)	Days	Oral	> 1000	mg/kg bw/day	No effect			
45	Target organ toxicity	Kidney weight	Rat	31 (PND 23-53)	Days	Oral	300	mg/kg bw/day	No effect			
49	Target organ toxicity	Kidney weight	Rat	28	Days	Oral	>20000	ppm	No effect			
50	Target organ toxicity	Kidney weight	Rat	28	Days	Oral	>2500	mg/kg bw/day	No effect			
51	Target organ toxicity	Kidney weight	Dog	Study part A: 21 Study Part B: 14	Days	Oral	>1000	mg/kg bw/day	No effect			
52	Target organ toxicity	Kidney weight	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect			
53	Target organ toxicity	Kidney weight	Rat	90	Days	Oral	>20000	ppm	No effect			
~~*54*~~	~~*Target organ toxicity*~~	~~*Kidney weight*~~	~~*Rat*~~	~~*90*~~	~~*Days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~			
55	Target organ toxicity	Kidney weight	Rat	90	Days	Oral	>20000	ppm	No effect			
56	Target organ toxicity	Kidney weight	Mouse	90	Days	Oral	>4500	mg/kg bw/day	No effect			
57	Target organ toxicity	Kidney weight	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect			

58	Target organ toxicity	Kidney weight	Dog	12	Months	Oral	>500	mg/kg bw/day	No effect			
59	Target organ toxicity	Kidney weight	Dog	1	Years	Oral	>1000	mg/kg bw/day	No effect			
60	Target organ toxicity	Kidney weight	Rat	21	Days	Dermal	>1000	mg/kg bw/day	No effect			
61	Target organ toxicity	Kidney weight	Rat	21	Days	Dermal	>1000	mg/kg bw/day	No effect			
62	Target organ toxicity	Kidney weight	Rabbit	21	Days	Dermal	>5000	mg/kg bw/day	**Increase**	A significant increase in mean relative organ weight was observed in females of the 5000 mg/kg bw/d group which was not considered toxicologically relevant since no histopathological effects were observed.		
63	Target organ toxicity	Kidney weight	Rabbit	28	Days	Dermal	>2000	mg/kg bw/day	No effect			
67	Target organ toxicity	Kidney weight	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect			
68	Target organ toxicity	Kidney weight	Mouse	2	Years	Oral	> 30000	ppm	No effect			
~~*70*~~	~~*Target organ toxicity*~~	~~*Kidney weight*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Kidney weight*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
73	Target organ toxicity	Kidney weight	Mouse	90	Days	Oral	>50000	ppm	**Increase**	Relative organ weight (relative to body weight) was increased (M 50000 ppm =+18.5%*) which was attributed to lower terminal body weight and thus not of toxicological relevance. No effects on		

									absolute as well as relative (to brain weight) organ weight were observed.		
76	Target organ toxicity	Kidney weight	Rat	90-92	Days	Oral	*>7500*	ppm	No effect	Absolute: F 7500 ppm=-8%*; F 5000 ppm=-11%*; F 2000 ppm=-13%* Relative: M 2000 ppm=+12%* ; F 2000 ppm=-9%* (not dose-dependent) RMS: considered there is no adverse effect on kidney weight	
78	Target organ toxicity	Kidney weight	Rat	90	Days	Oral	50000	ppm	**Increase**	Relative weight was increased in males at 25000 ppm and 50000 ppm, which is attributed to lower body weight at these doses.	
79	Target organ toxicity	Kidney weight	Mouse	90	Days	Oral	6250	ppm	**Increase**	Relative weight was increased in males at 6250 ppm, 12500 ppm, 25000 ppm, and 50000 ppm which is in line with reduced body weight from 25000 ppm.	
96	*Target organ toxicity*	*Kidney weight*	*Rat*	*90*	*Days*	*Oral*	*>7500*	*ppm*	*No effect*		
4	Target organ toxicity	Urinary bladder histopathology	Mouse	90	Days	Oral	50000	ppm	**Change**	Cystitis of the urinary bladder was observed in 4/12 males only at 50000 ppm (0/12 in the control group), which is a very high dose (> 6000 mg/kg bw/day), where also reduced body weight as well as pH reduction of urine were observed.	One study in mice showed cystitis developed in the urinary bladder. This effect was not reproduced in a second mouse study at the same dose level and exposure duration. Specific effects on the

11	Target organ toxicity	Urinary bladder histopathology	Dog	1	Years	Oral	>30000	ppm	No effect		urinary bladder were thus not observed in dog, mouse, and rat. RMS: It is noted that RMS removed the result from two studies (ID 70, 74) as RMS considered these studies to be unacceptable.	
13	Target organ toxicity	Urinary bladder histopathology	Rat	24	Months	Oral	>10000	ppm	No effect			
18	Target organ toxicity	Urinary bladder histopathology	Rat	2	Years	Oral	>15000	ppm	No effect			
20	Target organ toxicity	Urinary bladder histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
55	Target organ toxicity	Urinary bladder histopathology	Rat	90	Days	Oral	>20000	ppm	No effect			
59	Target organ toxicity	Urinary bladder histopathology	Dog	1	Years	Oral	>1000	mg/kg bw/day	No effect			
67	Target organ toxicity	Urinary bladder histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect			
68	Target organ toxicity	Urinary bladder histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect			
~~70~~	~~Target organ toxicity~~	~~Urinary bladder histopathology~~	~~Rat~~	~~life-time, all three generations~~	~~Weeks~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~			
~~70~~	~~Target organ toxicity~~	~~Urinary bladder histopathology~~	~~Rat~~	~~21 (PND0-21, exposure~~	~~Days~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~			

				~~through milk)~~							
73	Target organ toxicity	Urinary bladder histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect		
~~74~~	~~Target organ toxicity~~	~~Urinary bladder histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Weeks~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effects in F1 observed.~~	
~~74~~	~~Target organ toxicity~~	~~Urinary bladder histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Weeks~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effects in F2 observed.~~	
20	Target organ toxicity	Gall bladder histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect		No histopathological effects on the gall bladder were observed in mouse and rabbit. RMS: no comments
67	Target organ toxicity	Gall bladder histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect		
68	Target organ toxicity	Gall bladder histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect		
73	Target organ toxicity	Gall bladder histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect		
77	Target organ toxicity	Gall bladder histopathology	Rabbit	22 (GD 6-27)	Days	Oral	>2500	mg/kg bw/day	No effect		
79	Target organ toxicity	Gall bladder histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect		
1	Target organ toxicity	Liver histopathology	Rat	90	Days	Oral	>20000	ppm	No effect		Few studies report changes (increases and decreases) of liver weights (absolute and relative) in rat, dog and mouse within which no relevant histopathological changes were
2	Target organ toxicity	Liver histopathology	Rat	90	Days	Oral	>50000	ppm	No effect		
3	Target organ toxicity	Liver histopathology	Rat	90	Days	Oral	>30000	ppm	No effect		
4	Target organ toxicity	Liver histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect		

5	Target organ toxicity	Liver histopathology	Dog	90	Days	Oral	>1000	mg/kg bw/day	No effect		observed. One isolated published study (study ID 95) describes a disturbance of lipid metabolism. Specific effects on the liver were thus not observed in dog, mouse, and rat. RMS: It is noted that RMS removed the results from two studies (ID 70, 74), as RMS considered these studies to be unacceptable. RMS has added results from one additional study (ID 96).	
6	Target organ toxicity	Liver histopathology	Dog	90	Days	Oral	>10000	ppm	No effect			
7	Target organ toxicity	Liver histopathology	Dog	90	Days	Oral	>40000	ppm	No effect			
8	Target organ toxicity	Liver histopathology	Dog	90	Days	Oral	>50000	ppm	No effect			
9	Target organ toxicity	Liver histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect			
10	Target organ toxicity	Liver histopathology	Dog	1	Year	Oral	>50000	ppm	No effect			
11	Target organ toxicity	Liver histopathology	Dog	1	Year	Oral	>30000	ppm	No effect			
12	Target organ toxicity	Liver histopathology	Rat	1	Year	Oral	>20000	ppm	No effect			
13	Target organ toxicity	Liver histopathology	Rat	2	Years	Oral	>10000	ppm	No effect			
14	Target organ toxicity	Liver histopathology	Rat	2	Years	Oral	>30000	ppm	No effect			
15	Target organ toxicity	Liver histopathology	Rat	2	Years	Oral	6000	ppm	**Change**	Gross necropsy: increased masses in males at 20000 and/or 6000 ppm, treatment-related Histopathology, non-neoplastic findings: proliferative cholangitis and hepatitis in males at 20000 ppm at interim and terminal kill, treatment-related (not treatment-related: fatty vacuolisation in males at ≥ 6000 ppm, below historical control		

										levels) Histopathology, neoplastic findings: no treatment-related findings (hepatocellular adenoma in males at 20000 ppm, not statistically significant with Fisher'S Exact test but with Peto test, as no preneoplastic foci or adenocarcinomas were found and a dose-response was absent, findings were considered to be unrelated to treatment)
16	Target organ toxicity	Liver histopathology	Rat	2	Years	Oral	>1000	mg/kg bw/day	No effect	
17	Target organ toxicity	Liver histopathology	Rat	2	Years	Oral	*20000*	ppm	***Change***	RMS: Increase in liver adenoma in males only (8 at 20000 ppm versus 3 in control)
18	Target organ toxicity	Liver histopathology	Rat	2	Years	Oral	>15000	ppm	No effect	No relevant treatment-related histopathological changes were observed. (Non-neoplastic: no treatment-related findings (mononuclear cell foci frequently observed in both sexes but with a higher incidence in males at 1500 and 5000 ppm, highly variable finding in aging rats; lipid vacuolation, focal, diffuse or zonal distribution was frequently observed in either sex, no treatment relation/dose relation, statistically significant excess pigment in high dose females at terminal

										kill, considered not treatment-related due to low incidence and secondary nature of the condition; occasionally observed hepatic necrosis, focal/centrilobular distribution, subcaspular congestion/telangiecatsis, focal haemorrhage, cyst formation, congestion, bile duct proliferation, hyperplasia, dilatation or thickening, focal myelopoesis, malformation, thrombus formation, inflammatory cell infiltration, dilatation of sinusoids, basophilia or enlargement, periportal fibrosis, not treatment-related, foci/areas of altered hepatocytes as precursors of hepatic neoplasia in 0/51, 2/51, 6/51 and 2/51 males and in 32/51, 37/51, 33/51 and 36/51 females at 0, 1500, 5000 and 15000 ppm); neoplastic: no treatment-related findings (hepatocellular adenoma/carcinoma, cholangiocarcinoma in 1/51, 2/51, 1/51 and 1/51 males and 2/51, 0/51, 2/51 and 1/51 females at 0, 1500, 5000 and 15000 ppm))		

19	Target organ toxicity	Liver histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect	
20	Target organ toxicity	Liver histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect	
21	Target organ toxicity	Liver histopathology	Mouse	18	Months	Oral	>40000	ppm	No effect	
22	Target organ toxicity	Liver histopathology	Rat	10	Weeks	Oral	>15000	ppm	No effect	
23	Target organ toxicity	Liver histopathology	Rat	10 (pre-mating)	Weeks	Oral	>10000	ppm	No effect	
24	Target organ toxicity	Liver histopathology	Rat	10 for pre-mating rearing 8 for subsequent breeding	Weeks	Oral	>30000	ppm	No effect	
25	Target organ toxicity	Liver histopathology	Rat	10 for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Weeks	Oral	>10000	ppm	No effect	
26	Target organ toxicity	Liver histopathology	Rat	10 prior to mating, continued	Weeks	Oral	>10000	ppm	No effect	

				until termination						
49	Target organ toxicity	Liver histopathology	Rat	28	Days	Oral	>20000	ppm	No effect	
50	Target organ toxicity	Liver histopathology	Rat	28	Days	Oral	>2500	mg/kg bw/day	No effect	
52	Target organ toxicity	Liver histopathology	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect	
53	Target organ toxicity	Liver histopathology	Rat	90	Weeks	Oral	>20000	ppm	No effect	
~~*54*~~	~~*Target organ toxicity*~~	~~*Liver histopathology*~~	~~*Rat*~~	~~*90*~~	~~*Days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~	
55	Target organ toxicity	Liver histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	
56	Target organ toxicity	Liver histopathology	Mouse	90	Days	Oral	>4500	mg/kg bw/day	No effect	
57	Target organ toxicity	Liver histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect	
58	Target organ toxicity	Liver histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect	
59	Target organ toxicity	Liver histopathology	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect	
60	Target organ toxicity	Liver histopathology	Rat	21	Days	Dermal	1000	mg/kg bw/day	No effect	
61	Target organ toxicity	Liver histopathology	Rat	21	Days	Dermal	>1000	mg/kg bw/day	No effect	
62	Target organ toxicity	Liver histopathology	Rabbit	21	Days	Dermal	>5000	mg/kg bw/day	No effect	
63	Target organ toxicity	Liver histopathology	Rabbit	28	Days	Dermal	>2000	mg/kg bw/day	No effect	
65	Target organ toxicity	Liver histopathology	Rat	10 (GD 6-15)	Days	Oral	>1000	mg/kg bw/day	No effect	
67	Target organ toxicity	Liver histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	

68	Target organ toxicity	Liver histopathology	Mouse	2	Years	Oral	> 30000	ppm	**Change**	Centrilobular hepatocyte hypertrophy: 6%, 10%, 18% and 34% in control to high dose groups, respectively (no further neoplasms). This change may represent an adaptation to hepatocellular metabolism.
~~70~~	~~Target organ toxicity~~	~~Liver histopathology~~	~~Rat~~	~~life-time, all three generations~~	~~Weeks~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~	
~~70~~	~~Target organ toxicity~~	~~Liver histopathology~~	~~Rat~~	~~21 (PND0 21, exposure through milk)~~	~~Days~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~	
71	Target organ toxicity	Liver histopathology	Rat	28	Days	Oral	>50000	ppm	No effect	
73	Target organ toxicity	Liver histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect	
~~74~~	~~Target organ toxicity~~	~~Liver histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Weeks~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effects in F1 observed.~~
~~74~~	~~Target organ toxicity~~	~~Liver histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Weeks~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effects in F2 observed.~~
76	Target organ toxicity	Liver histopathology	Rat	90-92	Days	Oral	>7500	ppm	No effect	
95	Target organ toxicity	Liver histopathology	Mouse	Dams were exposed during gestation. Offspring samples	Days	Oral	5000	mg/L water	**Change**	Hepatic steatosis with excessive lipid droplet formation was observed.

				were collected on GD 19, PND 7, and PND 21						
96	*Target organ toxicity*	*Liver histopathology*	*Rat*	*90*	*Days*	*Oral*	*>7500*	*ppm*	*No effect*	
95	Target organ toxicity	Liver (fat metabolism)	Mouse	Dams were exposed during gestation. Offspring samples were collected on GD 19, PND 7, and PND 21	Days	Oral	5000	mg/L	**Change**	There were significant differences in the expression levels of the genes SREBP1C, SREBP2, Fasn, Hmgcr, Hmgcs and PPARa. The relative expression levels of the genes SREBP1C, SREBP2, Fasn, Acc, Scd, Hmgcr, Hmgcs1 and Hmgcs2 showed a significant increase in GD19 fetuses and PND7 and PND21 offspring. These genes are closely related to hepatic lipid production, so their elevation contributes to increased fat storage. However, this kind of increase does not match well to the trend in serum lipid content alteration. The levels of PPARa in PND7 males and PND21 females increased remarkably, which is likely due to the growing demand for lipid catabolism caused by the increased lipid content. (The expression levels of the genes SREBP1C (Sterol Regulatory Element

										Binding Protein 1C), SREBP2 (Sterol Regulatory Element Binding Protein 2), Fasn (Fatty acid synthase, which catalyzes fatty acid synthesis), Scd (Stearoyl-CoA Desaturase 1), Acc (Acetyl-CoACarboxylase), Hmgcr (3-hydroxy-3-methyl-glutaryl-CoA reductase), Hmgcs1 (3-hydroxy-3-methylglutaryl-CoA synthase 1), Hmgcs2 (3-hydroxy-3-methylglutaryl-CoA synthase 2) and PPARa (Peroxisome proliferator-activated receptor alpha) were determined. The relative expression levels of the above genes were normalized to b-actin expression.)
1	Target organ toxicity	Liver weight	Rat	90	Days	Oral	10000	ppm	**Decrease**	Absolute organ weight was reduced in males only at 1000 and 20000 ppm, no consistent trend, changes at 20000 ppm attributed to reduced body weight observed at this dose level.
2	Target organ toxicity	Liver weight	Rat	90	Days	Oral	*>50000*	*ppm*	*No effect*	~~Relative organ weight was increased in both sexes at 50000 ppm. However, histopathological changes were not observed.~~
3	Target organ toxicity	Liver weight	Rat	90	Days	Oral	>30000	ppm	No effect	
4	Target organ toxicity	Liver weight	Mouse	90	Days	Oral	>50000	ppm	No effect	

5	Target organ toxicity	Liver weight	Dog	90	Days	Oral	>1000	mg/kg bw/day	No effect	
6	Target organ toxicity	Liver weight	Dog	90	Days	Oral	>10000	ppm	No effect	
7	Target organ toxicity	Liver weight	Dog	90	Days	Oral	>40000	ppm	No effect	
8	Target organ toxicity	Liver weight	Dog	90	Days	Oral	10000	ppm	**Increase**	Absolute and relative organ weight was increased in males at ≥ 10000 ppm, but considered toxicologically not relevant due to the absence of histopathological findings
9	Target organ toxicity	Liver weight	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect	
10	Target organ toxicity	Liver weight	Dog	1	Year	Oral	>50000	ppm	No effect	
11	Target organ toxicity	Liver weight	Dog	1	Year	Oral	>30000	ppm	No effect	
12	Target organ toxicity	Liver weight	Rat	1	Year	Oral	>20000	ppm	No effect	
13	Target organ toxicity	Liver weight	Rat	2	Years	Oral	>10000	ppm	No effect	
14	Target organ toxicity	Liver weight	Rat	2	Years	Oral	>30000	ppm	No effect	
15	Target organ toxicity	Liver weight	Rat	2	Years	Oral	20000	ppm	**Decrease**	Absolute and relative organ weight decreased (-7%) in interim killed males at 20000 ppm.
16	Target organ toxicity	Liver weight	Rat	2	Years	Oral	100	mg/kg bw/day	**Decrease**	Relative organ weight reduced in interim kill in females at ≥ 100 mg/kg bw/day but no histopathological changes were observed. Absolute organ weight was reduced in interim kill females at

										100 and 1000 mg/kg bw/day)
17	Target organ toxicity	Liver weight	Rat	2	Years	Oral	20000	ppm	**Increase**	Relative organ weight increased at interim kill, absolute and relative (to brain weight) weight increased at terminal kill in males at 20000 ppm.
18	Target organ toxicity	Liver weight	Rat	2	Years	Oral	>15000	ppm	No effect	
19	Target organ toxicity	Liver weight	Mouse	18	Months	Oral	>10000	ppm	No effect	
20	Target organ toxicity	Liver weight	Mouse	18	Months	Oral	>5000	ppm	No effect	
21	Target organ toxicity	Liver weight	Mouse	18	Months	Oral	>40000	ppm	No effect	
22	Target organ toxicity	Liver weight	Rat	10	Weeks	Oral	>15000	ppm	No effect	
23	Target organ toxicity	Liver weight	Rat	10 (pre-mating)	Weeks	Oral	10000	ppm	**Increase**	Relative organ weight increased in F0 males at 10000 ppm, absolute values comparable to control group, considered to be incidental
24	Target organ toxicity	Liver weight	Rat	10 for pre-mating rearing 8 for subsequent breeding	Weeks	Oral	30000	ppm	**Increase**	Relative organ weight increased in F0+F1 males and females at 30000 ppm without any histopathological changes.
26	Target organ toxicity	Liver weight	Rat	10 prior to mating, continued until terminatio n	Weeks	Oral	>10000	ppm	No effect	

44	Target organ toxicity	Liver weight	Rat	21 (PND 22-42)	Days	Oral	> 1000	mg/kg bw/day	No effect	
45	Target organ toxicity	Liver weight	Rat	31 (PND 23-53)	Days	Oral	300	mg/kg bw/day	**Decrease**	Statictically significantly lower mean absolute liver weight (15.1% and 9.8% for 1000 and 300 mg/kg bw/day dose group, respectively) was observed. The effect was considered secondary to the decreased body weight changes.
49	Target organ toxicity	Liver weight	Rat	28	Days	Oral	>20000	ppm	No effect	
50	Target organ toxicity	Liver weight	Rat	28	Days	Oral	>2500	mg/kg bw/day	No effect	
51	Target organ toxicity	Liver weight	Dog	Study part A: 21 Study Part B: 14	Days	Oral	>1000	mg/kg bw/day	No effect	
52	Target organ toxicity	Liver weight	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect	
53	Target organ toxicity	Liver weight	Rat	90	Days	Oral	*>20000*	*ppm*	*No effect*	~~Decreased absolute and relative organ weight at 20000 ppm in males only, statistically not significant, and decreased relative weight at 6000 ppm in males. However, no histopathological changes were obsercvd.~~
~~*54*~~	~~*Target organ toxicity*~~	~~*Liver weight*~~	~~*Rat*~~	~~*90*~~	~~*Days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~	
55	Target organ toxicity	Liver weight	Rat	90	Days	Oral	>20000	ppm	No effect	
56	Target organ toxicity	Liver weight	Mouse	90	Days	Oral	>4500	mg/kg bw/day	No effect	Liver was weighed together with gall bladder.
57	Target organ toxicity	Liver weight	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect	

58	Target organ toxicity	Liver weight	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect	
59	Target organ toxicity	Liver weight	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect	Liver and drained gall bladder were weighed.
60	Target organ toxicity	Liver weight	Rat	21	Days	Dermal	>1000	mg/kg bw/day	No effect	
61	Target organ toxicity	Liver weight	Rat	21	Days	Dermal	>1000	mg/kg bw/day	No effect	
62	Target organ toxicity	Liver weight	Rabbit	21	Days	Dermal	>5000	mg/kg bw/day	No effect	
63	Target organ toxicity	Liver weight	Rabbit	28	Days	Dermal	>2000	mg/kg bw/day	No effect	
67	Target organ toxicity	Liver weight	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	Liver with gall bladder was weighed.
68	Target organ toxicity	Liver weight	Mouse	2	Years	Oral	> 30000	ppm	No effect	
~~*70*~~	~~*Target organ toxicity*~~	~~*Liver weight*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	
~~*70*~~	~~*Target organ toxicity*~~	~~*Liver weight*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	
73	Target organ toxicity	Liver weight	Mouse	90	Days	Oral	>50000	ppm	No effect	
76	Target organ toxicity	Liver weight	Rat	90-92	Days	Oral	>7500	ppm	No effect	
78	Target organ toxicity	Liver weight	Rat	90	Days	Oral	50000	ppm	**Increase**	Increase in relative organ weight observed in males only (at 6250 ppm; 12500 ppm; 25000 ppm and 50000 ppm).
79	Target organ toxicity	Liver weight	Mouse	90	Days	Oral	6250	ppm	**Increase**	Increase in relative organ weight observed in males only (at 6250 ppm; 12500

										ppm; 25000 ppm; 50000 ppm).	
96	*Target organ toxicity*	*Liver weight*	*Rat*	*90*	*Days*	*Oral*	*>7500*	*ppm*	*No effect*		
8	Target organ toxicity	Lung histopathology	Dog	90	Days	Oral	>50000	ppm	No effect		Organ specific toxicity of glyphosate was not observed in lung in three species up to a chronic exposure period. RMS: It is noted that RMS removed the results from two studies (ID 70, 74), as RMS considered these studies to be unacceptable. RMS has added results from one additional study (ID 96).
10	Target organ toxicity	Lung histopathology	Dog	1	Year	Oral	>50000	ppm	No effect		
13	Target organ toxicity	Lung histopathology	Rat	2	Years	Oral	>10000	ppm	No effect		
14	Target organ toxicity	Lung histopathology	Rat	2	Years	Oral	>30000	ppm	No effect		
15	Target organ toxicity	Lung histopathology	Rat	2	Years	Oral	>20000	ppm	No effect		
18	Target organ toxicity	Lung histopathology	Rat	2	Years	Oral	>15000	ppm	No effect		
19	Target organ toxicity	Lung histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect		
20	Target organ toxicity	Lung histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect		
21	Target organ toxicity	Lung histopathology	Mouse	18	Months	Oral	>40000	ppm	No effect		

25	Target organ toxicity	Lung histopathology	Rat	10 for pre-mating in F0, commencing at age of 8 weeks in F0 and continued for 2 successive generations up to weaning of F2	Weeks	Oral	>10000	ppm	No effect	
49	Target organ toxicity	Lung histopathology	Rat	28	Days	Oral	20000	ppm	No effect	
52	Target organ toxicity	Lung histopathology	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect	
53	Target organ toxicity	Lung histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	
~~*54*~~	~~*Target organ toxicity*~~	~~*Lung histopathology*~~	~~*Rat*~~	~~*90*~~	~~*Days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~	
55	Target organ toxicity	Lung histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	
56	Target organ toxicity	Lung histopathology	Mouse	90	Days	Oral	>4500	mg/kg bw/day	No effect	
57	Target organ toxicity	Lung histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect	
58	Target organ toxicity	Lung histopathology	Dog	12	Months	Oral	>500	mg/kg bw/day	No effect	Lung and trachea were examined.
59	Target organ toxicity	Lung histopathology	Dog	1	Years	Oral	>1000	mg/kg bw/day	No effect	

65	Target organ toxicity	Lung histopathology	Rat	10 (GD 6-15)	Days	Oral	>1000	mg/kg bw/day	No effect	
67	Target organ toxicity	Lung histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	
67	Target organ toxicity	Lung histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	
68	Target organ toxicity	Lung histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect	
~~*70*~~	~~*Target organ toxicity*~~	~~*Lung histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	
~~*70*~~	~~*Target organ toxicity*~~	~~*Lung histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	
73	Target organ toxicity	Lung histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect	
~~*74*~~	~~*Target organ toxicity*~~	~~*Lung histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F1 observed.*~~
~~*74*~~	~~*Target organ toxicity*~~	~~*Lung histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F2 observed.*~~
76	Target organ toxicity	Lung histopathology	Rat	90-92	Days	Oral	>7500	ppm	No effect	
96	*Target organ toxicity*	*Lung histopathology*	*Rat*	*90*	*Days*	*Oral*	*>7500*	*ppm*	*No effect*	
56	Target organ toxicity	Lung weight	Mouse	90	Days	Oral	>4500	mg/kg bw/day	No effect	

59a	Target organ toxicity	Lung weight	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect	
67	Target organ toxicity	Lung weight	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	
78	Target organ toxicity	Lung weight	Rat	90	Days	Oral	>50000	ppm	No effect	
79	Target organ toxicity	Lung weight	Mouse	90	Days	Oral	6250	ppm	**Increase**	Relative lung weight was increased in males (M at 6250 ppm; 12500 ppm; 25000 ppm; 50000 ppm; F no treatment-related effects).
13	Target organ toxicity	Trachea histopathology	Rat	2	Years	Oral	>10000	ppm	No effect	
18	Target organ toxicity	Trachea histopathology	Rat	2	Years	Oral	>15000	ppm	No effect	
55	Target organ toxicity	Trachea histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	
67	Target organ toxicity	Trachea histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	
68	Target organ toxicity	Trachea histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect	
~~*70*~~	~~*Target organ toxicity*~~	~~*Trachea histopathology*~~	~~*Rat*~~	~~*life time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	
~~*70*~~	~~*Target organ toxicity*~~	~~*Trachea histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	

76	Target organ toxicity	Trachea histopathology	Rat	90-92	Days	Oral	>7500	ppm	No effect		
96	*Target organ toxicity*	*Trachea histopathology*	*Rat*	*90*	*Days*	*Oral*	*>7500*	*ppm*	*No effect*		
8	Target organ toxicity	Lymph nodes histopathology	Dog	90	Days	Oral	>50000	ppm	No effect		Organ specific toxicity of glyphosate was not observed in lymph nodes in three species up to a chronic exposure period. RMS: It is noted that RMS removed the results from one study (ID 70), as this study was considered to be unacceptable. RMS: it is noted that RMS has added results from one additional study (ID 96).
13	Target organ toxicity	Lymph nodes histopathology	Rat	2	Years	Oral	>10000	ppm	No effect		
14	Target organ toxicity	Lymph nodes histopathology	Rat	2	Years	Oral	>30000	ppm	No effect		
15	Target organ toxicity	Lymph nodes histopathology	Rat	2	Years	Oral	>20000	ppm	No effect		
18	Target organ toxicity	Lymph nodes histopathology	Rat	2	Years	Oral	>15000	ppm	No effect		
19	Target organ toxicity	Lymph nodes histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect		
20	Target organ toxicity	Lymph nodes histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect		
21	Target organ toxicity	Lymph nodes histopathology	Mouse	18	Months	Oral	>40000	ppm	No effect		
49	Target organ toxicity	Lymph nodes histopathology	Rat	28	Days	Oral	>20000	ppm	No effect		

52	Target organ toxicity	Lymph nodes histopathology	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect	Mesenteric lymph nodes
53	Target organ toxicity	Lymph nodes histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	
55	Target organ toxicity	Lymph nodes histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	Histopathology was performed for control and high dose group animals only for mesenteric, submandibular lymph nodes.
57	Target organ toxicity	Lymph nodes histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect	
58	Target organ toxicity	Lymph nodes histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect	Mesenteric lymph nodes were examined.
59	Target organ toxicity	Lymph nodes histopathology	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect	Submandibular and mesenteric lymph nodes were examined.
67	Target organ toxicity	Lymph nodes histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	Mesentric lymph nodes were investigated.
68	Target organ toxicity	Lymph nodes histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect	Mediastinal, mesenteric and regional lymph nodes were examined.
~~*70*~~	~~*Target organ toxicity*~~	~~*Lymph nodes histopathology*~~	~~*Rat*~~	~~*life time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	~~*Mesenteric, mandibular, and cervical lymph nodes: No microscopic findings were considered compound related. The overall microscopic tissue alterations found throughout the study for each generation (F0, F1, and F2) were indicative of common incidental histological findings.*~~
~~*70*~~	~~*Target organ toxicity*~~	~~*Lymph nodes histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~	~~*Mesenteric and cervical lymph nodes: No microscopic findings were considered compound related. The overall microscopic tissue*~~

										~~*alterations were indicative of common incidental histological findings.*~~		
73	Target organ toxicity	Lymph nodes histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect	No effect on mesenteric lymph nodes was observed.		
76	Target organ toxicity	Lymph nodes histopathology	Rat	90-92	Days	Oral	>7500	ppm	No effect			
96	*Target organ toxicity*	*Lymph nodes histopathology*	*Rat*	*90*	*Days*	*Oral*	*>7500*	*ppm*	*No effect*			
13	Target organ toxicity	Pancreas histopathology	Rat	2	Years	Oral	>10000	ppm	No effect		Organ specific toxicity of glyphosate was not observed in pancreas in three species up to a chronic exposure period. RMS: It is noted that RMS removed the results from two studies (ID 70, 74), as these studies were considered to be unacceptable. RMS has added results from one additional study (ID 96).	
14	Target organ toxicity	Pancreas histopathology	Rat	2	Years	Oral	>30000	ppm	No effect			
15	Target organ toxicity	Pancreas histopathology	Rat	2	Years	Oral	>20000	ppm	No effect			
17	Target organ toxicity	Pancreas histopathology	Rat	2	Years	Oral	>20000	ppm	No effect			
18	Target organ toxicity	Pancreas histopathology	Rat	2	Years	Oral	>15000	ppm	No effect			
19	Target organ toxicity	Pancreas histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect			
20	Target organ toxicity	Pancreas histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			

22	Target organ toxicity	Pancreas histopathology	Rat	10	Weeks	Oral	>15000	ppm	No effect			
26	Target organ toxicity	Pancreas histopathology	Rat	10 prior to mating, continued until terminatio n	Weeks	Oral	>10000	ppm	No effect			
49	Target organ toxicity	Pancreas histopathology	Rat	28	Days	Oral	>20000	ppm	No effect			
52	Target organ toxicity	Pancreas histopathology	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect			
53	Target organ toxicity	Pancreas histopathology	Rat	90	Days	Oral	>20000	ppm	No effect			
~~*54*~~	~~*Target organ toxicity*~~	~~*Pancreas histopathology*~~	~~*Rat*~~	~~*90*~~	~~*Days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~			
55	Target organ toxicity	Pancreas histopathology	Rat	90	Days	Oral	>20000	ppm	No effect			
57	Target organ toxicity	Pancreas histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect			
58	Target organ toxicity	Pancreas histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect			
59	Target organ toxicity	Pancreas histopathology	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect			
67	Target organ toxicity	Pancreas histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect			
68	Target organ toxicity	Pancreas histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect			
~~*70*~~	~~*Target organ toxicity*~~	~~*Pancreas histopathology*~~	~~*Rat*~~	~~*life-time, all three generation s*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Pancreas histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			

				~~*through milk)*~~								
73	Target organ toxicity	Pancreas histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect			
~~*74*~~	~~*Target organ toxicity*~~	~~*Pancreas histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F1 observed.*~~		
~~*74*~~	~~*Target organ toxicity*~~	~~*Pancreas histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F2 observed.*~~		
76	Target organ toxicity	Pancreas histopathology	Rat	90-92	Days	Oral	>7500	ppm	No effect			
96	*Target organ toxicity*	*Pancreas histopathology*	*Rat*	*90*	*Days*	*Oral*	*>7500*	*ppm*	*No effect*			
59	Target organ toxicity	Pancreas weight	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect			
14	Target organ toxicity	Peripheral nerve histopathology	Rat	2	Years	Oral	>30000	ppm	No effect		Organ specific toxicity of glyphosate was not observed in peripheral nerves in three species up to a chronic exposure period. RMS: It is noted that RMS removed the results from one study (ID 70), as this study was considered to be unacceptable.	
18	Target organ toxicity	Peripheral nerve histopathology	Rat	2	Years	Oral	>15000	ppm	No effect			
20	Target organ toxicity	Peripheral nerve histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
55	Target organ toxicity	Peripheral nerve histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	The sciatic nerve was examined.		

58	Target organ toxicity	Peripheral nerve histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect	The sciatic nerve was examined.		
57	Sensitive to, but not diagnostic of, EATS	Pituitary histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect	The sciatic nerve was examined.		
59	Target organ toxicity	Peripheral nerve histopathology	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect	The sciatic nerve was examined.		
67	Target organ toxicity	Peripheral nerve histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	The sciatic nerve was examined.		
68	Target organ toxicity	Peripheral nerve histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect	The sciatic nerve was examined.		
~~*70*~~	~~*Target organ toxicity*~~	~~*Peripheral nerve histopathology*~~	~~*Rat*~~	~~*life time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Peripheral nerve histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
12	Target organ toxicity	Salivary glands histopathology	Rat	1	Year	Oral	8000	ppm	**Change**	Mild focal basophilia of the acinar cells of the parotid salivary glands in both sexes at ≥ 8000 ppm, treatment-related but not toxicologically significant (2/24, 0/24, 3/24 and 13/24 males and 2/24, 0/24, 6/24 and 15/24 females at 0, 2000, 8000 and 20000 ppm)	In some oral rat studies and in one mouse study, cellular alterations in salivary glands were observed upon histopathological examination. The glyphosate taskforce believes these salivary gland findings are a non-adverse adaptive	

16	Target organ toxicity	Salivary glands histopathology	Rat	2	Years	Oral	100	mg/kg bw/day	**Change**	Interim kill: mild cellular alterations of submaxillary salivary glands at ≥ 300 mg/kg bw/day in males and at 1000 mg/kg bw/day in females; mild to severe cellular alterations of the parotid salivary gland in males at ≥ 100 mg/kg bw/day and in females at ≥ 300 mg/kg bw/day, terminal kill: cellular alterations of submaxillary salivary glands at ≥ 100 mg/kg bw/day in males and at 1000 mg/kg bw/day in females; cellular alterations of the parotid salivary gland in both sexes at ≥ 100 mg/kg bw/day	response to treatment with a low pH diet (See CA 5.10). RMS: It is noted That RMS removed the results from two studies (ID 70, 74), as these studies were considered to be unacceptable. RMS added the results from one additional study (ID 96).	
18	Target organ toxicity	Salivary glands histopathology	Rat	2	Years	Oral	>15000	ppm	No effect			
20	Target organ toxicity	Salivary glands histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
26	Target organ toxicity	Salivary glands histopathology	Rat	10 prior to mating, continued until terminatio n	Weeks	Oral	3000	ppm	**Change**	Hypertrophy of acinar cells with prominent granular cytoplasms in the parotid salivary gland in F0 and F1 males and females at ≥ 3000 ppm and in the submaxillary salivary gland in F0 females at ≥ 3000 ppm, (parotid: 2/27, 2/28, 3/28 and 12/26 F0 males and 1/24, 0/24, 4/23 and 10/23 F1 males and in 0/28, 2/27, 5/28 and 17/28 F0 females and 0/24, 0/23,		

										4/24 and 9/23 F1 females at 0, 1000, 3000 and 10000 ppm; submaxillary: 0/28, 1/27, 4/28 and 14/28 F0 females and 0/24, 0/23, 0/28 and 3/23 F1 females at 0, 1000, 3000 and 10000 ppm) hypertrophy of acinar cells with prominent granular cytoplasms in the submaxillary salivary gland in females at ≥ 3000 ppm (0/28, 1/27, 4/28 and 14/28 F0 females and in 0/24, 0/23, 0/24 and 3/23 F1 females at 0, 1000, 3000 and 10000 ppm)		
52	Target organ toxicity	Salivary glands histopathology	Rat	90	Days	Oral	30	mg/kg bw/day	**Change**	Increased incidence of cellular alteration in the parotid salivary glands in both sexes at 30, 300 and 1000 mg/kg bw/day and increased severity of cellular alteration in the parotid salivary glands in both sexes at 1000 mg/kg bw/day and in males at 300 mg/kg bw/day	
57	Target organ toxicity	Salivary glands histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect	Mandibular salivary glands were investigated.	
58	Target organ toxicity	Salivary glands histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect	Mandibular salivary glands were investigated.	
59	Target organ toxicity	Salivary glands histopathology	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect	Submaxillary, sublingual, parotid salivary glands were examined.	
67	Target organ toxicity	Salivary glands histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	Parotid, sublingual and submaxilliar salivary glands were investigated. Histopathological examination was	

										performed for control and high dose group.		
68	Target organ toxicity	Salivary glands histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect	Mandibular salivary glands were investigated.		
69	Target organ toxicity	Salivary glands histopathology	Rat	5.5 (GD 3 till 21 days post partum)	Weeks	Oral	3000	ppm	**Change**	F0: Macroscopic changes to the salivary glands (enlarged/firm/congested/ swollen) were observed in 0, 2, 6 and 8 animals respectively in Groups 1 to 4 of F0 generation. Dose-related incidence and degree of granular basophilic cytoplasm of acinar cells was seen with 0, 2, 0 and 0 animals showing minimal effects, 0, 0, 2 and 0 animals showing moderate effects and 0, 0, 8 and 9 animals showing marked effects in Groups 1 to 4, respectively. This change was associated with hypertrophy of acinar cells with 0, 2, 2 and 0 animals with minimal hypertrophy and 0, 0, 8 and 9 animals in Groups 1 to 4 respectively with moderate hypertrophy of the acinar cells. Prominent mitoses were also seen in 2 animals at 30000 ppm, but not in lower treatment levels or the controls. F1: Post mortem examination of F1 generation at PND 42 revealed swollen/enlarged parotid salivary glands in		

										5/10 males and 2/10 females at 30000 ppm, and in 1/10 males at 3000 ppm. No histopathological examinations were performed.		
69	Target organ toxicity	Salivary glands histopathology	Rat	only secondary exposure through milk from PND 0-21	Weeks	Oral	3000	ppm	**Change**	Post mortem examination of weanlings at PND 21 revealed four pups with congested salivary glands at 10000 ppm and one pup with congested salivary glands at 3000 ppm. Since no similar findings were seen at 30000 ppm the significance of these incidences is unclear. No histopathological examinations were performed.		
~~*70*~~	~~*Target organ toxicity*~~	~~*Salivary glands histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Salivary glands histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			

~~*74*~~	~~*Target organ toxicity*~~	~~*Salivary glands histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F1 observed.*~~	
~~*74*~~	~~*Target organ toxicity*~~	~~*Salivary glands histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F2 observed.*~~	
76	Target organ toxicity	Salivary glands histopathology	Rat	90-92	Days	Oral	>7500	ppm	No effect		
78	Target organ toxicity	Salivary glands histopathology	Rat	90	Days	Oral	3125	ppm	**Change**	Parotid and submandibular salivary glands in M and F: Cytoplasmic alterations (basophilic change and hypertrophy of acinar cells) in M and F at 3125 ppm; 6250 ppm; 12500 ppm; 25000 ppm; 50000 ppm	
79	Target organ toxicity	Salivary glands histopathology	Mouse	90	Days	Oral	6250	ppm	**Change**	Parotid salivary gland: Increase of basophilia in acinar cells (Cytoplasmic alteration) in M and F at 6250 ppm; 12500 ppm; 25000 ppm; 50000 ppm	
96	*Target organ toxicity*	*Salivary glands histopathology*	*Rat*	*90*	*Days*	*Oral*	*6250*	*ppm*	*No effect*		
16	[Not in list]	Salivary glands weight	Rat	2	Years	Oral	100	mg/kg bw/day	**Increase**	Paratoid salivary glands: Absolute and relative weight increased in interim kill males at ≥ 100 mg/kg bw/day Sublingual and submaxillary salivary glands: Absolute and relative weight increased in interim kill animals of both sexes at 1000 mg/kg bw/day, increased abs+rel	

									weight in terminal kill females at 300 mg/kg bw/day		
52	[Not in list]	Salivary glands weight	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect		
67	[Not in list]	Salivary glands weight	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	Salivary glands (paratoid, sublingual and submaxillary): Absolute organ weight was not affected.	
18	Target organ toxicity	Skeletal muscle histopathology	Rat	2	Years	Oral	>15000	ppm	No effect		No effects on the histopathology of skeletal muscels were observed in rats and mice including different life stages. RMS: It is noted that RMS removed the results from one study (ID 70), as this study was considered to be unacceptable.
20	Target organ toxicity	Skeletal muscle histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect		
67	Target organ toxicity	Skeletal muscle histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	Thigh was investigated.	
68	Target organ toxicity	Skeletal muscle histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect	The biceps femoris was examined.	
~~70~~	~~Target organ toxicity~~	~~Skeletal muscle histopathology~~	~~Rat~~	~~life-time, all three generations~~	~~Weeks~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~		
~~70~~	~~Target organ toxicity~~	~~Skeletal muscle histopathology~~	~~Rat~~	~~21 (PND0-21, exposure through milk)~~	~~Days~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~		
73	Target organ toxicity	Skeletal muscle histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect		
7	Target organ toxicity	Skin histopathology	Dog	90	Days	Oral	>40000	ppm	No effect		No specific effects on the histopathology of

14	Target organ toxicity	Skin histopathology	Rat	2	Years	Oral	10000	ppm	Change	No relevant treatment-related histopathological changes were observed. (Gross necropsy: all animals: hair loss in at 30000 ppm (treatment relation unclear); Histopathology, non-neoplastic: terminal kill animals: decreased incidences of plantar granuloma in males at 30000 ppm (12/18, 11/20, 11/18 and 8/29) and increased incidences in females at 10000 ppm (6/15, 8/19, 13/16 and 7/14) at 0, 3000, 10000 and 30000 ppm, animals found dead/killed in extremis: follicular hyperkeratosis in males at 30000 ppm (3/32, 2/30, 1/32 and 10/21) and plantar granuloma in females at 30000 ppm (3/35, 6/31, 7/34 and 10/36) at 0, 3000, 10000 and 30000 ppm; neoplastic: no treatment-related findings)	skin were observed in dogs, rats and mice. Hair loss was observed in some studies in rodents. RMS: It is noted that RMS removed the results from one study (ID 70), as this study was considered to be unacceptable.	

18	Target organ toxicity	Skin histopathology	Rat	2	Years	Oral	>15000	ppm	No effect			
19	Target organ toxicity	Skin histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect			
20	Target organ toxicity	Skin histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
21	Target organ toxicity	Skin histopathology	Mouse	18	Months	Oral	>40000	ppm	No effect			
29	Target organ toxicity	Skin histopathology	Rat	10 (GD 6-15)	Days	Oral	>1000	mg/kg bw/day	No effect			
60	Target organ toxicity	Skin histopathology	Rat	21	Days	Dermal	>1000	mg/kg bw/day	No effect			
62	Target organ toxicity	Skin histopathology	Rabbit	21	Days	Dermal	>5000	mg/kg bw/day	No effect			
~~*70*~~	~~*Target organ toxicity*~~	~~*Skin histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Skin histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			

6	Target organ toxicity	Oesophagus histopathology	Dog	90	Days	Oral	>10000	ppm	No effect		No specific effects on the GI tract including oesophagus, stomach and small intestines were observed in dog, mouse, rabbit, an rat. Distention of the caecum was observed in rat and mouse which is in line with the observation of increased absolute and relative weight of the caecum. RMS: It is noted that RMS removed the results from studies ID70 and ID74, as these studies were considered to be unacceptable. RMS added result from one additional study (ID 96).	
20	Target organ toxicity	Oesophagus histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
59	Target organ toxicity	Oesophagus histopathology	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect			
67	Target organ toxicity	Oesophagus histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect			
68	Target organ toxicity	Oesophagus histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect			
~~70~~	~~Target organ toxicity~~	~~Oesophagus histopathology~~	~~Rat~~	~~life-time, all three generations~~	~~Weeks~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~			
~~70~~	~~Target organ toxicity~~	~~Oesophagus histopathology~~	~~Rat~~	~~21 (PND0-21, exposure through milk)~~	~~Days~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~			
~~74~~	~~Target organ toxicity~~	~~Oesophagus histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Weeks~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effects in F1 observed.~~		
~~74~~	~~Target organ toxicity~~	~~Oesophagus histopathology~~	~~Rat~~	~~F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)~~	~~Weeks~~	~~Oral~~	~~>300~~	~~ppm~~	~~No effect~~	~~No effects in F2 observed.~~		
78	Target organ toxicity	Oesophagus histopathology	Rat	90	Days	Oral	>50000	ppm	No effect			
79	Target organ toxicity	Oesophagus histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect			
17	Target organ toxicity	Stomach histopathology	Rat	2	Years	Oral	*800*	ppm	***Change***	No relevant treatment-related histopathological changes were observed. (Histopathology: inflammation of gastric squamous mucosa in		

										females at 8000 ppm (0/59, 3/60, 9/60 and 6/59 at 0, 2000, 8000 and 20000 ppm), findings predominantly observed in decedent animals, inflammation in surviving animals restricted to each one surviving male and female at 20000 ppm, no dose relation, considered not treatment-related) RMS: inflammation of gastric squamous mucosa in females at 8000 ppm (0/59, 3/60, 9/60 and 6/59 at 0, 2000, 8000 and 20000 ppm), findings predominantly observed in decedent animals, inflammation in surviving animals restricted to each one surviving male and female at 20000 ppm		
18	Target organ toxicity	Stomach histopathology	Rat	2	Years	Oral	>15000	ppm	No effect			
19	Target organ toxicity	Stomach histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect			
20	Target organ toxicity	Stomach histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
26	Target organ toxicity	Stomach histopathology	Rat	10 prior to mating, continued until	Weeks	Oral	>10000	ppm	No effect			

				termination								
31	Target organ toxicity	Stomach histopathology	Rabbit	13 (GD 7-19)	Days	Oral	400	mg/kg bw/day	**Change**	Macroscopic findings in 2/4 females at 400 mg/kg bw/day that died/were killed in extremis, treatment-related (fluid-filled large intestines, haemorrhage, ulceration and sloughing of the stomach, duodenum, congestion and colon, rectum and appendix gas distended; the animal killed in extremis had blood and dead fetuses in the uterus, which was attributed to the general poor state of the animals)		
55	Target organ toxicity	Stomach histopathology	Rat	90	Days	Oral	>20000	ppm	No effect			
57	Target organ toxicity	Stomach histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect	Stomach and oesophagus were histopathologically examined.		
58	Target organ toxicity	Stomach histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect			
59	Target organ toxicity	Stomach histopathology	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect			
67	Target organ toxicity	Stomach histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	Histopathological examination was performed of the glandular and non-glandular stomach.		
68	Target organ toxicity	Stomach histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect			

69	Target organ toxicity	Stomach histopathology	Rat	5.5 (GD 3 till 21 days post partum)	Weeks	Oral	3000	ppm	**Change**	Gross necropsy: Distended and/or congested stomach was seen in 0, 2, 5 and 4 animals in Groups 1 to 4 respectively. These findings generally followed the trend noted in the clinical signs observed. No histopathology performed.		
~~*70*~~	~~*Target organ toxicity*~~	~~*Stomach histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Stomach histopathology*~~	~~*Rat*~~	~~*21 (PND0 21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
73	Target organ toxicity	Stomach histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect	No effect on gastro-intestinal tract was observed.		
~~*74*~~	~~*Target organ toxicity*~~	~~*Stomach histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effect on gastro-intestinal tract was observed.*~~		
~~*74*~~	~~*Target organ toxicity*~~	~~*Stomach histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*F2: No effect on gastro-intestinal tract was observed.*~~		
76	Target organ toxicity	Stomach histopathology	Rat	90-92	Days	Oral	>7500	ppm	No effect	No effect on gastro-intestinal tract was observed.		
77	Target organ toxicity	Stomach histopathology	Rabbit	22 (GD 6-27)	Days	Oral	>2500	mg/kg bw/day	No effect			
96	*Target organ toxicity*	*Stomach histopathology*	*Rat*	*90*	*Days*	*Oral*	*>7500*	*ppm*	*No effect*			

2	Target organ toxicity	Small and large intestines histopathology	Rat	90	Days	Oral	1000	ppm	**Change**	Macroscopical findings: Caecum enlarged/distended and fluid-filled in 10/10 males and 10/10 females at 50000 ppm; microscopical findings: atrophy in 5/10 males and 5/10 females at 50000 ppm and for 1/10 males and 2/10 females at 10000 ppm, probably attributed to caecal distention		
3	Target organ toxicity	Small and large intestines histopathology	Rat	90	Days	Oral	10000	ppm	**Change**	Macroscopic finding: Caecum distention in 9/12 males and 7/12 females at 30000 ppm and in 3/12 males and 0/12 females at 10000 ppm		
4	Target organ toxicity	Small and large intestines histopathology	Mouse	90	Days	Oral	50000	ppm	**Change**	Macroscopic finding: Caecum distention in 12/12 males and 10/12 females at 50000 ppm and in 1/12 females at 10000 ppm at necropsy, no histopathological findings		
8	Target organ toxicity	Small and large intestines histopathology	Dog	90	Days	Oral	>50000	ppm	No effect			
13	Target organ toxicity	Small and large intestines histopathology	Rat	2	Years	Oral	>10000	ppm	No effect			

14	Target organ toxicity	Small and large intestines histopathology	Rat	2	Years	Oral	>30000	ppm	No effect			
14	Target organ toxicity	Small and large intestines histopathology	Rat	2	Years	Oral	30000	ppm	**Change**	Macroscopical finding: Significantly increased incidence of caecum distention (m: 32/78; f: 18/78) in both sexes at 30000 ppm , treatment-related but without histopathological abnormalities.		
18	Target organ toxicity	Small and large intestines histopathology	Rat	2	Years	Oral	>15000	ppm	No effect			
19	Target organ toxicity	Small and large intestines histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect			
20	Target organ toxicity	Small and large intestines histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
21	Target organ toxicity	Small and large intestines histopathology	Mouse	18	Months	Oral	40000	ppm	**Change**	Macroscopical finding: Caecum distention in males (28%) and females (36%) at 40000 ppm (14/50 males and 18/50 females at 40000 ppm, findings predominantly observed in terminal kill animals (11/29 males, 16/35 females); anal prolaps in the anus of 5/50 males at 40000 ppm,		

										no findings in any other group, related to findings of loose stool Histopathology, non-neoplastic: no treatment-related findings; neoplastic: no treatment-related findings		
24	Target organ toxicity	Small and large intestines histopathology	Rat	10 for pre-mating rearing 8 for subsequent breeding	Weeks	Oral	30000	ppm	**Change**			
49	Target organ toxicity	Small and large intestines histopathology	Rat	28	Days	Oral	20000	ppm	No effect			
53	Target organ toxicity	Small and large intestines histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	Oesophagus and stomach were also analysed.		
~~*54*~~	~~*Target organ toxicity*~~	~~*Small and large intestines histopathology*~~	~~*Rat*~~	~~*90*~~	~~*Days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~			
55	Target organ toxicity	Small and large intestines histopathology	Rat	90	Days	Oral	>20000	ppm	No effect			
57	Target organ toxicity	Small and large intestines histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect			
58	Target organ toxicity	Small and large intestines histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect			
59	Target organ toxicity	Small and large intestines histopathology	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect			
67	Target organ toxicity	Small and large intestines histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect			

68	Target organ toxicity	Small and large intestines histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect			
69	Target organ toxicity	Small and large intestines histopathology	Rat	5.5 (GD 3 till 21 days post partum)	Weeks	Oral	3000	ppm	**Change**	Gross pathology: Distended caecum was seen in 0, 0, 0 and 4 animals in Groups 1 to 4 respectively.Watery and/or dark contents in the gastro-intestinal tract were observed in 0, 2, 7 and 8 animals in Groups 1 to 4 respectively. These findings generally followed the trend noted in the clinical signs observed. No histopathology performed.		
69	Target organ toxicity	Small and large intestines histopathology	Rat	only secondary exposure through milk from PND 0-21	Weeks	Oral	>30000	ppm	No effect	No effect observed at necropsy.		
69	Target organ toxicity	Small and large intestines histopathology	Rat	3 (PND 21-42)	Weeks	Oral	30000	ppm	**Change**	Gross pathology: Soft gastro-intestinal contents were noted in 7/10 males and 9/10 females at 30000 ppm; grey/blue contents of the jejunum were noted in 2/10 females at this dosage. No histopathological examinations were performed.		
~~*70*~~	~~*Target organ toxicity*~~	~~*Small and large intestines histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			

~~70~~	~~Target organ toxicity~~	~~Small and large intestines histopathology~~	~~Rat~~	~~21 (PND0 21, exposure through milk)~~	~~Days~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~			
3	Target organ toxicity	Small and large intestines weight	Rat	90	Days	Oral	30000	ppm	**Increase**	Caecum: Absolute and relative weight statistically significantly increased in both sexes, which is in line with the observed distention.		
4	Target organ toxicity	Small and large intestines weight	Mouse	90	Days	Oral	10000	ppm	**Increase**	Caecum: Absolute and relative weight increased (m: +15%/+11%; f: +22%/+17%) in both sexes at ≥ 10000 ppm (stat. significant at 50000 ppm), which is in line with the observed distention.		
14	Target organ toxicity	Small and large intestines weight	Rat	2	Years	Oral	10000	ppm	**Increase**	Caecum: Absolute and relative weight increased (>20%) in both sexes at 10000 ppm (occasional stat. significance), at 30000 ppm stat. significant over the entire study period, which is in line with the observed distention.		
21	Target organ toxicity	Small and large intestines weight	Mouse	18	Months	Oral	40000	ppm	**Increase**	Caecum: Absolute and relative weight stat. significantly increased in both sexes at 40000 ppm, which is in line with the observed distention.		
18	Target organ toxicity	Spinal cord histopathology	Rat	2	Years	Oral	>15000	ppm	No effect		No effects on the histopathology of the spinal cord was observed in dog, mouse, and rat.	
26	Target organ toxicity	Spinal cord histopathology	Rat	10 prior to mating,	Weeks	Oral	>10000	ppm	No effect			

				continued until termination							RMS: It is noted that RMS removed the results from one study (ID 70), as this study was considered to be unacceptable.	
55	Target organ toxicity	Spinal cord histopathology	Rat	90	Days	Oral	>20000	ppm	No effect	Cervical, thoracic and lumbar sections of spinal cord were examined.		
58	Target organ toxicity	Spinal cord histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect	Cervical, midthoracic and lumbar sections of spinal cord were examined.		
67	Target organ toxicity	Spinal cord histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	Cervical, thoracic and lumbar sections of spinal cord were examined.		
68	Target organ toxicity	Spinal cord histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect			
~~70~~	~~Target organ toxicity~~	~~Spinal cord histopathology~~	~~Rat~~	~~life time, all three generations~~	~~Weeks~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~			
~~70~~	~~Target organ toxicity~~	~~Spinal cord histopathology~~	~~Rat~~	~~21 (PND0-21, exposure through milk)~~	~~Days~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~			
73	Target organ toxicity	Spinal cord histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect			
2	Target organ toxicity	Spleen histopathology	Rat	90	Days	Oral	>50000	ppm	No effect		No specific effects on spleen were observed in dog, mouse, and rat. RMS: It is noted that RMS removed results from two studies (ID 70, 74), as these studies were considered to be	
13	Target organ toxicity	Spleen histopathology	Rat	2	Years	Oral	>10000	ppm	No effect			

14	Target organ toxicity	Spleen histopathology	Rat	2	Years	Oral	>30000	ppm	No effect		unacceptable. RMS added results for one study (ID 96).	
18	Target organ toxicity	Spleen histopathology	Rat	2	Years	Oral	>15000	ppm	No effect			
19	Target organ toxicity	Spleen histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect			
20	Target organ toxicity	Spleen histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
21	Target organ toxicity	Spleen histopathology	Mouse	18	Months	Oral	>40000	ppm	No effect			
22	Target organ toxicity	Spleen histopathology	Rat	10	Weeks	Oral	>15000	ppm	No effect			
29	Target organ toxicity	Spleen histopathology	Rat	10 (GD 6-15)	Days	Oral	>1000	mg/kg bw/day	No effect			
49	Target organ toxicity	Spleen histopathology	Rat	28	Days	Oral	>20000	ppm	No effect			
50	Target organ toxicity	Spleen histopathology	Rat	28	Days	Oral	>2500	mg/kg bw/day	No effect			
52	Target organ toxicity	Spleen histopathology	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect			
53	Target organ toxicity	Spleen histopathology	Rat	90	Days	Oral	>20000	ppm	No effect			
~~*54*~~	~~*Target organ toxicity*~~	~~*Spleen histopathology*~~	~~*Rat*~~	~~*90*~~	~~*Days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~			
55	Target organ toxicity	Spleen histopathology	Rat	90	Days	Oral	>20000	ppm	No effect			

57	Target organ toxicity	Spleen histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect			
58	Target organ toxicity	Spleen histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect			
59	Target organ toxicity	Spleen histopathology	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect			
67	Target organ toxicity	Spleen histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect			
68	Target organ toxicity	Spleen histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect			
~~*70*~~	~~*Target organ toxicity*~~	~~*Spleen histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Spleen histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
73	Target organ toxicity	Spleen histopathology	Mouse	90	Days	Oral	>50000	ppm	No effect			
~~*74*~~	~~*Target organ toxicity*~~	~~*Spleen histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F1 observed.*~~		
~~*74*~~	~~*Target organ toxicity*~~	~~*Spleen histopathology*~~	~~*Rat*~~	~~*F0 (M 20; F 20); F1 (M 20; F 27); F2 (M 20; F 27)*~~	~~*Weeks*~~	~~*Oral*~~	~~*>300*~~	~~*ppm*~~	~~*No effect*~~	~~*No effects in F2 observed.*~~		
76	Target organ toxicity	Spleen histopathology	Rat	90-92	Days	Oral	>7500	ppm	No effect			
96	*Target organ toxicity*	*Spleen histopathology*	*Rat*	*90*	*Days*	*Oral*	*>7500*	*ppm*	*No effect*			
2	Target organ toxicity	Spleen weight	Rat	90	Days	Oral	*>50000*	*ppm*	*No effect*	~~Absolute weight reduced in both sexes at 50000 ppm which was attributed to reduced body weight.~~		

										~~Since no histopathological changes were observed, a specific toxicological effect on spleen is not deduced.~~		
5	Target organ toxicity	Spleen weight	Dog	90	Days	Oral	>1000	mg/kg bw/day	*No effect*	~~Absolute and relative weight (not significantly) decreased in males only at 30 mg/kg bw/day (-16 and -7%), at 300 mg/kg bw/day (25 and -19) and at 1000 mg/kg bw/day (-35 and -10%). In addition, no histopathological changes observed, therefore toxicological significance is doubtful.~~		
22	Target organ toxicity	Spleen weight	Rat	10	Weeks	Oral	>15000	ppm	No effect			
22	Target organ toxicity	Spleen weight	Rat	10	Weeks	Oral	>15000	ppm	No effect			
23	Target organ toxicity	Spleen weight	Rat	10 (pre-mating)	Weeks	Oral	>10000	ppm	No effect			
23	Target organ toxicity	Spleen weight	Rat	10 (pre-mating)	Weeks	Oral	>10000	ppm	No effect			
36	Target organ toxicity	Spleen weight	Mouse	28	Days	Oral	> 5000	ppm	No effect			
51	Target organ toxicity	Spleen weight	Dog	Study part A: 21 Study Part B: 14	Days	Oral	100	mg/kg bw/day	**Decrease**	Study part A (21 days of treatment): Absolute and relative spleen weight were considered reduced in the female animal. Study part B (14 days of treatment): no abnormalities observed		
52	Target organ toxicity	Spleen weight	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect			

53	Target organ toxicity	Spleen weight	Rat	90	Days	Oral	20000	ppm	**Increase**	Absolute weight increased in females only in all treatment groups (reaching statistical significance in high dose group only), relative weight statistically signif. increased for the high dose group only; relative weight (relative to brain weight) not statistically significantly increased. However, no effect was observed during macroscopic and microscopic examination.		
56	Target organ toxicity	Spleen weight	Mouse	90	Days	Oral	>4500	mg/kg bw/day	No effect			
59	Target organ toxicity	Spleen weight	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect			
67	Target organ toxicity	Spleen weight	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect			
68	Target organ toxicity	Spleen weight	Mouse	2	Years	Oral	> 30000	ppm	No effect			
~~*70*~~	~~*Target organ toxicity*~~	~~*Spleen weight*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Spleen weight*~~	~~*Rat*~~	~~*life time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
73	Target organ toxicity	Spleen weight	Mouse	90	Days	Oral	>50000	ppm	No effect	Absolute and relative (to body and brain weight) organ weight was not affected.		

13	Target organ toxicity	Thymus histopathology	Rat	2	Years	Oral	>10000	ppm	No effect	No relevant treatment-related histopathological changes were observed. (Neoplastic findings, surviving animals: no treatment-related findings; macroscopic: involution in 25/56, 35/54, 40/49 and 32/50 dead and moribund rats and 25/44, 0/46, 0/50 and 34/50 surviving rats of the 0, 100, 1000 and 10000 ppm group, age-related)	No histopathologic changes of the thymus were observed in dog, rat and mouse. An inconsistent change of relative thymus weights was observed in male rats and mice at very high doses (>1000 mg/kg bw/day). Overall, no specific effects on thymus were induced by glyphosate. RMS: thymus histopathology was not performed in study 54, therefore RMS has removed these results. It is noted that RMS removed the results from one study (ID 70), as this study was considered to be unacceptable. Results from an additional study were added (ID 96).	
18	Target organ toxicity	Thymus histopathology	Rat	2	Years	Oral	>15000	ppm	No effect	No relevant treatment-related histopathological changes were observed. (Non-neoplastic: no treatment-related findings (moderate to severe lymphoid atrophy in rats of both sexes among all groups, no effect on thymic atrophy); neoplastic: no treatment-related findings (lymphocytic thymoma, carcinoma in 0/51, 1/51, 1/51 and 2/51 males and 7/51, 2/51, 4/51 and 4/51 females at 0, 1500, 5000 and 15000 ppm))		
19	Target organ toxicity	Thymus histopathology	Mouse	18	Months	Oral	>10000	ppm	No effect	No relevant treatment-related histopathological changes were observed. (Gross pathology, dead/moribund animals: enlarged in 0/22, 1/20, 0/22 and 3/27 males and 0/16, 3/16, 1/20 and 2/20 females at 0, 100, 1000 and 10000 ppm, associated with neoplasms of the		

										hemolymphoreticular system, no dose relation; histopathology, non-neoplastic findings terminal kill animals: involution in 13/28 and 6/23 males and in 6/34 and 7/30 females at 0 and 10000 ppm, no involution in 9/28 and 9/23 males and in 20/34 and 14/30 females at 0 and 10000 ppm, not treatment-related)		
20	Target organ toxicity	Thymus histopathology	Mouse	18	Months	Oral	>5000	ppm	No effect			
22	Target organ toxicity	Thymus histopathology	Rat	10	Weeks	Oral	>15000	ppm	No effect			
52	Target organ toxicity	Thymus histopathology	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect			
53	Target organ toxicity	Thymus histopathology	Rat	90	Days	Oral	>20000	ppm	No effect			
~~*54*~~	~~*Target organ toxicity*~~	~~*Thymus histopathology*~~	~~*Rat*~~	~~*90*~~	~~*Days*~~	~~*Oral*~~	~~*>20000*~~	~~*ppm*~~	~~*No effect*~~	RMS: thymus histopathology not performed.		
55	Target organ toxicity	Thymus histopathology	Rat	90	Days	Oral	>20000	ppm	No effect			
56	Target organ toxicity	Thymus histopathology	Mouse	90	Days	Oral	>4500	mg/kg bw/day	No effect			
57	Target organ toxicity	Thymus histopathology	Dog	6	Months	Oral	>300	mg/kg bw/day	No effect			
58	Target organ toxicity	Thymus histopathology	Dog	1	Year	Oral	>500	mg/kg bw/day	No effect			
59	Target organ toxicity	Thymus histopathology	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect			
67	Target organ toxicity	Thymus histopathology	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect			

68	Target organ toxicity	Thymus histopathology	Mouse	2	Years	Oral	> 30000	ppm	No effect			
~~*70*~~	~~*Target organ toxicity*~~	~~*Thymus histopathology*~~	~~*Rat*~~	~~*life-time, all three generations*~~	~~*Weeks*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
~~*70*~~	~~*Target organ toxicity*~~	~~*Thymus histopathology*~~	~~*Rat*~~	~~*21 (PND0-21, exposure through milk)*~~	~~*Days*~~	~~*Oral*~~	~~*>30*~~	~~*mg/kg bw/day*~~	~~*No effect*~~			
76	Target organ toxicity	Thymus histopathology	Rat	90-92	Days	Oral	>7500	ppm	No effect			
96	*Target organ toxicity*	*Thymus histopathology*	*Rat*	*90*	*Days*	*Oral*	*>7500*	*ppm*	*No effect*			
22	Target organ toxicity	Thymus weight	Rat	10	Weeks	Oral	>15000	ppm	No effect			
23	Target organ toxicity	Thymus weight	Rat	10 (pre-mating)	Weeks	Oral	>10000	ppm	No effect			
36	Target organ toxicity	Thymus weight	Mouse	28	Days	Oral	> 5000	ppm	No effect			
52	Target organ toxicity	Thymus weight	Rat	90	Days	Oral	>1000	mg/kg bw/day	No effect			
56	Target organ toxicity	Thymus weight	Mouse	90	Days	Oral	>4500	mg/kg bw/day	No effect			
59	Target organ toxicity	Thymus weight	Dog	1	Year	Oral	>1000	mg/kg bw/day	No effect			
67	Target organ toxicity	Thymus weight	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	**Increase**	Males: Absolute thymus weight was increased in the intermediate and high dose groups (P<0.01 and P<0.05 respectively) compared to control. Thymus weight was also increased in the intermediate and high dose groups after covariance analysis. The increase in		

										high dose males was due to one animal which had an enlarged thymus infiltrated with lymphoma cells. Moreover, since no effect was observed at necropsy or histopathological examination, the increased thymus weight is considered not toxicologically relevant. Females: No effect on organ weight was observed.		
78	Target organ toxicity	Thymus weight	Rat	90	Days	Oral	50000	ppm	**Decrease**	Relative organ weight was decreased in males only (50000 ppm= -13%*), where also decreased body weight gain and signs of general systemic toxicity were observed.		
79	Target organ toxicity	Thymus weight	Mouse	90	Days	Oral	50000	ppm	**Increase**	Relative organ weight was increased in males only, where also decreased body weight gain and signs of general systemic toxicity were observed.		
18	[Not in list]	Further examined organs	Rat	2	Years	Oral	>15000	ppm	No effect	Nasal cavities: histopathology, (non-)neoplastic: no treatment-related findings (dilatation of subepithelial glands in rats of either sex, spontaneous change, statistically significantly decreased in males at 15000 ppm, incidental; chronic inflammatory lesions adjacent to the palate, associated with plant material/ hair	Specific effects on further examined orans or treatment-related neoplasia were not observed. RMS: It is noted that RMS removed the results from one study (ID 70), as this study was considered to be unacceptable.	

										fragments, reaction to foreign material impacted ti gland ducts; inflammatory/non-inflammatory exudate overlying the endothelium, focal epithelial ulceration, thrombus formation, fungal growth and dental hyperplasia occasionally observed); histopathology, neoplastic: no treatment-related findings (polypoid adenoma in 2/51, 1/51, 0/51 and 0/51 males at 0, 1500, 5000 and 15000 ppm) Pharynx: histopathology, non-neoplastic: no treatment-related findings (inflammatory cell lesions, inflammatory exudate and mucous cell hyperplasia/hypertrophy in a few animals) histopathology, neoplastic: squamous cell papilloma in 1/51 females at 15000 ppm Larynx: histopathology, (non-)neoplastic: no treatment-related findings (distention of glands commonly observed among all control and treated rats of either sex; focal ulceration and debris in the ventral pouch, considered incidental) Tongue: histopathology, (non-)neoplastic: no treatment-related findings		

										(isolated instances of mononuclear cell infiltrates and mucous cysts in the epithelium in males, without toxicological significance); histopathology, neoplastic: no treatment-related findings (benign granular cell tumor in 1/51 females at 15000 ppm)		
20	[Not in list]	Further examined organs	Mouse	18	Months	Oral	>5000	ppm	No effect	Nasal cavities: no treatment-related findings (focal epithelial hyperplasia in both sexes frequently observed, epithelial inflammation, exudate overlaying the epithelium, dilatation of subepithelial glands, focal epithelial ulceration, prominent fibroplasia and resorption of bone occasionally observed; dental dysplasia and dental erosion/abscess formation in a few control and treated males) Pharynx: no treatment-related findings (mononuclear cell infiltrates, exudate overlaying the epithelium, focal epithelial hyperplasia in a few animals, extensive inflammation and abscess formation in the supra-pharyngeal tissues in one control mouse) Larynx: no treatment-related findings (dilatation		

										of subepithelial glands and epithelial/subepithelial inflammatory cell infiltrates, incidental) Trachea: no treatment-related findings (dilatation of subepithelial glands frequently observed in both sexes, isolated instances of inflammation) Tongue: no treatment-related findings (focal inflammation, fibrosis, ulceration, vasculitis and abscess formation occasionally observed)		
67	[Not in list]	Neoplastic findingd	Mouse	2	Years	Oral	> 1000	mg/kg bw/day	No effect	There were no statistically significant increases in incidence of any tumour. The number of animals with tumours, both benign and malignant, was similar between the control and high dose groups (m+f). (Animals with multiple tumour types was slightly increased in the high dose group of both sexes (males: 16/50 and females: 11/50) compared to control (males: 11/50 and females: 6/50) causing a slight increase in the total number of tumours in the high dose group of both sexes (males: 60 and females: 43) compared to control (males: 49 and females: 36); Haemangiosarcoma was evident in 4/50 high dose		

										males, 2/50 low dose females and 1/50 high dose females (not significant) compared to the respective controls (m+f: 0/50). Histiocytic sarcoma in the lymphoreticular/haemopoietic tissue was evident in 2 low and 2/50 high dose males and 3 low, 3 intermediate and 1/50 high dose females (not significant) compared to the respective controls (m+f: 0/50). The incidences of haemangiosarcoma and histiocytic sarcoma were higher in all groups of both sexes exposed to the test substance. Similar incidences of haemangiosarcoma and histiocytic sarcoma have been seen in other studies using mice of a similar age and strain (historic control data). Due to the lack of a dose relationship, statistical significance and the incidences in this study falling within the historic control ranges, these changes are not considered to be due to test substance treatment.)		

68	[Not in list]	Neoplastic findingd	Mouse	2	Years	Oral	> 30000	ppm	No effect	There were no statistically significant increases in incidence of any tumour. (Neoplastic findings were those commonly encountered in mice: Bronchiolaralveolar tumors of the lungs, hepatocellular neoplasms, and tumors of the lymphoreticular system accounted for the majority encountered. There were no suspected test substance-associated trends in the incidence of these tumors or in any of the other spontaneously occurring neoplasms. Lymphoreticular tumors tended to be more frequent in treated animals, particularly the females. The numbers were relatively small and differences from the control failed to provide supportive evidence that the neoplasms had a test substance relationship. The other neoplasms that occurred with any frequency in treated mice only were renal tubule adenomas (males: 3 present at the high-dose; 1 at the mid-dose level). However, the distribution of this benign tumor was considered spurious and unrelated to treatment.		

										Renal tubule adenomas (males only; 3 in high-dose and 1 in the mid-dose) -> spurious and unrelated to treatment due to the absence of other renal lesions.)		
~~70~~	~~[Not in list]~~	~~Overall microscopic evaluation~~	~~Rat~~	~~life-time, all three generations~~	~~Weeks~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~	~~The overall microscopic tissue alterations found throughout the study for each generation (F0, F1, and F2) were indicative of common incidental histological findings.~~		
~~70~~	~~[Not in list]~~	~~Overall microscopic evaluation~~	~~Rat~~	~~21 (PND0-21, exposure through milk)~~	~~Days~~	~~Oral~~	~~>30~~	~~mg/kg bw/day~~	~~No effect~~	~~F3: The overall microscopic tissue alterations were indicative of common incidental histological findings.~~		