## *SUMMARY OF ANIMAL DEVELOPMENTAL TOX. STUDIES (Prenatal Component)*

CHEMICAL: **FLUOXETINE** ***Table 4.3***

REFERENCE: *A Preliminary Teratology Study on Fluoxetine (Lilly Compound 110140) in the Rat. Lilly Research Laboratories Study No R-77, IND ——— Toxicology Report No7 / 1979 by J S Wold and J.K. Markham*

| | | | | |
|---|---|---|---|---|
| **Species, strain** | Rat, Fischer 344 | | | |
| **Exposure – compound and doses** | Fluoxetine Hydrochloride, purity 96% (aqueous solution), 0,10,20,40 *mg/kg/d* | | | |
| **Exposure timing and duration** | Gest. days 6-15 (Plug day=day 0) | | | |
| **Route of administration** | Oral (gavage) | | | |
| **Gestation day of sacrifice** | Gest. day 20 | | | |
| **Dose – Response** (yes/no) | yes | | | |
| *Dose Levels (mg/kg/day)→* | **0 (Control)** | **10** | **20** | **40** |
| **N animals per group** | 5 | 5 | 5 | 5 |
| **N pregnant dams/litters per group** | 5/5 | 1/1 | 4/3 | 4/1 |
| **NOAEL and LOAEL prenatal dvlpm.** | | | | |
| **Pre-implantation lethality**[2] per dam | 15% | • | • | 15.6%(-) |
| N implants/ N Corpora lutea per dam (% change vs control) | 10/11.8 | • (1 dam only) | 9 /• C.L. unknown (C.L. 2 dams only) | 9.7/11.5 |
| **Post-implantation lethality**[3] per litter | 4% | 0 (1 litter only) | 25% (↑5-fold) | 93%(↑23-fold) |
| - Dead (mean per litter) | 0.2 | 0 | 0 (-) | 0 (-) |
| - Resorbed (aborted) - mean per litter | 0.2 | 0 | 2.3 (↑100%) | 9.0 (↑50-fold) |
| - N litters completely resorbed/ N total | 0/5 | 0/1 | 1/3 (30%) | 3/4 (75%) |
| **N live fetuses** per litter | 9.6 | 12 (1 litter only) | 5.3 (↓45%) | 0.75 (↓92%) |
| **Sex ratio** (proportion males, %) | • | • | • | • |
| **Fetal weight** per litter % change vs control | • | • | • | • |
| **Sex-differentiated fetal weight** | • | • | • | • |
| **Incidence of malformations** per litter (if elevated, describe malformations below) | 0% (gross external only) | 0%(-) (gross external only) | 0%(-) (gross external only) | 0%(-)(gross external only) |
| **Malformations by type**[†] (rate and description) | | | | |
| - External[†] | 0% | 0%(-) | 0%(-) | 0%(-) |
| - Visceral[†] | • | • | • | • |
| - Skeletal[†] | • | • | • | • |
| **Incidence of variations** per litter | • | • | • | • |
| **Maternal toxicity** | | | | |
| NOAEL & LOAEL maternal toxicity | | | | |
| Body weight, initial-final, *g* (%vs cntrl): | 177-241 | • | 185-170 (↓30%) | 188 - • (all dead) |
| - prior to dosing | 182 (g.day 7) | • | 182 (-) | 178.3 (-) |
| - during dosing: | 199 (g.day 14) | • | 168 (↓15%) | 142.3 (↓28.5%) |
| | 241 (g.day 20) | • | 170 (↓30%) | • (all dead) |
| Weight gain, % (% change vs cntrl) | 36.3 | • | 18.2 (↓50%) | • (all dead) |
| Pregnancy-adjusted weight (yes/no) | no | no | no | no |
| Food consumption, *g/day* (% vs cntrl) | | | | |
| - prior to dosing | 8.9 (g.d.0-6) | • | 10.1 | 9.0 |
| - during dosing: | 9.9 (g.d.7-13) | • | 2.9 (↓71%(+) | 1.0 (↓90%(+) |
| | 12.8 (g.d.14-19) | • | 5.3 (↓60%(+) | • (all dead) |
| Clinical signs | (-) | • | Anorexia + marked wt loss | Anorexia + marked wt loss |
| Endpoints above attributable / non-attributable to pharmacological effect? (yes/no) | | | no | no |
| Maternal mortality | 0 | 0 | 50% (2/4) | 100% (5/5) |
| Necropsy findings | | | Acute upper resp. tract infection | Acute upper resp. tract infection |

[1] Effect to be presented as relative to control values; [2] Pre-implantation lethality (%) = [(*n* C.L–*n* impl.)/ *n* C.L.}x100;
[3] Post-implantation lethality (%) = (*n* Dead+Resorbed (aborted)/*n* implants)x100; [4] N live / N total fetuses per litter;
[†] Describe specific malformations which are increased over their control rates

Key: (– ) no change; • no observation; (+ ) statistically significant change or trend(p<0 05); (± )statistically non-significant change;↑ increase; ↓decrease;

*Table 4.3 (continued)*

| FLUOXETINE | REFERENCE: *A Preliminary Teratology Study on Fluoxetine (Lilly Compound 10140) in the Rat. INC* — Lilly Research Laboratories, Toxicology Report No7, Study No R-77, 1979 by J.S Wold and J.K. Markham.* | | | | |
|---|---|---|---|---|---|
| **Summary** | **NOAEL** | | **LOAEL** | | **Most sensitive endpoint** (Limiting parameter) |
| | Female | Male | Female | Male | |
| **General Toxicity** | N.A. | N.A. | N.A. | N.A. | |
| **Reproductive Toxicity** incl: | | | | | |
| - **Fertility** | N.A. | N.A. | N.A. | N.A. | |
| - **Prenatal Developmental Toxicity** | Not determinable | | Not determinable | | ***Excessive ↑ in postimplantation embryofetal loss** & proportion of dams that had resorptions at 20 and 40 mg/kg/day* |
| - **Postnatal Development.Toxicity** | N.A. | | N.A. | | |
| - **Maternal toxicity** during gestation | Not determinable | | Not determinable | | *100% **maternal mortality** at 40, and 50% - at 20 mg/kg/day* |

N.A.= not applicable

| | |
|---|---|
| **Conclusion** | Fluoxetine hydrochloride at oral doses of 20 and 40 mg/kg/day on gest.days 6 through 15 in Fischer 344 rat results in dose-dependent acute maternal toxicity (anorexia, marked wt.loss, mortality) and in embryolethality (early resorptions) involving 25% to over 90% of conceptuses at 20 and 40 mg/kg/day respectively. No stillbirths, no gross external malformations (even at these extreme exposures). |
| **Confounding factors and other comments** | Insufficient N pregnant animals to allow determining nature and magnitude of effect at the lowest dose level (10 mg/kg/day): only 1 pregnant animal in the lowest dose group. Intermediate & high doses cause overt maternal toxicity/mortality which confound the assessment of developmental effects per se. Only gross external malformations recorded (real malformation Incidence unknown) |
| **Evaluation*** *Criteria:* | Limitations: a preliminary, dose-finding study, limited to acute effects at maternally toxic doses. LOAEL can not be determined because of insufficient N pregnant dams (1 only) at the lowest dose level (10mg/kg/day). |
| *Adequacy of experimental model* | Yes |
| *Adequacy of dose and route of adm.* | Doses too high; route adequate |
| *Adequacy of timing &duration of exposure* | Yes |
| *Sufficient n animals per group* | No |
| *Presence of dose/effect or dose/response relationship* | Yes |
| *Appropriate statistical analysis* | No |
| *Concordance with pharmacokinetic/ pharmacodynamic properties of agent* | Not applicable at these high doses |
| *Data consistent with other studies* | No data |
| **Study reliable** (yes/no) | Reliability limited |

*(with regard to reliability of extrapolating study data to humans)

**Note for the database:** 1.The lowest dose level group (10 mg/kg/day) contained only 1 pregnant female and should not be included in the database at all. 2. For the remaining dose groups, no mean (only individual) values of reproduction data are provided in the original report. In this summary, the mean group data are calculated on the basis of those individual data. 3. Although N animals insufficient, this study should be entered in the database since it would complement the information about dose/effect relationship in combination with the next (lower doses) teratogenicity study in the same rat strain.

## *SUMMARY OF ANIMAL DEVELOPMENTAL TOX. STUDIES (Prenatal Component)*

CHEMICAL: **FLUOXETINE** **Table 4.4**

REFERENCE *A Teratology Study on Fluoxetine (Lilly Compound 110140) in the Rat. Lilly Research Laboratories Study R-207, IND ~~~ Toxicology Report No. 8 /1979 by J. S. Wold & J. K. Markham*

| | | | | |
|---|---|---|---|---|
| **Species, strain** | Rat, Fischer 344 | | | |
| **Exposure – compound and doses** | Fluoxetine Hydrochloride, purity 96% (aqueous solution);0, 2, 5, 12.5*mg/kg/d* | | | |
| **Exposure timing and duration** | Gest. days 6-15 (plug day=day 0) | | | |
| **Route of administration** | Oral (gavage) | | | |
| **Gestation day of sacrifice** | Gest. day 20 | | | |
| **Dose – Response** (yes/no) | yes | | | |
| *Dose Levels (mg/kg/day)→* | **0 (Control)** | **2** | **5** | **12.5** |
| **N dams/litters per group** | 25/25 | 19/19 | 22/21 | 18/17 |
| **NOAEL and LOAEL prenatal dvlpm.** | | | | NOAEL |
| **Pre-implantation lethality**[2] per dam | 27% | 19.6% (-) | 21% (-) | 32% ↑(±) |
| N implants/ N Corpora lutea<br>(% change vs control) | 8.6/11.8 | 9.4/11.7<br>(-) | 9.5/12<br>(-) | 7.8/11.4<br>*n* impl.↓10% (±) |
| **Post-implantation lethality**[3] per litter | 9.3% | 6.4% (-) | 7.4% (-) | 9% (-) |
| - Dead (mean per litter) | 0 | 0 (-) | 0 (-) | 0 (-) |
| - Resorbed (aborted) - mean per litter | 0.8 | 0.6 (-) | 0.7 (-) | 0.7 (-) |
| Early:Late resorptions ratio | 18:1 | 11:0 | 14:1 | 13:0 |
| Females affected of total, % | 52%(13/25) | 44% (8/18) | 57% (12/21) | 39% (7/18) |
| - N litters completely resorbed/ N total | 0/25 | 0/19 (-) | 0/22 (-) | 1/18 (-) |
| **N live fetuses** per litter | 7.9 | 8.8 (-) | 8.8 (-) | 7.1 ↓10% (±) |
| **Fetal viability** (gestat.survival index)[4] | 100% | 100%(-) | 100%(-) | 100%(-) |
| **Sex ratio** (proportion males) | 48% | 53% (-) | 52%(-) | 60% (↑25%) |
| **Fetal weight** per litter, *g*<br>% change vs control | 3.20 | 3.20<br>(-) | 3.10<br>(-) | 3.29<br>(-) |
| **Sex-differentiated fetal weight** | • | • | • | • |
| **Incidence of malformations** per litter<br>(if elevated, describe malformations below) | 0.5% | 0%(-) | 0%(-) | 0%(-) |
| **Malformations by type**[†] (rate and description) | | | | |
| - External[†] | | | | |
| - Visceral[†] | 0.5% (1/197) | | | |
| - Skeletal[†] | | | | |
| **Incidence of variations** per litter | 1.5% (3/197) | 1% (2/162) | 1.6% (3/184) | 0.8% (1/127) |
| **Maternal toxicity** | | | | |
| NOAEL & LOAEL maternal toxicity | | | NOAEL | LOAEL |
| Body weight, initial-final, *g* (%vs cntrl):<br>- prior to dosing<br>- during dosing: | 189-246<br>197 (g.day 7)<br>210 (g.day 14)<br>246 (g.day 20) | 191-256 (-)<br>197 (-)<br>212 (-)<br>256 (-) | 191-254 (-)<br>196 (-)<br>209 (-)<br>254 (-) | 188 -236 (-)<br>188 (-)<br>191 ↓9%(±)<br>236 (-) |
| Weight gain, % (% change vs cntrl) | 30 | 33 (-) | 33 (-) | 25 ↓5%(±) |
| Pregnancy-adjusted weight (yes/no) | no | no | no | no |
| Food consumption, *g/day* (% vs cntrl)<br>- prior to dosing:<br>- during dosing: | 7.2 (g.d. 0-6)<br>9.6 (g.d. 7-13)<br>11.3 (g.d.14-19) | 7.6 (-)<br>9.2 (-)<br>11.5 (-) | 7.2 (-)<br>8.2 (↓15%)<br>12 (-) | 6.9 (-)<br>4.8 (↓50%)<br>10.8 (-) |
| Clinical signs | (-) | (-) | (-) | (-) |
| Endpoints above attributable to pharmacological effect of the compound? | | | yes | yes |
| Maternal mortality | 0 | 0 | 0 | 0 |
| Necropsy findings | • | • | • | • |

[1] Effect to be presented as relative to control values; [2] Pre-implantation lethality (%) = [(*n* C.L–*n* impl.)/ *n* C.L.}x100;
[3] Post-implantation lethality (%) = (*n* Dead+Resorbed (aborted)/*n* implants)x100; [4] N live / N total fetuses per litter;
[†] Describe specific malformations which are increased over their control rates
Key: (– ) no change; • no observation; (+ ) statistically significant change or trend(p<0.05); (± )statistically non-significant change;↑ increase; ↓decrease;

*Table 4.4 (continued)*

| FLUOXETINE | REFERENCE: *A Teratology Study on Fluoxetine (Lilly Compound 110140) in the Rat. Lilly Research Laboratories Study R-207, IND —— Toxicology Report No.8 /1979 by J. S Wold & J. K. Markham* | | | | |
|---|---|---|---|---|---|
| **Summary** | **NOAEL** | | **LOAEL** | | **Most sensitive endpoint** (Limiting parameter) |
| | Female | Male | Female | Male | |
| **General Toxicity** | N.A. | N.A. | N.A. | N.A. | |
| **Reproductive Toxicity** incl: | | | | | |
| **- Fertility** | N.A. | N.A. | N.A. | N.A. | |
| **- Prenatal Developmental Toxicity** | **12.5** mg/kg/day | | Not determined | | ***No effect*** |
| **- Postnatal Development.Toxicity** | N.A. | | N.A. | | |
| **- Maternal toxicity** during gestation | **5** mg/kg/day | | **12.5** mg/kg/day | | ***Decreased food consumption*** |

N.A.= not applicable

| | |
|---|---|
| **Conclusion** | Fluoxetine hydrochloride at oral doses of 2, 5 and 12.5 mg/kg/day on gest.days 6 through 15 in Fischer 344 rat results in dose-dependent depression of maternal food intake, significant at the highest dose and in non-significant but dose-dependent transient decrease in maternal wt gain during 2nd wk of treatm. at 12 5 mg/kg/day. These effects are most probably due to the pharmacologic action of the agent. No signs of developmental toxicity even at the maternally effective dose. Increased proportion of male fetuses at the highest dose (probably a chance finding). No selective embryo/fetotoxicity. NOEL: 12.5 mg/kg/day |
| **Confounding factors and other comments** | Decreased litter size at the highest dose group (12.5 mg/kg/day) is due to the higher pre-implantation embryonic lethality and is not treatment-related since dosing was started after implantation. The higher pre-implantation lethality is due to 2 dams which had a single implant. site each. The somewhat higher fetal wt in the same group is explained by confounding factors: smaller litter size and higher proportion of males. Evaluation on true effect on fetal wt. hindered by the lack of sex-differentiated weight measurement. |
| **Evaluation*** *Criteria:* | Study reliable. Altered sex ratio at the highest exposure non-concordant with other studies at similar and higher dose levels (most probably due to chance). Limitation: Conclusion about effect on fetal weight can not be made (see confounding factors). |
| *Adequacy of experimental model* | Yes |
| *Adequacy of dose and route of adm.* | Yes |
| *Adequacy of timing &duration of exposure* | Yes |
| *Sufficient n animals per group* | Yes |
| *Presence of dose/effect or dose/response relationship* | Yes |
| *Appropriate statistical analysis* | Yes |
| *Concordance with pharmacokinetic/ pharmacodynamic properties of agent* | Yes |
| *Data consistent with other studies* | Yes (with exception of the change in the sex ratio of progeny) |
| **Study reliable** (yes/no) | Yes |

*(with regard to reliability of extrapolating study data to humans)

**Note for the database:** Please, see the **Confounding factors and other comments** above

## *SUMMARY OF ANIMAL DEVELOPMENTAL TOX. STUDIES (Prenatal Component)*

CHEMICAL: **FLUOXETINE** **Table 4.5**

REFERENCE: *A PreliminaryTeratology Study on Fluoxetine (Lilly Compound 110140) in the Rabbit. Lilly Research Laboratories Study B-7017, IND ___ Toxicology Report No 9 /1979 by J. S. Wold & J. K. Markham*

| | | | | |
|---|---|---|---|---|
| **Species, strain** | Rabbit, Dutch Belted | | | |
| **Exposure – compound and doses** | Fluoxetine Hydrochloride, purity 96% (aqueous solution);0, 2.5, 7.5, 15 *mg/kg/d* | | | |
| **Exposure timing and duration** | Gest. days 6-18 | | | |
| **Route of administration** | Oral (gavage) | | | |
| **Gestation day of sacrifice** | Gest. day 28 | | | |
| **Dose – Response** (yes/no) | yes | | | |
| *Dose Levels (mg/kg/day)→* | **0 (Control)** | **2.5** | **7.5** | **15** |
| **N animals per group** | 5 | 5 | 5 | 5 |
| **N pregnant dams/litters per group** | 5/5 | 5/5 | 4/4 | 5/4 |
| **NOAEL and LOAEL prenatal dvlpm.** | | | | |
| **Pre-implantation lethality**[2] per dam | 20% | 26% | 3% | 30% ↑(±) |
| N implants/ N Corpora lutea | 4.8/ 6 | 5.6/ 7.6 | 5.8/ 6 | 5.2/ 7.4 |
| **Post-implantation lethality**[3] per litter | 0 % | 21%(↑) | 17% (↑) | 27% (↑) |
| - Dead (mean per litter) | 0 | 0 (-) | 0 (-) | 0 (-) |
| - Resorbed - mean per litter | 0 | 0.6 (↑) | 1.0 (↑) | 0.6 (↑) |
| - Aborted - mean per litter | 0 | 0.6 (↑) | 0 | 0.8 (↑) |
| Early:Late resorptions ratio | • | • | • | • |
| Females affected of total, % | 0/5 | 3/5 | 4/4 | 3/5 |
| N litters completely resorbed(aborted)/total | 0/5 | 1/5 | 0/4 | 2/5 |
| **N live fetuses** per litter | 4.8 | 4.0 | 4.8 (-) | 2.8 ↓40% (±) |
| **Fetal viability** (gestat.survival index)[4] | • | • | • | • |
| **Sex ratio** (proportion males) | • | • | • | • |
| **Fetal weight** per litter,*g* (%vs control) | • | • | • | • |
| **Sex-differentiated fetal weight** | • | • | • | • |
| **Incidence of malformations** per litter (if elevated, describe malformations below) | 0% gross extern. only | 0%(-) gross extern. only | 0%(-) gross extern. only | 0%(-) gross extern. only |
| **Malformations by type**[†] | | | | |
| - External[†] | 0 | 0 | 0 | 0 |
| - Visceral[†] | • | • | • | • |
| - Skeletal[†] | • | • | • | • |
| **Incidence of variations** per litter | • | • | • | • |
| **Maternal toxicity** | | | | |
| NOAEL & LOAEL maternal toxicity | • | • | • | • |
| Body weight, initial-final, *g* (%vs cntrl): | 2000-2050 | 1990-2140 (-) | 2060-1960 (↓5% | 2000-1860 (↓10% |
| - prior to dosing | 2020 (g.day 6) | 2010 (-) | 2030 (-) | 2010 (-) |
| - during dosing: | 2010 (g.day 18) | 1980 (-) | 1900 (↓5% | 1690 (↓15% |
| - post-dosing | 2050 (g.day 27) | 2140 (-) | 1960 (↓5% | 1860 (↓10% |
| Weight gain, % (% change vs cntrl) | 2.2% | -0.2% (↓) | -4.8% (↓) | -7.8% (↓) |
| Pregnancy-adjusted weight (yes/no) | no | no | no | no |
| Food consumption, *g/day* (% vs cntrl) | | | | |
| - prior to dosing: | 85 (g.d. 0-5) | 82 (-) | 70 (-) | 90 (-) |
| - during dosing: | 64 (g.d. 6-18) | 69 (-) | 31 (↓50%) | 7 (↓90%) |
| - post-dosing | 47 (g.d. 19-27) | 69 (-) | 53 (-) | 49 (-) |
| Clinical signs | (-) | (-) | (-) | anorexia |
| Endpoints above attributable to the pharmacological effect of compound? | | | yes | yes |
| Maternal mortality | 0 | 0 | 0 | 0 |
| Necropsy findings | 1/5 | 1/5 (unrelated to treatment) | 0 | 3/5 (unrelated to treatment) |

[1] Effect to be presented as relative to control values; [2] Pre-implantation lethality (%) = [(*n* C.L–*n* impl.)/ *n* C.L.}x100;
[3] Post-implantation lethality (%) = (*n* Dead+Resorbed (aborted)/*n* implants)x100; [4] N live / N total fetuses per litter;
[†] Describe specific malformations which are increased over their control rates

Key: (– ) no change; • no observation; (+ ) statistically significant change or trend($p<0.05$); (± )statistically non-significant change;↑ increase; ↓decrease;

| | | | | | ***Table 4.5 (continued)*** |
|---|---|---|---|---|---|
| FLUOXETINE | REFERENCE. *A PreliminaryTeratology Study on Fluoxetine (Lilly Compound 110140) in the Rabbit. Lilly Research Laboratories Study B-7017, IND Toxicology Report No. 9 /**1979** by J. S. Wold & J. K. Markham* | | | | |
| **Summary** | **NOAEL** | | **LOAEL** | | **Most sensitive endpoint** (Limiting parameter) |
| | Female | Male | Female | Male | |
| **General Toxicity** | N.A. | N.A. | N.A. | N.A. | |
| **Reproductive Toxicity** incl: | | | | | |
| **- Fertility** | N.A. | N.A. | N.A. | N.A. | |
| **- Prenatal Developmental Toxicity** | x | | x | | ↑ ***postimplantation lethality*** *(abortions and resorptions);* |
| **- Postnatal Development.Toxicity** | N.A. | | N.A. | | |
| **- Maternal toxicity** during gestation | x | | x | | ***Depressed food consumption, ↓body weight & wt gain*** |

N.A.= not applicable; x = not known (N animals per group is insufficient to determine LOAEL and NOAEL)

| | |
|---|---|
| **Conclusion** | Fluoxetine hydrochloride oral treatment of pregnant Dutch Belted rabbits during organogenesis (g.day 6 through 18) by 2.5, 7.5 and 15 mg/kg/day causes a marked dose-dependent depression in maternal food consumption and body wt loss during the dosing period at the intermediate and high dose levels. Increased embryonic and fetal loss (resorptions and late abortions) found in all exposed groups, including that not showing maternal effects (2.5 mg/kg/day) in a dose-dependent manner. No malformations (at gross examination). N animals per group is insufficient to determine LOAEL and NOAEL |
| **Confounding factors and other comments** | Insufficient number of animals to determine LOAEL and NOAEL<br>Embryofetal loss in the control group "uncommonly low" for the species (authors' comment) |
| **Evaluation*** | A preliminary, dose-finding study to assess developmental toxicity of fluoxetine in a second (non-rodent) species. Reliability limited by the small number of animals per group. |
| *Criteria:* | |
| *Adequacy of experimental model* | Yes |
| *Adequacy of dose and route of adm.* | Yes |
| *Adequacy of timing &duration of exposure* | Yes |
| *Sufficient n animals per group* | No (this is a preliminary study) |
| *Presence of dose/effect or dose/response relationship* | Yes |
| *Appropriate statistical analysis* | No (Insufficient n of animals) |
| *Concordance with pharmacokinetic/ pharmacodynamic properties of agent* | yes |
| *Data consistent with other studies* | yes |
| **Study reliable** (yes/no) | Yes, with limitations |

*(with regard to reliability of extrapolating study data to humans)

| | |
|---|---|
| **Note for the database:** | Mean group values for the reproduction data are not given in the original report . In this summary, they are calculated on the basis of the individual data provided in the report. For the database, the mean group values are preferable. |

## *SUMMARY OF ANIMAL DEVELOPMENTAL TOX. STUDIES (Prenatal Component)*

CHEMICAL: **FLUOXETINE** — ***Table 4.6***

REFERENCE: *A Teratology Study on Fluoxetine (Lilly Compound 110140) in the Rabbit. Lilly Research Laboratories Study B-7087, IND ____ Toxicology Report No. 10 /**1979** by J. S. Wold & J. K. Markham*

| | | | | |
|---|---|---|---|---|
| **Species, strain** | Rabbit, Dutch Belted | | | |
| **Exposure – compound and doses** | Fluoxetine Hydrochloride, purity 96% (aqueous solution);0, 2.5, 7.5, 15 *mg/kg/d* | | | |
| **Exposure timing and duration** | Gest. days 6-18 | | | |
| **Route of administration** | Oral (gavage) | | | |
| **Gestation day of sacrifice** | Gest. day 28 | | | |
| **Dose – Response** (yes/no) | yes | | | |
| *Dose Levels (mg/kg/day)→* | **0 (Control)** | **2.5** | **7.5** | **15** |
| **N animals per group** | 15 | 15 | 15 | 15 |
| **N pregnant dams/litters per group** | 15/15 | 14/14 | 14/14 | 13/8 |
| **NOAEL and LOAEL prenatal dvlpm.** | | | NOAEL | LOAEL |
| **Pre-implantation lethality**[2] per dam | 12.3% | 15.9% (-) | 9.7% (-) | 12% (-) |
| N implants/ N Corp. lutea,% change vs cnt | 7.8/ 8.9 | 7.4/ 8.8 (-) | 8.4/9.3 (-) | 8/9.1 (-) |
| **Post-implantation lethality**[3] per litter | 9.3% | 8.1% (-) | 7.1% (-) | 51%(↑) |
| - Dead + aborted (mean per litter) | 0 | 0 (-) | 0 (-) | 2.9 (↑) |
| - Resorbed (mean per litter) | 0.8 | 0.6 (-) | 0.6 (-) | 1.2 (↑) |
| Early:Late Resorptions ratio | 12:1 | 8:1 | 4:5 | 13:11 (incl.abortions) |
| Females affected of total, % | 33% (5/15) | 29% (4/14) | 43% (6/14) | 54%(7/13) |
| N litters completely resorbed(aborted)/total | 0/15 | 0/14 | 0/14 | 3/11 |
| **N live fetuses** per litter | 7.0 | 8.8 (-) | 8.8 (-) | 4.7 (↓ 33%) |
| **Fetal viability** (gestat.survival index)[4] | 100% | 100%(-) | 100%(-) | 84% (↓) (52/62) |
| **Sex ratio** (proportion males) | 58% | 53% (-) | 61% (-) | 38% (↓)**(+)** |
| **Fetal weight** per litter, *g*<br>% change vs control | 33.1 | 32.3<br>(-) | 31.1(↓ 6%)<br>(±) | 30.0 (↓ 9%)<br>(±) |
| **Sex-differentiated fetal weight** | • | • | • | • |
| **Incidence of malformations** per litter | 0% | 1% (1/94) | 0% | 0% |
| **Malformations by type**[†] (rate & descript.) | | | | |
| - External[†] | 0 | 0 | 0 | 0 |
| - Visceral[†] | 0 | 1% omphalocele | 0 | 0 |
| - Skeletal[†] | 0 | 1% bipartite stern | 0 | 0 |
| **Incidence of variations** per litter | 4.8% (5/105) | 13% (12/94) | 13% (14/108) | 17.3% (9/52) (↑) |
| Type of variations | 13 ribs | 13 ribs | 13 ribs | 13 ribs;wavy ribs |
| **Maternal toxicity** | | | | |
| NOAEL & LOAEL maternal toxicity | | | NOAEL | LOAEL |
| Body weight, initial-final, *g* (%vs cntrl):<br>- prior to dosing<br>- during dosing<br>- post dosing | 3180 - 3270<br>3170 (g.d. 6)<br>3200 (g.d. 18)<br>3270 (g.d. 27) | 3180 - 3170 (-)<br>3180 (-)<br>3120 (-)<br>3170 (-) | 3170 - 3210 (-)<br>3170 (-)<br>3030 (↓5%)<br>3210 (-) | 3210-3040 (↓7%<br>3230 (-)<br>2840 (↓11%)<br>3040 (↓7%) |
| Weight gain, % (% change vs cntrl) | +2.8 % | -0.4% ↓(±) | +1.2% ↓(±) | -8.1% ↓ **(+)** |
| Pregnancy-adjusted weight (yes/no) | no | no | no | no |
| Food consumption, *g/day* (% vs cntrl)<br>- prior to dosing:<br>- during dosing.<br>- post dosing | <br>126 (g.d. 0-5)<br>117 (g.d. 6-18)<br>94 (g.d. 19-27) | <br>117 (-)<br>87 (↓25%)<br>94 (-) | <br>114 (-)<br>50 (↓57%)<br>112 (-) | <br>120 (-)<br>14 (↓88%)<br>62 (↓34%) |
| Clinical signs | (-) | (-) | (-) | Anorexia, diarrhea |
| Endpoints above attributable to pharmacological effect of the compound? | | yes | yes | Partially |
| Maternal mortality | 0 | 0 | 0 | 15% (2/13) |
| Necropsy findings | | | | Acute pneumonia, fatty liver |

[1] Effect to be presented as relative to control values; [2] Pre-implantation lethality (%) = [(*n* C.L–*n* impl.)/ *n* C.L.]x100;
[3] Post-implantation lethality (%) = (*n* Dead+Resorbed (aborted)/*n* implants)x100; [4] N live / N total fetuses per litter;
[†] Describe specific malformations which are increased over their control rates
Key: (– ) no change, • no observation; (+ ) statistically significant change or trend(p<0.05); (± )statistically non-significant change;↑ increase; ↓decrease;

| | | | | | |
|---|---|---|---|---|---|
| | | | | | ***Table 4.6 (continued)*** |
| FLUOXETINE | REFERENCE: *A Teratology Study on Fluoxetine (Lilly Compound 110140) in the Rabbit. Lilly Research Laboratories Study B-7087, IND —— Toxicology Report No. 10 /**1979** by J. S. Wold & J. K. Markham* | | | | |
| **Summary** | **NOAEL** | | **LOAEL** | | **Most sensitive endpoint** (Limiting parameter) |
| | Female | Male | Female | Male | |
| **General Toxicity** | N.A. | N.A. | N.A. | N.A. | |
| **Reproductive Toxicity** incl: | | | | | |
| **- Fertility** | N.A. | N.A. | N.A. | N.A. | |
| **- Prenatal Developmental Toxicity** | **7.5** mg/kg/day | | **12.5** mg/kg/day | | ↑ ***postimplantation lethality*** *(abortions and late resorptions);* ***↓litter size, live fetuses*** *↑incidence of skeletal variations (n.s)* *↓fetal weight (n.s)* |
| **- Postnatal Development.Toxicity** | N.A. | | N.A. | | |
| **- Maternal toxicity** during gestation | **7.5** mg/kg/day | | **12.5** mg/kg/day | | ***↓food consumption*** ***↓body wt and body wt gain during the dosing period*** |

N.A.= not applicable; n.s. = non-significant

| | |
|---|---|
| **Conclusion** | F hydrochloride oral(gavage) treatment of rabbits during g.days 6-18 at 2.5, 7.5 & 15 mg/kg/day induces maternal & embryofetal toxicity at the highest dose level: ↑maternal mortality,↑abortions &late resorptions, ↑rate of skeletal variations(n s.), ↓fetal weight (n.s.). Adverse embryofetal effects are present only at maternally toxic dose level (*no selective embryo/fetotoxicity*). **LOAEL** prenatal and maternal toxicity:**15** mg/kg/day (the considerable reduction of maternal food intake at 7.5 mg/kg/day is not a sign of toxicity since it is not accompanied by wt loss and is related to the pharmacological action of the agent). **NOAEL** 7.5 mg/kg/day. |
| **Confounding factors and other comments** | ***A.*** Over 20% of the pregnant females (3 of 13) at the highest dose (15 mg/kg/day) aborted (and were sacrificed shortly before term), but were not taken into account by the authors in determining the average group values of the prenatal endpoints. No abortions were induced by the lower dose levels.Thus, the embryofetal loss at the highest dose level was underestimated and the dose-effect relationship with respect to this endpoint was confounded. The dead fetuses were not taken into account in determining the gestation survival index at the same dose level. In the present summary however, the females that aborted and the aborted fetuses were included in determining the average group values for the enpoints at the highest dose level. ***B.*** There was one case of maternal mortality at the intermediate dose (7.5 mg/kg/day) due to improper handling (injection of fluid into trachea) and not to a treatment-related effect (not included in this summary). ***C.*** The significantly lower proportion of male fetuses at the highest dose is probably a random no-drug-related effect (no dose-dependence) but it may be the reason for the lower mean fetal wt in this dose group. |
| **Evaluation*** *Criteria:* | Study reliable after taking into account the confounding factors (see above) and the Note for database (below) |
| *Adequacy of experimental model* | Yes |
| *Adequacy of dose and route of adm.* | Yes |
| *Adequacy of timing &duration of exposure* | Yes |
| *Sufficient n animals per group* | Yes |
| *Presence of dose/effect or dose/response relationship* | Yes |
| *Appropriate statistical analysis* | Yes, but the spontaneous abortions at the highest dose gr are not taken into acct. |
| *Concordance with pharmacokinetic/ pharmacodynamic properties of agent* | Yes |
| *Data consistent with other studies* | Yes |
| **Study reliable** (yes/no) | Yes |

*(with regard to reliability of extrapolating study data to humans)

| | ***Table 4.6 (continued)*** |
|---|---|
| FLUOXETINE | REFERENCE: *A Teratology Study on Fluoxetine (Lilly Compound 110140) in the Rabbit. Lilly Research Laboratories Study B-7087, IND ~~~ Toxicology Report No. 10 /**1979** by J S. Wold & J. K. Markham* |
| **Note for the database**: | **(a).**The authors' original summary tables should not be used when entering embryofetal data pertaining to the highest dose level (15 mg/kg/day) – for explanation, see "confounding factors" above. The present summary can be used as a source of data for this dose group. **(b).** At the intermediate dose level (7.5 mg/kg/day), there was 1 maternal death only (due to improper handling) which is not included in this summary – it should not be entered in the database (as maternal mortality) because this maternal death had no relation to the exposure. |

***FLUOXETINE***

## *TABLES*

| ***Table 1. EVALUATION OF HUMAN STUDIES*** *(surveys and epidemiological studies)* | | | | |
|---|---|---|---|---|
| **A.Abstracted data** | *Goldstein et al, 1995* | *Goldstein, Marvel, 1993* | *Chambers et al, 1996 (as cited by Johnson, 1997)* | *Pastuszak et al, 1993 Koren et al, 94 (same st)* |
| Type of study | Descriptive prospective case survey (uncontrolled) | Descriptive prospective case survey (uncontrolled) | Analytical epidemiological prospective cohort study | Analytical epidemiological prospective cohort study |
| N subjects studied | 112 deliveries (115 babies) | 544 deliveries | 228 vs 254 controls | 128 vs 2 controls per case |
| Dose | Range: 10 - 80 mg/day | N.D. | Mean: 25 or 28 mg/day | Mean:25.8 mg/day |
| Time of gest. exposure | 3rd trimester to delivery | N.D. | Before 25 gest.wk ("early") | 1st trimester |
| Duration of dosing | As above | N.D. | or contin.after 25 wk ("late" | during 1st trimester only |
| Effects on offspring: | | | | |
| - *Abortions* | N.D. | | | |
| Spontaneous | N.D. | 15.9% (?) | 10.5% vs 9.1% in contrl (-) | ↑ 14.8 vs 7.8% in ctrl (±) |
| Therapeutic & elective | N.D. | 16.7% (?) | 12 or 15% (?) | 8.6 vs 6.2% in ctrl (-) |
| - *Perinatal death* | N.D. | 0.4% (-) | N.D. | Not increased (-) |
| - *Altered birthweight* | N.D. | N.D. | ↓ after "late" exposure (+) | ↑ rate of wt>4 kg, ns (±) |
| - *Prematurity* | 2.7% (-) | N.D. | ↑ after "late" exposure (+) | 7% vs 8% in ctrl (-) |
| - *Congenital malformations* | | | | |
| Major | 3.5% (-) | 3.4% (-) | 5.5% vs 4% in ctrl (-) | 2% vs 1.8% (-) |
| Minor | N.D. | N.D. | ↑ in early exp.15 vs 6% (+) | ↑ (6% vs 1%, ns) (±) |
| - *Postnatal complications* | 13% (?) (irritability,sleepiness, hyperbilirubinemia) | N.D. | ↑ poor neonat. adaptation: (jitteriness, respiratory difficulties) (+) | ↑ neonat. complic.5 vs 1%: (resp.problems,sepsis& seizures,jaundice),ns (±) |
| - *Developmental delays* | N.D. | N.D. | N.D. | N.D. |
| - *Neurobehavioral deviations* | N.D. | N.D. | N.D. | N.D. |
| - *Effects on mother* | N.D. | N.D. | N.D. | N.D. |
| **B.Evaluation of study:** | | | | |
| *-Reliability of study design* | Limited | Limited | Good | Good |
| *-Adequate control group* | No (historical control) | No (historical control) | Yes (nonterat. drug users) | Yes, age-matched, treated with either nonterat.drugs or other antidepressants |
| *-Sufficient N of subjects* | No | Yes | Yes | No (limited power ) |
| *-Adequate assessment of:* | | | | |
| Exposure (dose,timing) | Yes | No | Yes | Yes |
| Outcome | Incomplete | Incomplete | Sufficient | Sufficient |

| | | | | |
|---|---|---|---|---|
| *-Dose/effect (response) rel.*<br>*-Stat.analysis of relation exposure / outcome*<br>*-Control of confounders*<br>Maternal age<br>Gravidity, parity<br>Previous advers.outcom.<br>Concurrent disease<br>Socioeconomic<br>Concomitant medication<br>Smoking, alcohol use<br>Occupation<br>Other | N.D.<br>No<br><br>Incomplete<br>Yes<br>Yes<br>N.D.<br>Yes<br>No<br>Yes<br>No<br>No | N.D.<br>No<br><br>Unknown (no information) | N.D.<br>Yes (regression analysis)<br><br>Yes<br>Yes<br>Yes<br>Yes<br>Yes<br>N.D.<br>Yes<br>Yes<br>N.D. | N.D.<br>Yes, appropriate<br><br>Yes<br>Yes<br>Yes<br>Yes<br>Yes<br>No<br>No<br>Yes<br>No |
| **CONCLUSION** | **Reliability limited:** Data based on voluntary reports (incomplete, biased); no control group; insufficient sample size for a descriptive study; incomplete control of potential confounders | **Reliability limited:** All comments to *Goldstein '95* apply to this study as well, except for n subjects. Incomplete source (a letter to the editor); | **Reliability good**, but: -Role of depressive illness as a confounder can not be excluded; -Maternal age is higher in F-exposed group; -Possible multiple drug confounding (30%of F-treated women were parallelly taking other psychoactive drugs) | **Reliability good:** Study design appropriate, "positive" control allows controlling for effect of depression; potential confounders taken into account. Criticism:statistical power insufficient, e.g. the sample size would have the power to detect a 4-fold increase in risk of major malform and a limited power to show that the elevated risk of miscarriage (RR=1.9) is significant. |

*Reliability of design: Good = controlled epidemiological study; Limited = uncontrolled survey; Poor = case report

Symbols used: (-) = no change in comparison to background, reference value or control
(+) = statistically significant change
(±) = trend or statistically non-significant change
(?) = unable to assess N.D.= no data

**Table 1. (continued)**

| **A.Abstracted data** | *Nulman et al., 1997* | *McElhatton et al., 1996* | *Shick-Boschetto et al, 1992* | *Brunel et al, 1994* |
|---|---|---|---|---|
| Type of study | Analytical epidemiological prospective cohort study | Teratol.inf.database(prospective case survey, uncontrolled) | Teratol.inf.database (prospective case surveys, uncontrolled) | |
| N subjects studied | 55 vs 2 contr.grps:(a)80 exp.to other antidepessants(b)84 to non-teratogens | 96 (30% of those had multidrug exposure besides fluoxetine) | 81 (for 21 of these, outcomes not available) | 17 |
| Dose | N.D.(presumably within the therapeutic range - 20-80 mg/day) | N.D. (presumably within the therapeut.range - 20-80 mg/day) | N.D. (therapeutic range?) | N.D. |
| Time of gest. exposure | 1st trimester (37 subjects), or throughout gest. (18 subjects) | "mostly" 1st trimester | 1st trimester | 1st trim. |
| Duration of dosing | As above | As above | As above | |
| Effects on offspring: | Stress on postnat.behavioral assesm. | | | |
| - *Abortions* | | | | |
| Spontaneous | ↑13.6% vs 9% in (a), ns (±) | 13% (?) | 15.8% (?) | 0 |
| Therapeutic & elective | ↑ 7.9% vs 1.5% in (a),ns (±) | 15% (?) | 3.5% (?) | 4 of 17 |
| - *Perinatal death* | (-) | 1% (-) | 0 (-) | 0 |
| - *Altered birthweight* | (-) | (-) | N.D. | N.D. |
| - *Prematurity* | (-) | 6% (-) | 3.5% (-) | 0 |
| - *Congenital malformations* | (-) | | | |
| Major | 3.6%vs 3.7 in(a)& 2.4 in(b) | 2% (-) | 0 (-) | 0 |
| Minor | (-) | 2% (-) | 3.5% (-) | 0 |
| - *Postnatal complications* | (-) | 3% (?) withdrawal symptoms, bradicardia, respirat. problems, periventricular bleeding | N.D. | 0 |
| - *Developmental delays* | (-),assessed at 6 to 9 mnth of age | N.D. | N.D. | N.D. |
| - *Neurobehavioral deviations* | (-)up to 7yrs of age (IQ, language dvlpmt,temperament,mood,arousability, distractability, activity) of offspring exposed either during 1st trimester or troughout gestation (after adjustment for confounders) | N.D. | N.D. | N.D. |
| - *Effects on mother* | N.D. | N.D. | 5% complications of pregn. | N.D. |
| **B.Evaluation of study:** | | | | |
| *-Reliability of study design* | Good | Limited | Limited | Poor |
| *-Adequate control group* | Yes, 2 types of ctrl | No (no control group) | No (no control group) | No |

| | | | | |
|---|---|---|---|---|
| *-Sufficient N of subjects* | No (particularly of those treated throughout gestation) | No (not sufficient for a descriptive uncontrolled survey) | No | No |
| *-Adequate assessment of:* | | | | |
| Exposure (dose,timing) | Dose not shown | No (Dose not reported) | No (Dose not reported) | N.D. |
| Outcome | Yes | Yes | (?) (only abstract available) | (?) |
| *-Dose/effect (response) rel.* | N.D. | N.D. | N.D. | N.D. |
| *-Stat.analysis of relation exposure / outcome* | Yes (multiple regression) | No | No | No |
| *-Control of confounders* | Yes, comprehensive | Some confounders registered but not taken into account | No | No |
| Maternal age | Yes | Yes | | |
| Gravidity, parity | Yes | Yes | | |
| Previous advers.outcom. | Yes | Yes | | |
| Concurrent disease | Yes | Yes | | |
| Socioeconomic | Yes | N.D. | | |
| Concomitant medication | Yes | Yes | | |
| Smoking, alcohol use | Yes | N.D. | | |
| Occupation | N.D. | N.D. | | |
| Other | Yes, several additional | No | | |
| **CONCLUSION** | **Reliability good:** Appropriate study design;wide spectrum of potential confounders taken into acct. Comprehensive assessment of neurobehavioral devlpmnt with controlling for appropriate confounders, incl.maternal IQ,depression level,maternal/infant interactions &time of exposure. Adequate stat. analysis. Criticism: Dose not indicated; The small number of subjects (particularly of those treated throughout gestation) does not allow definite conclusion about effect of "late" gestational exp. | **Reliability limited:** No control; Multidrug exposure in about 30% of cases; Dose, time and duration of exposure not well specified; confounding variables not taken into account: No stat. analysis of relation between exposure and effect. | **Reliability limited:** (see comments on McElhatton et al, 96); incomplete source of information (abstract only) | **Poor:** N of subjects absolutel y insuff. for meaning ful conclusi ons |

*Reliability of design: Good = controlled epidemiological study; Limited = uncontrolled survey; Poor = case report

Symbols used: (-) = no change in comparison to background, reference value or control; (+) = statistically significant change; (±) = trend or statistically non-significant change; (?) = unable to assess; N.D.= no data

| Table 1-a. EVALUATION OF HUMAN STUDIES (case reports) | | | |
|---|---|---|---|
| **A.Abstracted data** | *Mhanna et al,1997 (a letter to the editor)* | *Spencer, 1993* | *Venditelli et al, 1995* |
| Type of study | Case report | Case report | Case report |
| N subjects studied | 1 | 1 | 1 |
| Dose | 60 mg/day | 20 mg/day | 'one tablet' (20 mg?) a day, simultan. with other drugs (benzodiazepine, vitamins B1,B6 and heptaminol) |
| Time of gest. exposure | N.D. | 1st trimester to birth | First 2 months |
| Duration of dosing | N.D. | 'most of pregnancy' | 2 months |
| Effects on offspring: | | | |
| - *Spontaneous abortion* | No | no | no |
| - *Perinatal death* | No | no | no |
| - *Altered birthweight* | No | no | no |
| - *Prematurity* | No | no | no |
| - *Congenital malformations* | | | |
| Major | No | no | Yes, meningocele |
| Minor | No | no | no |
| - *Postnatal complications* | Yes: jitteriness,hypertonia,scattered petechiae (skin of face and trunk), cephalohematoma. Improvement in 2 weeks post partum | Yes: jitteriness,hypertonia, impending seizures, acrocyanosis, irritability, tremor. Improvement in 4 days post partum. | N.D. |
| - *Developmental delays* | N.D. | N.D. | N.D. |
| - *Neurobehav. deviations* | N.D. | N.D. | N.D. |
| - *Effects on mother* | N.D. | N.D. | No |
| **B.Evaluation of study:** | | | |
| -*Reliability of study design* | Poor | Poor | Poor |
| -*Adequate control group* | N.A. | N.A. | N.A. |
| -*Sufficient N of subjects* | N.A. | N.A. | N.A. |
| -*Adequate assessment of:* | | | |
| Exposure (dose,timing) | Yes (in addition, maternal and baby serum levels of fluoxetine and its major metabolite are measured) | Yes ((in addition, maternal and baby cord blood levels of fluoxetine and its major metabolite are measured and screen for other psychoactive drugs performed in maternal & infant urine) | No: Confounding by multiple exposure to other drugs in doses higher than F |

| *Table 1-a. (continued)* | | | |
|---|---|---|---|
| Outcome | Yes | Yes | Yes |
| *-Dose/effect (response) rel.* | N.A. | N.A. | N.A. |
| *-Stat.analysis* | N.A. | N.A. | N.A. |
| *-Control of confounders* | Partial | Yes, but incomplete | Yes, but incomplete |
| Maternal age | yes | yes | yes |
| Gravidity, parity | no | yes | yes |
| Previous advers.outcom. | no | yes | yes |
| Concurrent disease | no | yes | no |
| Socioeconomic | no | no | no |
| Concomitant medication | yes | yes | yes |
| Smoking, alcohol use | no | no | yes |
| Occupation | no | no | no |
| Other | | | |
| *-Consistency of resultswith those from other studies:* | | | |
| Human | *Spencer,'93; Chambers et al, '96)* | Yes | No |
| Animal | *Stanford&Patton '93* | Yes | No |
| *-Plausibility of results in view of pharmacokinetics & pharmacodynamics* | Yes: in agreement with fluoxetine (F) pharmacodynamics (excitability, eff.on muscle tone, eff. on platelets and vessels) and kinetics (time of improvement consistent with F and its major metabolite's half-life) | Yes | No |
| **CONCLUSION** | **Data reliable:** Good assessment of exposure and outcome; consistency with lit.data of postnatal clinical manifestations of F overdose and with pharmacokinetic and -dynamic properties of F | **Data reliable:** Good assessment of exposure and outcome, relevant lab.analysis for excluding exposure to other drugs; symptoms consistent with most common side effects of F in adults, and their disappearance con-<br>cordant with F decrease in cord blood. | **Data unreliable:** A confounding multidrug exposure during pregnancy simultaneously with F; F dose not specified; data inconsistent with other human or animal studies |

*Reliability of design: Good = controlled epidemiological study; Limited = uncontrolled survey; Poor = case report

Symbols used: (-) = no change in comparison to background, reference value or control; (+) = statistically significant change; (±) = trend or statistically non-significant change; (?) = unable to assess; N.D.= no data; N.A.= not applicable; F= fluoxetine

## Table 2. EVALUATION OF HUMAN STUDIES: SUMMARY

| | Surveys and epidemiological studies | | | | | | | | Case reports | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Goldstein, Marvel, '93* | *Goldstein et al, '95* | *Chambers et al,'96* | *Pastuszak et al,'93* | *Nulman et al, '97* | *McElhatton et al, '96* | *Shick-Bos-chetto, '92* | *Brunel et al, 94* | *Spencer, '93* | *Venditelli et al, '95* | *Mhanna et al, '97* |
| Dose *(mg/day)* | N.D. | 10-80 | 25 (mean) | 25 (mean) | N.D. | N.D. | N.D. | N.D. | 20 | '1 tablet' (?) | 60 |
| Time of exposure | N D. | 3rd trimester to delivery | 'Early' : < 25 wk gest. 'Late":> 25 wk gest | 1st trimester only | 67% - 1st trimester 33%- entire gestation | 1st trimester 'most' | 1st trimester | 1st trimester | Entire gestation | first 2 months of gestation | N D. |
| Spontaneous abortions | 15.9%(?) | N.D. | 10.5% (-) | 15%↑ (±) | 14%↑ (±) | 13% (?) | 15.8%(?) | (-) | N.A. | N.A. | N.A. |
| Perinat.death | (-) | N.D. | N.D. | (-) | (-) | (-) | (-) | (-) | N.A. | N.A. | N.A. |
| Altered birth weight | N.D. | N.D. | ↓ (+) 'late'exp. | ↑ (±) | (-) | (-) | N.D. | N.D. | (-) | (-) | (-) |
| Prematurity | N.D. | (-) | ↑ (+) 'late' exp. | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) |
| Malformations : | | | | | | | | | | | |
| - major | 3.4%(-) | 3.5%(-) | 5.5% (-) | 2% (-) | 3.6% (-) | 2% (-) | 0 (-) | 0(-) | (-) | (+) meningocel | (-) |
| - minor | N.D. | N.D. | 15%↑(+) 'early' exp. | 6%↑ (±) | (-) | 2% (-) | 3.5%(-) | 0(-) | (-) | (-) | (-) |
| Postnatal complications | N.D. | 13% (?) irritability, sleepiness, jaundice | ↑ (+) jitteriness, respiratory problems | 5%↑ (±) resp.probl, seizures, jaundice | (-) | 3% (?) withdrawal sympt,resp. probl,peri-ventricular bleeding | N.D. | N.D. | jitteriness, hypertonia, tremor, impending seizures, cyanosis | N.D. | jitteriness, hypertonia, petechiae, cephal-hematoma |
| Development. delays | N.D. | N.D. | N.D. | N.D. | (-) | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. |
| Neurobehav. deviations | N.D. | N.D. | N.D. | N.D. | (-) | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. |
| **Reliability of study** | **Limited** (no control) | **Limited** (no control) | **Good** | **Good** | **Good** | **Limited** (no control) | **Limited** (no control) | **Poor** (sample size small) | **Good** | **Poor** (multidrug exposure) | **Good** |

Symbols used: (-) = no change in comparison to background, reference value or control; (+) = statistically significant change; (±) = trend or statistically non-significant change; (?) = unable to assess; N.D.= no data; N.A.= not applicable; F= fluoxetine

**Table 3. EVALUATION OF ADVERSE OUTCOMES IN HUMANS:** *LIKELIHOOD OF CAUSAL RELATION TO FLUOXETINE GESTATIONAL EXPOSURE*

| *Outcomes* | *Observed effect* | *Criteria for causation* (according to Hill, 1965)* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Reliability of the source(s) of data* | *Strength of evidence* | *Consistency of evidence* | *Specificity of effect* | *Temporality of effect* | *Dose-responce* | *Plausibility of effect (or lack of effect)* | *Coherence with existing knowledge* |
| Spontaneous abortion | *Rate: 13-16% Increase (?)* | (+) | (-) | (+) 5 of 6 studies | (-) | (+) | N.D. | (?) | N.D. |
| Perinatal death | *No effect* | (+) | (+) | (+) 5 of 5 studies | (-) | (+) | N.D. | (+) | (+) |
| Altered birthweight: | *a. ↓ by F exp. after 25 g.wk* | (+) | (+) | (-) 1 of 7 studies | (+) | (+) | N.D. | (+) | (+) |
| | *b. ↑ by F exp. in 1st trimest.* | (+) | (-) | (-) 1 of 7 studies | (-) | (+) | N.D. | (-) | (-) |
| Prematurity | *↑ by F exp. after 25 g.wk* | (+) | (+) | (-) 1 of 9 studies | (-) | (+) | N.D. | (-) | (-) |
| Congenital malformations: | | | | | | | | | |
| - Major | *No effect* | (+) | (+) | (+) 7 of 7 studies | (-) | (+) | N.D. | (+) | (+) |
| - Minor | *Increase (?)* | (+) | (-) | (-) 2 of 5 studies | (-) (No pattern) | (+) | N.D. | (?) | (-) |
| Postnatal complications | *Increased* | (+) | (+) | (+) 6 of 7 studies | (+) | (+) | N.D. | (+) | (+) |
| Developmental delays | *No effect (?)* | (+) | (+) | N.A. 1 study only | N.A. | (+) | N.D. | (+) | (+) |
| Neurobehavioral effects | *No effect (?)* | (+) | (+) | N.A. 1 study only | N.A. | (+) | N.D. | (-) | (±) |

***Description of criteria:**

*-Reliability of data sources:*(+)= good (at least one controlled epidemiological study); (±)=limited (lack of controlled epidemiological studies); (-)= poor (data source unreliable)
*-Strength of evidence:* (+)= statistically significant; (-)= statistically non-significant
*-Consistency of evidence:* N studies confirming a particular effect /N available studies on that effect. (+)= data consistent; (-) = inconsistent
*-Specificity of effect:* (+)= the observed effect is specific for fluoxetine; (-)= the observed effect is not specific for the agent
*-Temporality of effect:* (+)= the study design ensures that the exposure has taken place prior to outcome
*-Plausibility of effect:* (+)= the effect is plausible having in mind the structure, pharmacodynamics and pharmacokinetics of the agent
*-Coherence with existing knowledge:* (+)= the effect is in accordance with existing knowledge

**Symbols used:** (+)= criterion met; (-)= criterion unmet; (±)= criterion partially met; (?)= unable to assess; N.D.=no data; N.A.= not applicable; F= fluoxeti

## Table 5. COMPARATIVE SUMMARIES AND EVALUATION OF ANIMAL STUDIES

### 5.1. Fertility

Drug name: **FLUOXETINE**

| **FERTILITY** COMPONENT | *A Fertility Study on Fluoxetine Hydrochloride in the Female Rat.. Lilly Research Laboratories Study No RO 7179 /**1980** by J. Wold , N. Owen & E. Adams* | | *A Fertility Study, Incl. Behav.& Reprod. Assessm of $F_1$ Generation, in the Wistar Rat Given Fluox.Hydrochloride in the Diet. Lilly Res. Labs Study R10280 & RO4781/**1982**, G.Brophy, N Owen & J.Hoyt* | |
|---|---|---|---|---|
| **Species, strain** | Rat, Wistar | | Rat, Wistar | |
| **Exposure doses, timing & duration**<br>- **Males**<br>- **Females** | Fluoxetine Hydrochloride, purity 96% (aqueous solution)<br>**0**<br>**0; 2; 5; 12.5** mg/kg/day, 2 wks before mating+gest.+lactation | | Fluoxetine Hydrochloride, purity 96% (aqueous solution)<br>**0; 1.5; 3.9; 9.7**mg/kg/day, 10 wks before mating + breeding<br>**0; 1.3; 3.1; 7.4** mg/kg/d, 3 wks before mating+gest.+lactation | |
| **Route of administration** | Oral (gavage) | | Oral (diet) | |
| **Dose – Response** (yes/no) | yes | | yes | |
| **Effects**[1] (relative to control values): | | | | |
| ***$F_0$ Generation*** | **M** | **F** | **M** | **F** |
| N animals per group | 0 | 30 | 40 | 40 |
| ***General Toxicity*** | N.A. | | | |
| *NOAEL / LOAEL* | | **5 / 12.5** mg/kg/day | **3.9 / 9.7** mg/kg/day | **3.1 / 7.4** mg/kg/day |
| *Body weight* (% change, period) | | ↓10%(±) at 12.5 mg/kg/d | **↓5%(+)** at 9.7 mg/kg/d | **↓8%(+)** at 7.4 mg/kg/d |
| *Weight gain* (%change, period) | | **↓66%(+)** at 12.5 mg/kg/d | **↓5%(+)** at 9.7 mg/kg/d | **↓60%(+)** at 7.4 mg/kg/d |
| *Organ weight** | | • | • | • |
| *Food consumption (period)* | | ↓12-25%(±) at 12.5 mg/kg/d | (-) | **↓19%(+)** at 7.4 mg/kg/d |
| *Clinical signs* | | (-) | (-) | (-) |
| *Histopathology/gross necropsy findngs* | | (-) | (-) | (-) |
| Effects listed above attributable to pharmacological effect of compound? | | Yes | Yes | Yes |
| *Mortality* | | (-) | (-) | (-) |
| ***Fertility Parameters*** | N.A. | | | |
| *NOAEL / LOAEL* | | **12.5 / >12.5** mg/kg/day | **9.7 / >9.7** mg/kg/day | **7.4 / > 7.4** mg/kg/day |
| *Reproductive organs (wt*, morphology)* | | • | • | • |
| *Effect on gametes* (+description) | | • | • | • |
| *Hormonal effects (&estrous cycle length)* | | • | • | • |
| *Fertility index* (% pregnant of mated) | (-) | | ↓ ~10% (±) at the intermediate & highest dose | |
| *Pre-implantation lethality*[2] per dam | (-) | | ↑ 2-fold at all dose levels | |
| *N implants/ N Corpora lutea* | Corpora Lutea↓10% at 5 mg/kg/d & ↓20%(± ) at12.5mg/kg/d | | Implantations ↓ 14% (±) at the lowest & highest dose | |
| *Post-implantation lethality*[3] per litter | ↑ by 33% (± ) at 12.5mg/kg/d | | (-) | |
| *Litter size* (N live fetuses per litter) | ↓16% (± ) at 12.5 mg/kg/d | | ↓10%(± ) at the lowest & highest dose | |

[1] Effect presented as relative to control values. Key: (– ) no change; • no observation; (+ ) statistically significant change or trend($p<0.05$); (± )statistically non-significant change;↑ increase; ↓decrease; M male; F female; * adjusted for body weight; N.A.=not applicable

[2]Pre-implantation lethality (%) = [(*n* C.L–*n* impl.)/ *n* C.L.]x100; [3] Post-implantation lethality (%) = (*n* Dead+Resorbed (aborted)/*n* implants)x100

| 5.1. Fertility (continued) | | |
|---|---|---|
| **FLUOXETINE** | | |
| **FERTILITY** COMPONENT | *A Fertility Study on Fluoxetine Hydrochloride in the Female Rat.. Lilly Research Laboratories Study No RO 7179 /**1980** by J. Wold , N. Owen & E. Adams* | *A Fertility Study, Incl. Behav.& Reprod. Assessm.of $F_1$ Generation, in the Wistar Rat Given Fluox.Hydrochloride in the Diet. Lilly Res. Labs Study R10280 & RO4781/**1982**, G.Brophy, N.Owen & J.Hoyt* |
| **Conclusion & affected endpoints** | Fluoxetine hydrochloride oral dosing (gavage) of female Wistar rats 2 wks prior to mating and during gestation and lactation, at 2, 5, and 12.5 mg/kg/day results in no significant effect on female fertility, even at doses that produce significant general effects.<br>•*General tox. endpoints*<br>-Reduction of female *food consumption* (n.s)<br>**-Decrease in *female weight gain*** (st.significant )during 2nd week of dosing in the premating period.<br>LOAEL: 12.5 mg/kg/day; NOAEL: 5 mg/kg/day<br>•*Fertility endpoints*<br>NOAEL: 12.5mg/kg/day<br>-↓*litter size* and n *corpora lutea* per dam at 12.5mg/kg/d (n.s* but dose-dependent) | Fluoxetine hydrochloride oral treatment (diet) of Wistar rats, at 1.5, 3.9 and 9.7mg/ kg/day for 10 wks (males) and 1.3, 3.1 and 7.4 mg/kg/day for 4 wks (females) prior to mating and during gestation and lactation, results in no stat.significant effect on fertility in a two-generation study, even at doses that produce significant general effects.<br>•*General tox. endpoints*<br>**-Reduced *food consumption, body wt & wt gain* in both sexes** (st.significant) during first weeks of treatment (more expressed in the females)<br>Females: LOAEL. 7.4 mg/kg/d; NOAEL: 3.1 mg/kg/day<br>Males : LOAEL: 9.7 mg/kg/d; NOAEL: 3.9 mg/kg/day<br>•*Fertility endpoints*<br>NOAEL: 7.4 mg/kg/d (Females); 9.7 mg/kg/d (Males)<br>-↑ *pre-implantation embryolethality* at NOAEL (ns* but dose-dependent)<br>-↓ *fertility index* at NOAEL (ns* but dose-dependent) |
| **Confounding factors & comments** | The general effects may be due to the well known apetite-suppressing pharmacologic action of fluoxetine and are not necessarily a sign of maternal toxicity. | -*Exposure:* Dose levels are approximates (time-weighted estimates of F intake through diet)<br>-*General toxicity measures: a)* Initial *wt* of $F_0$ males in highest dose group is significantly lower than control at the start (confounds exposure-induced weight decrease) *b)* weight loss and food consumption decrease may not be a sign of toxicity, as they are charasteristic of the pharmacological action of this drug.<br>**-Fertility: *The dose-dependent increase in pre-implantation lethality parallelled by a dose-dependent although non-significant decrease in fertility index are not taken into acct. in determining NOAEL for fertility.*** |
| **Evaluation** | Conclusions reliable and can be used for comparison with human studies | In general, study reliable but confounded mainly with regard to exposure quantitation due to dosing through diet. *Limitations*: Information on endpoints affected should be used for qualitative rather than quantitative comparisons. LOAEL and NOAEL levels determined in the study may not be sufficiently accurate. |

*n.s.= non-significant

## 5.2. Prenatal Developmental Toxicity

Effect presented as relative to control values.
Key: (- ) no change; • no observation; (+ ) statistically significant change or trend(p<0.05); (± )statistically non-significant change;↑ increase; ↓decrease

Drug Name: FLUOXETINE

| DEVELOPMENTAL TOXICITY- **PRENATAL** COMPONENT | *A Fertility Study on Fluox Hydrochloride in the Female Rat. Lilly Res Labs Study No RO 7179/1980 by J Wold, N Owen & E. Adams* | *A Fertility Study Incl Behav & Reprod Asses of F1 Gener, in Wistar Rat Given Fluox Hydrochloride in the Diet Lilly Res Labs Study R10280 &RO4781/82* | *A Preliminary Teratol Study on Fluoxetine in Rat Lilly Res Labs. Study No R-77, IND ~~~ Toxicol Report No7 / 1979 by J S Wold and J K Markham* | *A Teratology Study on Fluoxetine in the Rat Lilly Res Labs Study R-207, IND ~~~ Toxicol Report No 8 /1979 by J S Wold & J K. Markham* | *A Preliminary Teratol Study on Fluoxetine in the Rabbit, Lilly Res. Labs Study B7017, IND ~~~ Toxicol Report No 9 /1979, Wold & Markham* | *A Teratology Study on Fluoxetine in the Rabbit Lilly Res Labs Study B7087, IND ~~~ Toxicol Report No 10 /1979 by J S Wold & J K Markham* |
|---|---|---|---|---|---|---|
| **Species, strain** | Rat, Wistar | Rat, Wistar | Rat, Fischer 344 | Rat, Fischer 344 | Rabbit, Dutch Belt. | Rabbit, Dutch Belt. |
| **Prenat.exposure** (mg/kg/day) | Maternal: **0, 2, 5, 12.5** | Maternal: **1.3, 3.1, 7.4** Paternal: **1.5, 3.9, 9.7** | Maternal: **0, 10, 20, 40** | Maternal: **0, 2, 5, 12.5** | Maternal: **0, 2.5, 7.5, 15** | Maternal: **0, 2.5, 7.5, 15** |
| **Prenat. exposure– timing & duration** | 2 wks before mating + G.days 0-20 | Maternal: 3 wks before mating + G.d. 0-20 | G.days 6 - 15 | G.days 6 - 15 | G.days 6 - 18 | G.days 6 - 18 |
| **Route of administration** | Oral (gavage) | Oral (diet) | Oral (gavage) | Oral (gavage) | Oral (gavage) | Oral (gavage) |
| **Gestation day of sacrifice** | G.Day 20 | G.Day 20 | G.Day 20 | G.Day 20 | G.Day 28 | G.Day 28 |
| **Dose-response** (yes/no) | yes | yes | yes | yes | yes | yes |
| **N dams/litters per group** | 8÷10 / 8÷10 | 14÷17 / 14÷17 | 1÷5 / 1÷5 | 18÷25 / 17÷25 | 4÷5 / 4÷5 | 13÷15 / 8÷15 |
| **NOAEL prenatal development** | **12.5** mg/kg/day | **7.4** mg/kg/day | • | **12.5** mg/kg/day | • | **7.5** mg/kg/day |
| **LOAEL prenatal development** | **>12.5** mg/kg/day | **>7.4** mg/kg/day | • | **>12.5** mg/kg/day | • | **15** mg/kg/day |
| **Pre-implantation lethality**[2] per dam | (-) | ↑ 2-fold at all doses | N.A. | N.A. | N.A. | N.A. |
| N implants/ N Corpora lutea per dam | CL,I ↓20%(± ) at12.5 | I ↓~10%(± )all doses | (-) | I ↓10%(± )at 12.5 | (-) | (-) |
| **Post-implantation lethality**[3] /litter | ↑by 33%(±) at 12.5 | (-) | ↑5-23 fold at20& 40 | (-) | ↑17-27%,all doses | ↑ 5-fold at 15 mg/kg |
| - Dead (mean *n* per litter) | (-) | (-) | (-) | (-) | (-) | (-) |
| - Resorbed (aborted), mean *n* / litter | (-) | (-) | ↑10-50 fold at20& 40 | (-) | ↑, all doses | ↑ 5-fold at 15 mg/kg |
| Early:Late resorptions ratio | (-) | (-) | • | (-) | • | Late:Early ↑ 10-15 - fold at 15 and 7.5mg |
| Females affected of total, % | (-) | (-) | • | (-) | ↑, all doses | ↑ 10-21%at 7.5 & 15 |
| N litters completely resorbed/ N total | (-) | (-) | ↑30-75% at 20 & 40 | (-) | ↑40% at 15 | ↑27% at 15mg |
| **Litter size** (N live fetuses per litter) | ↓ by 16%(± ) at12.5 | ↓ by 10%(± ) at 7.4 | ↓ 45-92% at 20 & 40 | ↓ by 10%(± ) at 12.5 | ↓ by 40% at 15 | ↓ by 33% at 15mg |
| **Sex ratio** (proportion of males, % ) | (-) | (-) | • | ↑ by 25% (± ) at 12.5 | • | ↓ by 20% at15mg(+) |
| **Fetal weight** per litter | (-) | (-) | • | (-) | • | ↓ 6-9% at 7.5 & 15 |
| **Sex-differentiated fetal weight** | • | • | • | • | • | • |
| **Incidence of malformations** / litter | (-) | (-) | (-) | (-) | (-) | (-) |
| **Malformations by type**[†] (rate& descr) | | | | | | |
| - External[†] | (-) | (-) | (-) | (-) | (-) | (-) |
| - Visceral[†] | • | (-) | • | (-) | • | (-) |
| - Skeletal[†] | • | (-) | • | (-) | • | (-) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Incidence of variations**/ litter | • | (-) | • | (-) | • | ↑ 3-4-fold , all doses |
| - Visceral[†] | • | (-) | • | (-) | • | (-) |
| - Skeletal[†] | • | (-) | • | (-) | • | ↑ 3-4-fold , all doses |
| **Maternal toxicity** during gestation | | | • | | | |
| NOAEL maternal toxicity<br>LOAEL maternal toxicity | **12.5** mg/kg/day<br>**>12.5** mg/kg/day | **7.4** mg/kg/day<br>**>7.4** mg/kg/day | •<br>• | **5** mg/kg/day<br>**12.5** mg/kg/day | •<br>• | **7.5** mg/kg/day<br>**15** mg/kg/day |
| Body weight (%vs control): (period) | ↓10%(± ) at12.5 G.day 0-20 | ↓8-10%(+) at 7.4 G.day 0-20 | ↓15-30% at 20 & 40 G.day 6-14 | ↓9%(± ) at 12.5 G.day 6-14 | ↓5 -15% at7 5 & 15 G.day 18 | ↓5 -11% at 7.5 & 15 G.day 18 |
| %Weight gain during gestation (% change vs control) | (-) | (-) | ↓50% at 20<br>• at 40 | ↓5%(± ) at 12.5 | ↓7-10% at 7 5 & 15 | ↓10% at 15 mg (+) |
| Pregnancy-adjusted weight (yes/no) | no | no | no | no | no | no |
| Food consumption (indicate period) | ↓8-15%(± ) at5, 12.5 G.day 1-20 | ↓9%(± ) at 7.4 G.day 20 | ↓71-90% at 20 & 40 G.day 7-13 | ↓50% (+) at 12.5 G.day 7-13 | ↓50-90% at 7.5&15 G.day 6-18 | ↓25-88% at 2.5 -15 mg, G.day 6-18 |
| Clinical signs | (-) | (-) | Yes, at 20 & 40 | (-) | Yes, at 15mg/kg/d | Yes, at 15mg/kg/d |
| Necropsy findings | • | (-) | Yes, at 20 & 40 | • | (-) | Yes, at 15mg/kg/d |
| Endpoints above attributable to pharmacological effect of the compound? | yes | yes | no | yes | yes | partially |
| Maternal mortality | (-) | (-) | 50-100% at 20 & 40 | (-) | (-) | 15% at 15 mg/kg/d |

Key: (- ) no change; • no observation; (+ ) statistically significant change or trend($p<0.05$); (± )statistically non-significant change;↑ increase; ↓decrease

[2] Pre-implantation lethality (%) = [(*n* C.L–*n* impl.)/ *n* C.L.}x100; [3] Post-implantation lethality (%) = (*n* Dead+Resorbed (aborted)/*n* implants)x100; [4]N live / N total fetuses per litter;

[†] Abnormalities which are increased over their control rates ; NA=non-applicable (treatment started after implantation)

| | | | | | | |
|---|---|---|---|---|---|---|
| **Conclusion & affected endpoints** | No significant developmental or maternal effects at maternal oral doses of up to 12.5mg/kg/d (NOAEL) during pre-mating + gestation<br>•*Maternal endpoints:*<br>(12.5 mg/kg/day)<br>-↓ b.wt (n.s)<br>-↓ food cons. (n.s)<br>•*Developmental :*<br>(12.5 mg/kg/day)<br>-↓ c.l., implants, litter size (n.s)<br>-↑embryolethality (resorption rate) (n.s) | No parental toxicity or signif. developm. effects at maternal & paternal oral doses of up to respectively 7.4 & 9.7 mg/kg/day during pre-mating + gestation (NOAEL).<br>•*Maternal endpoints:*<br>(7.4 mg/kg/day)<br>-↓ b.wt (sign)<br>-↓ food cons. (n.s)<br>•*Developmental :*<br>( 7.4 mg/kg/day)<br>-↓ implants (n.s)<br>-↓litter size (n.s)<br>-↑ embryolethality (pre-implantation) (ns.but dose-depdnt) | Acute maternal toxicity and embryo-lethality(but no gross teratogenicity) at maternal oral doses of 20 & 40 mg/kg/d during organo-genesis (g.d 6-15).<br>•*Maternal endpoints:*<br>(20 & 40 mg/kg/d)<br>-↓ b.wt , b.wt gain<br>-↓ food cons.<br>-↑ mortality<br>•*Developmental :*<br>(20 & 40 mg/kg/d)<br>Excessive + dose-dependent<br>-↑embryolethality (resorption rate)<br>-↓litter size | No signs of developmental toxicity at maternally effective oral doses of up to 12.5 mg/ kg/d during organogenesis (g.d. 6-15)<br>NOAEL: 12.5 mg/kg/d<br>•*Maternal endpoints:*<br>(12.5 mg/kg/day)<br>-↓ food cons. (st.sign)<br>-↓ b.wt (n.s)<br>•*Developmental :*<br>None at up to and incl. 12.5 mg/kg/day | Rabbit embryo-lethality(resorptions& abortions) but no gross malform. at matern. oral doses of 2.5 to 15mg/kg/d during organogensis Matern.eff.at≥7.5 mg<br>•*Maternal endpoints:*<br>(7.5 & 15 mg/kg/d)<br>-↓ b.wt , b.wt gain<br>-↓ food cons.<br>•*Developmental :*<br>-↑embryofetal loss (resorption & abortion rates) at all dose levels | Prenatal developm. toxicity in the rabbit only at matern. toxic dose of 15 mg/kg/d during organogensis NOAEL: 7.5mg/kg/d<br>•*Maternal endpoints:*<br>(15 mg/kg/day):<br>-↓ b.wt , b.wt gain<br>-↓ food cons.<br>-↑ mortality<br>•*Developmental :*<br>(15 mg/kg/day):<br>-↑ embryofetal loss (abortions,resorpt.)<br>-↓litter size<br>-↑rate of skeletal variations (n.s)<br>-↓fetal weight (n.s) |

## 5.2. Prenatal Developmental Toxicity (Continued)

**FLUOXETINE**

| DEVELOPMENTAL TOXICITY- **PRENATAL** COMPONENT | *A Fertility Study on Fluox Hydrochlonde in the Female Rat Lilly Res Labs Study No RO 7179 /1980 by J Wold , N Owen & E. Adams* | *A Fertility Study Incl. Behav & Reprod Asses of F1 Gener., in Wistar Rat Given Fluox Hydrochloride in the Diet. Lilly Res Labs Study R10280 &RO4781/82* | *A Preliminary Teratol Study on Fluoxetine in Rat. Lilly Res Labs Study No R-77, IND : ——Toxicol Report No7 / 1979 by J S Wold and J K Markham* | *A Teratology Study on Fluoxetine in the Rat Lilly Res Labs Study R-207, IND —— Toxicol Report No 8 /1979 by J S Wold & J K Markham* | *A Preliminary Teratol Study on Fluoxetine in the Rabbit. Lilly Res. Labs Study B7017, IND —— Toxicol Report No 9 /1979, Wold & Markham* | *A Teratology Study on Fluoxetine in the Rabbit Lilly Res Labs Study B7087, IND —— Toxicol Report No 10 /1979 by J S Wold & J K. Markham* |
|---|---|---|---|---|---|---|
| **Confounding factors & comments** | - Maternal b.wt. not adjusted for wt of uterine content (this confounds inter-group comparisons due to the smaller litter size at the highest dose).<br>-Fetal wt comparison confounded by imprecise timing of pregnancy & group diff. in litter size<br>- Only gross external malformations are examined (actual malformation incidence unknown) | - Dose levels are approximate due to dosing through diet.<br>- Maternal b.wt. not adjusted for wt of uterine content (this confounds inter-group comparisons due to the smaller litter size at the highest dose).<br>-Fetal wt comparison confounded by imprecise timing of pregnancy & inter-group differences in litter size. | -Insufficient N pregn. animals in all dose groups,particularly at the lowest dose level (10mg/kg/day)-n=1. Effect at this dose can't be determined.<br>- Intermediate & high doses cause overt maternal toxicity and mortality which may be the reason for developm. toxicity.<br>-Only gross external malformations recorded (actual malformation Incidence unknown). | -Lower litter size in the highest dose gr. is unrelated to exposure, due to lower *n* implants in same group before start of exposure.<br>-↑ proportion of males same gr. probably random effect – not found in other studies.<br>-Mean fetal wt same group slightly over cntrl (confounded by smaller litter size & higher proportion of males at this dose) | -N animals / group insufficient to determine NOAEL and LOAEL;<br>-N animals/group insufficient for stat. evaluation.of results | - The embryofetal loss at the highest dose level was underestimated: over 20% of pregn. females in this group (3 of 13) aborted, but were not taken into account in determining the mean embryofetal loss group values.<br>- The lower mean fetal wt in this dose group might be due to the significantly lower proportion of male fetuses. |
| **Evaluation** | Study reliable but assessm.of following endpoints may be imprecise: malform. incidence (applies to gross extern.defects only); maternal wt & fetal wt. changes relative to control | Study reliable but confounded mainly with regard to dose quantitation due to dosing through diet. Following endpoints are imprecisely assessed due to confounding: effect on maternal & fetal wt, values of NOAEL & LOAEL. | A preliminary, dose-finding study, limited to acute effects at maternally toxic doses. LOAEL can not be determined because of insuff. N animals in the lowest dose group.<br>Use for human comparisons only qualitatively with regard to cases of poisoing. | Study reliable. Altered sex ratio (↑ males) at the highest exposure non-concordant with other studies at similar and higher dose levels ( probably due to chance).<br>Limitation:<br>Conclusions about effect on fetal weight limited by the above-stated confounding factors. | A preliminary, dose-finding study to assess developmental toxicity of fluoxetine in a second (non-rodent) species. Reliability limited by the small number of animals per group. | Study reliable. Altered sex ratio (decreased males) at highest exposure is non-concordant with other studies and is probably due to chance. Effect on fetal wt (n.s.) at this dose confounded by the altered sex ratio and should not be considered. |

## 5.3. Postnatal Developmental Toxicity

Effect presented as relative to control values.
Key: (– ) no change; • no observation; (+ ) statistically significant change or trend($p<0.05$); (± )statistically non-significant change;↑ increase; ↓decrease

Drug Name: FLUOXETINE

| DEVELOPMENTAI TOXICITY- **POSTNATAL** COMPONENT | *A Fertility Study on Fluoxetine Hydrochloride in the Female Rat.. Lilly Research Laboratories Study No RO 7179 /**1980** by J. Wold , N. Owen & E. Adams* | *A Fertility Study, Incl. Behav.& Reprod. Assessm of $F_1$ Generation, in the Wistar Rat Given Fluox.Hydrochloride in the Diet. Lilly Res. Labs Study R10280 & RO4781/**1982**, G.Brophy, N Owen & J.Hoyt* |
|---|---|---|
| **Species, strain** | Rat, Wistar | Rat, Wistar |
| **$F_1$ Postnatal exposure:** (check)<br>- Maternal dosing continued thr. lactation<br>- Other modes of postnatal exposure *(if yes, describe mode , timing & duration)*<br>- Maternal dosing discontinued at birth<br>- Treated pups fostered to untreated dams<br>- Control pups fostered to treated dams | <br>✓□<br>□<br><br>□<br>□<br>□ | <br>✓□<br>□<br><br>□<br>□<br>□ |
| **Dose Levels:** - Prenatal:<br>maternal→<br>paternal→<br>- Postnatal → | **0; 2; 5; 12.5** mg/kg/day, 2 wks before mating+gestation<br>**0**<br>**0; 2; 5; 12.5** mg/kg/day (through lactation) | **0; 1.3; 3.1; 7.4** mg/kg/day, 3 wks before mating+gestation<br>**0; 1.5; 3.9; 9.7**mg/kg/day, 10 wks before mating + breeding<br>**0; 1.3; 3.1; 7.4** mg/kg/day (through lactation) |
| **Route of administration** | Oral ( maternal gavage) | Oral (maternal diet) |
| **Dose-response** (yes/no) | yes | yes |
| **N dams/litters per group** | 16÷19 | 14÷18 |
| **NOAEL postnatal development**<br>**LOAEL postnatal development** | **5** mg/kg/day<br>**12.5** mg/kg/day | **1.3** mg/kg/day (maternal) + **1.5** mg/kg/day (paternal)<br>**3.1** mg/kg/day (maternal) + **3.9** mg/kg/day (paternal) |
| **Gestation length** | (-) | (-) |
| **Liveborn/ total litter size** per dam | ↓10%(±) at 12.5 mg/kg/d | (-) |
| **Stillbirths** per litter | ↑50%(±) at 12.5 mg/kg/d | (-) |
| **Sex ratio** prior to culling (% males) | (-) | (-) |
| **Birth weight** per litter(%change vs cntrl) | ↓ 9% **(+)** at 12.5 mg/kg/d | ↓12%(±) at 7.4 mg/kg/d |
| Sex-adjusted birth weight (yes/no) | no | no |
| **Progeny culled to** (number per litter)<br>On postnatal day | no | 10<br>1 |
| **Postnatal wt** (% change vs cntrl) at:<br>-Preweaning* (day 7)<br>(day 14)<br>-Weaning* (day 21)<br>-Maturity* | <br>↓ 11% **(+)** at 12.5 mg/kg/d<br>(-)<br>(-)<br>• | <br>↓ 17% **(+)** at 7.4 mg/kg/d<br>(-)<br>↓ 6%(±) at 7.4 mg/kg/d<br>↓ 17% **(+)** at 3.1 and 7.4 mg/kg/d (males, p.n.day 58) |

| *5.3. Postnatal Developmental Toxicity (continued)* | | |
|---|---|---|
| % wt. gain change vs control by sex:<br>- males (indicate period)<br>- females (indicate period) | • | <br>(-) p.day 58-120<br>(-) p.day 58-120 |
| **Survival** (%of liveborn pups viable) at:<br>- Preweaning* (day 7)<br>(day 14)<br>- Weaning* (day 21)<br>- Maturity * | <br>↓ 31% (+) at 12.5 mg/kg/d<br>↓ 34% (+) at 12.5 mg/kg/d<br>↓ 35% (+) at 12.5 mg/kg/d | <br>↓ 14% (±) at 7.4 mg/kg/d<br>↓ 16% (±) at 7.4 mg/kg/d<br>↓ 12% (±) at 7.4 mg/kg/d |
| **Malformation rates** vs control<br>Age of obtaining malform. data | (-)<br>• | (-)<br>weaning |
| **Malformations type**<br>(description if elevated over control) | N.A. | N.A. |
| ***Deviation/Variation rates***<br>Age of obtaining data | • | (-)<br>weaning |
| **Growth & development**<br>(developm. milestones vs control) | • | • |
| **Food consumption** (period) | • | (-) p.n. day 58-120 |
| **Efficiency of food utilization** (period) | • | (-) p.n day 58-120 |
| **Neurobehavioral development:** | • | (-) |
| Tests&Timing Abnormal effects→ | | |
| | • | Auditory startle (-) |
| | • | Visual placing (-) |
| | • | Rotarod (-) |
| | • | Poke hole (-) |
| **Reproductive performance $F_1$** | • | |
| Fertility index (% pregnant of total mated | • | (-) |
| N live $F_2$ fetuses(pups) per litter (mean) | • | (-) |
| Pre-implantation lethality<br>(N implants/Corpora lutea per dam) | • | • |
| Post-implantation lethality<br>(N dead+resorbed(aborted)/ N implants) | • | • |
| $F_2$ Birth weight per litter (p.d.1) | • | (-) |
| Maternal ($F_1$) wt gain (% vs control) | • | (-) |
| **Other organ system effects** | • | • |
| **Histopathology** and/or<br>**Gross necropsy** | • | • |

[1] Effects presented as relative to control values; * Periods of preweaning, weaning, postweaning and maturity specific for the species under study (for rat: preweaning=PND 1-21, weaning=PND 21, and maturity ≈ 3 months of age).

Key: (– ) no change; • no observation; (+ ) statistically significant change or trend($p<0.05$); (± )statistically non-significant change,↑ increase; ↓decrease; N.A.= not applicable

| 5.3. Postnatal Developmental Toxicity (continued) | | |
|---|---|---|
| **FLUOXETINE:** | | |
| **POSTNATAL** COMPONENT | *A Fertility Study on Fluoxetine Hydrochloride in the Female Rat.. Lilly Research Laboratories Study No RO 7179 /**1980** by J. Wold , N. Owen & E. Adams* | *A Fertility Study, Incl. Behav & Reprod Assessm.of $F_1$ Generation, in the Wistar Rat Given Fluox.Hydrochloride in the Diet. Lilly Res. Labs Study R10280 & RO4781/**1982**, G.Brophy, N.Owen & J.Hoyt* |
| **Conclusion & affected endpoints** | Fluoxetine hydrochloride oral dosing (gavage) of female Wistar rats 2 wks prior to mating and during gestation and lactation by 2, 5, and 12.5 mg/kg/day results in significant effect on postnatal development of $F_1$ progeny at the highest dose. No significant maternal effects or prenatal toxicity are induced by this dose level. Postnatal manifestations are a more sensitive index of Fluox. developmental toxicity in comparison to prenatal.<br>LOAEL: 12.5 mg/kg/day; NOAEL. 5 mg/kg/day<br><br>•*Postnatal developm. endpoints:*<br>- ↑ **stillbirths** (st.significant), 12.5 mg/kg/day<br>- ↓ **birthweight** (st.significant), 12.5 mg/kg/day<br>- ↓ **survival** and **wt.gain** of progeny in 1st postnatal week (st.significant), 12.5 mg/kg/day | Fluoxetine hydrochloride oral treatment (diet) of Wistar rats at approximate doses of 1.5, 3.9 and 9.7mg/ kg/day for 10 wks (males), and 1.3, 3.1 and 7.4 mg/kg/day for 4 wks (females) prior to mating and during gestation and lactation, results in in significant effect on postnatal wt and survival of $F_1$ progeny at the maternal doses of 3.1 and 7.4 mg/kg/day. No significant maternal effects or prenatal toxicity are induced by these dose levels. Postnatal manifestations are a more sensitive index of Fluox. developmental toxicity in comparison to prenatal. No effect on neurobehavioral development.<br>LOAEL: 3.1 mg/kg/day (maternal) + 3.9 mg/kg/day (paternal)<br>NOAEL: 1.3 mg/kg/day (maternal) + 1.5 mg/kg/day (paternal)<br><br>•*Postnatal developm endpoints:*<br>- ↓ **birthweight** (n.s), 7.4 mg/kg/day<br>- ↓ **postnatal weight** (st.significant) in 1st postnatal week (7.4 mg/kg/d) and at maturity(3.1 and 7.4 mg/kg/day)<br>- ↓ **survival** of progeny in 1st postnatal week (n.s. but dose-dependent (3.1 and 7.4 mg/kg/d) |
| **Confounding factors & comments** | -Progeny not culled; postnatal weight not sex-differentiated<br>-Decrease in progeny wt appears not dose-dependent (result of confounding by litter size which is biggest at the lowest dose level) | -The apparent "selective" effect of fluoxetine on postnatal parameters (progeny survival and weight) at doses much lower than those affecting the prenatal endpoints, might actually be due to higher than prenatal maternal and pup exposures (a two-fold increase of maternal food consumption during lactation was reported in this study; also the pups could have been additionally exposed to fluoxetine through the maternal chow).<br>- Postnatal behavior first assessed at the age of 2 to 3 months (eventual earlier behavioral deviations might have been omitted). |
| **Evaluation** | The conclusions of the study *reliable* despite of confounding factors: the effect on the most sensitive endpoints (↓ birth wt, early postnatal survival & wt gain) is clearly present at the highest dose although the litter size is the smallest .<br>*Limitations*: Postnatal evaluations are limited to progeny weight & survival and based on observations during the preweaning period only. | In general, study reliable but confounded mainly with regard to exposure quantitation due to dosing through diet. *Limitations*: Information on endpoints affected should be used for qualitative rather than quantitative comparisons. LOAEL and NOAEL levels determined in the study may not be sufficiently accurate. |

## Table 6. EVALUATION of ADVERSE OUTCOMES IN EXPERIMENTAL ANIMALS: ENDPOINTS (SUMMARY)

| Outcomes | Observed Effect (compared to control) | N studies reporting this finding Vs N studies designed to look for it | Species (and N studies per species) | NOEL [1] mg/kg/day | Exposure (N studies) | | | Effect Statist. Signif. (pro-portion stud's) | Effect Dose-depen-dent (pro-portion stud's) | Confounding factors | Plausi-bility[2] of finding | Consis tency[3] of finding |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Maternl only / Matrnl+ Paternl | Timing | | | | | | |
| | | | | | | Organo genesis only | Premating +gestation +lactation | | | | | |
| **Maternal** | | | | | | | | | | | | |
| -Weight loss* | ↓ 5-15% | 5/5* | Rat 3/3*<br>Rabbit 2/2 | **3.1** to **5**<br>**2.5** | 2/1<br>2/0 | 1<br>2 | 2<br>0 | (+) 1/3<br>(+) 1/2 | (+) 3/3<br>(+) 2/2 | -Gravid uterine weight not substracted (effect overerestimated)<br>-Wt loss not a sign of toxicity (pharmaco-dynamic effect of F) | (+) | (+) |
| -Decreased food consumption* | ↓ 8-88% | 5/5* | Rat 3/3*<br>Rabbit 2/2 | **3.1** to **5**<br>**2.5** | 2/1<br>2/0 | 1<br>2 | 2<br>0 | (+) 1/3<br>ND | (+) 3/3<br>(+) 2/2 | May not be a toxic eff. (Fsuppresses apetite) | (+) | (+) |
| -Altered gestational length | **No effect** | 2/2 | Rat 2/2 | **7.4** to **12.5** | 1/1 | 0/2 | 2/2 | NA | NA | No | (?) | (+) |
| -Mortality | ↑at toxic doses only | 2/6 | Rat 1/4<br>Rabbit 1/2 | **>12.5<20**<br>**7.5** | 1/0<br>1/0 | 1<br>1 | 0<br>0 | NSD<br>NSD | (+) 1/1<br>(+) 1/1 | Insufficient number of observations | (+) | **NSD** |
| **Prenatal** | | | | | | | | | | | | |
| -Embryofetal loss*: | | | | | | | | | | | | |
| Pre-implantation** | ↑ by 50% | 1 / 2** | Rat 1/ 2** | **<1.3** | 0/1 | 0 | 1 | ND | (±) 1/1 | **Both** parents dosed | (?) | **NSD** |
| Post-implantation* | ↑ by 33% to 5-fold | 3/5* | Rat 1/3*<br>Rabbit 2/2 | **12.5**<br>**7.5** | 1/0<br>2/0 | 0<br>2 | 1<br>0 | (-)<br>ND | (±) 1/1<br>(+) 2/2 | Effect in rabbit under-estimated (abortions not incl.in dat analysis | (?) | (±) |
| -Litter size* | ↓ 10-40% | 5/5* | Rat 3/3*<br>Rabbit 2/2 | **5**<br>**7.5** | 2/1<br>2/0 | 1<br>2 | 2<br>0 | (-)<br>ND | (+) 3/3<br>(+) 2/2 | No | (?) | (+) |
| -Fetal weight | ↓ 9% | 1/4 | Rat 0/3<br>Rabbit 1/1 | **12.5**<br>**7.5** | 1/0 | 1 | 0 | (-) | (+) 1/1 | Effect underestimated (smaller litter sizes at higher doses) & con-founded byaltered sex ratio at high doses | (+) | (-) |
| -Sex ratio altered | ↑**M** by20%<br>↓**M** by25% | 1 /4<br>1 /4 | Rat 1/3<br>Rabbit 1/1 | **5**<br>**7.5** | 1/0<br>1/0 | 1<br>1 | 0<br>0 | (-)<br>(+) 1/1 | (-) | Most likely random variability | (-) | (-) |
| -Birth defects: | | | | | | | | | | | | |
| Malformations | **No effect** | 6/6 | Rat 0/4<br>Rabbit 0/2 | **40**<br>**15** | 3/1<br>2/0 | 2<br>2 | 2<br>0 | NA<br>NA | NA<br>NA | In 3 of 6 st only gross external m examined | (?) | (+) |
| Variations & deviations | ↑skeletal, 3-fold | 1/3 | Rat 0/2<br>Rabbit 1/1 | **12.5**<br>**7.5** | 1/1<br>1/0 | 1<br>1 | 1<br>0 | NA<br>(-) | NA<br>(±) 1/1 | No | (?) | (-) |

Shaded areas highlight the most reliable outcomes according to the following criteria. prevalence, consistent across studies and species, significant, dose-dependent, plausible & coherent with existing information

Table 6. **EVALUATION of ADVERSE OUTCOMES IN EXPERIMENTAL ANIMALS: ENDPOINTS SUMMARY (continued)**

| Outcomes | Observed Effect (compared to control) | N studies reporting this finding Vs N studies designed to look for it | Species (and N studies per species) | NOEL[1] mg/kg/day | Exposure (N studies) | | | Effect Statist. Signif. (pro-portion stud's) | Effect Dose-depen-dent (pro-portion stud's) | Confounding factors | Plausi-bility[2] of finding | Consis tency[3] of finding |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Maternl only / Matrnl+ Paternl | Timing | | | | | | |
| | | | | | | Organo genesis only | Premating +gestation +lactation | | | | | |
| **Postnatal** | | | | | | | | | | | | |
| -Liveborn litter size | ↓ 10% | 1/ 2 | Rat 1/ 2 | **5** | 1/ 0 | 0 | 1 | (-) | (+) | no | (+)*** | **NSD** |
| -Stillbirths | ↑ 2-fold (14 vs 7%) | 1/ 2 | Rat 1/ 2 | **5** | 1/ 0 | 0 | 1 | (+) | (+) | no | (+)*** | **NSD** |
| -Birth weight | ↓ 9-12% | 2/ 2 | Rat 2/ 2 | **3.1 to 5** | 1/1 | 0 | 2 | (+) 1/2 | (+) | Effect underestimated (litter size biggest at the lowest dose), NOEL at 3.1 uncertain (dosing through diet) | (+) | (+) |
| -Sex ratio at birth | **No effect** | 0/ 2 | Rat 0/ 2 | **7.4 to 12.5** | 1/1 | 0 | 2 | NA | NA | no | (+) | (+)[0] |
| -Postnatal Survival | ↓ 14-30% (1st p.n. wk) | 2/ 2 | Rat 2/ 2 | **3.1 to 5** | 1/1 | 0 | 2 | (+) 1/2 | (+) | NOEL at 1.3 and 3 1 may be underestimate (dosing through diet & ↑ 2-fold in matrn.food intake during lactation | (+) | (+) |
| -Postnatal Weight & wt.gain | ↓ 11-17% (1st p.n. wk & maturity) | 2/ 2 | Rat 2/ 2 | **1.3 to 5** | 1/1 | 0 | 2 | (+) 1/2 | (+) | | (+) | (+) |
| -Developmental landmarks | ND | | | | | | | | | | | |
| -Neurobehavioral developm. | **No effect** ($F_1$sensory-motor funct. tested at adolescenc. & maturity) | 1/ 1 | Rat 1/ 1 | **7.4** | 0/1 | 0 | 1 | NA | NA | Postnatal behavior first assessed at age of 2 to 3 months (earlier behavioral deviations might have been omitted) | (?) | **NSD** |
| -Other organ system effects | ND | | | | | | | | | | | |

* Acute maternal toxicity studies (one preliminary dose-finding study in the rat) not taken into account for these outcomes to avoid confounding by maternal poisoning (*A Preliminary Teratol Study on Fluoxetine in Rat. Lilly Res. Labs. Study No R-77, IND — Toxicol. Report No7 / 1979 by J.S Wold and J.K. Markham)*

** Studies with no pre-implantation exposures are not taken into account for the preimplantation lethality outcome;

*** These outcomes plausible having in mind the tendency to increased prenatal embryofetal loss;

[0] Consistent with the majority of the prenatal studies.

Abbreviations and symbols used: **F**= fluoxetine; **ND**=no data; **NSD**=no sufficient data (n observations insuffissient); **NA**=not applicable; **(?)**=unknown; **(±)**=uncertain, inconclusive.

Terminology used: [1]NOEL (instead of NOAEL) in order to accommodate different types of effects (incl.those that may not be adverse but due to pharmacological effect of compound); [2]Plausibility= the effect (or lack of it) is plausible with regard to pharmacokinetics& pharmacodynamics of compound.[3]Consistency= the effect (or lack of it) is consistent across studies.

## *Table 7. FLUOXETINE PHARMACOKINETICS & PHARMACODYNAMICS : ANIMAL to HUMAN COMPARISONS*

| *SIMILARITIES between lab.animals and humans* | *DIFFERENCES between lab. animals and humans* |
|---|---|
| ***Pharmacodynamics:*** | ***Pharmacodynamics:*** |
| • **Common mechanism of action** (Selective serotonin reuptake inhibitor)<br>• **Common sites of action** (Presynaptic terminals, platelets)<br>• **Similar manifestations of adverse effect, overdose, toxicity** (anorexia, ↓ food consumption, weight loss, hyperreactivity, tremors, asthenia)<br>• **Similar toxicometric parameters:** low general toxicity in lab. animals and man - $LD_{50}$=250 mg/kg (mouse); 450mg/kg (rat); Humans: no lethality at overdoses up to 3000 mg (about 50 mg/kg) single dose *(Sommi et al, 1987; Gram, 1994)*<br>• **Increases prolactin release in both rat and human** *(Benfield, 1986)* | • **Different neuroendocrine effects on some hypothalamic releasing-factors** *(Benfield et al, 1986; Sommi et al, 1987)* :<br>- Rat: ↑hypothalamic secretion of corticotropic-releasing factor & vasopressin leading to increased ACTH and vasopressin in plasma<br>- Man: No change in serum cortisol, ACTH, or growth hormone (meaning higher specificity & selectivity, less side effects → less toxicity?)<br>• **No dose-effect relationship between dose and therapeutic effect in the human** *(Gram, 1994)* |
| ***Pharmacokinetics**** | ***Pharmacokinetics**** |
| • **Absorption:**<br>- well absorbed by both man and lab.animals; similar recovery *(Sommi et al, 1987)*<br>- similar time (4-8 h ) to peak plasma & tissue levels *(Sommi, 1987; Pohland et al, 1989)*<br>- extensive tissue distribution and binding *(Benfield et al, 1986)*<br>• **Metabolism:**<br>- similar metabolic system (demethylated hepatically to Nor-fluoxetine)<br>- identical active metabolite (Nor-fluoxetine) Note: More than half the metabolic end products are unknown *(Bergstrom et al, 1988 as cited by Gram, 1994)* | • **Differences in elimination and clearance:**<br>**Humans eliminate and clear F more slowly than rodents** (Half-life in human=70h. compared to 7-8 h. in the rat) *(Rickels, '90; Caccia et al, '90, cited by Vorhees&al,'94)*<br>• **Very large inter-individual variations in elimination, clearance and steady-state plasma level in humans** (reasons: genetic polymorphism of a liver cytochrome P-450 that may be responsible for F metabolism; different proportions of the active enantiomers of F and nor-F) *(Gram, 1994)* This may have consequences for clinical effects, tolerability & interactions with other drugs. |

* In non-pregnant organism (pharmacokinetics in pregnancy has not been studied in the human)

## *Table 8. FLUOXETINE DEVELOPMENTAL TOXICITY : ANIMAL to HUMAN COMPARISONS*

| *Endpoints* | *Animal studies* | | | | | *Human studies* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Adverse Outcomes* | *Observed effect* | *N studies reporting effect / N performed* | *Species* | *NOEL (mg/kg/day)* | *Adverse Outcomes* | *Observed effect* | *N studies reporting effect / N performed* | *Dose (mg/kg/day)* |
| ***Maternal effects*** | Weight loss | (+)<br>(+) | 3/3<br>2/2 | Rat<br>Rabbit | 3.1<br>2.5 | Weight loss | (+) | Non-pregnant studies only | **< 1**<br>(20-80 mg/d) |
| | Decreased food consumption | (+)<br>(+) | 3/3<br>2/2 | Rat<br>Rabbit | 3.1<br>2.5 | Loss of appetite (anorexia) | (+) | Non-pregnant studies only | **< 1**<br>(20-80 mg/d) |
| | Reduced gestational length | (-) | 0/2 | Rat | 12.5 | Premature birth | (?) | 1/7 | **< 1**<br>(25 mg/day) |
| | Maternal mortality<br>(up to the indicated dose levels) | (-)<br>(-) | 0/4<br>0/2 | Rat<br>Rabbit | 12.5<br>7.5 | Maternal mortality | (-) | 0/7 | **< 1**<br>(20-80 mg/d) |
| ***Prenatal effects*** | Increased embryo/fetal loss<br>(resorptions, abortions) | (±)<br>(+) | 1/3<br>2/2 | Rat<br>Rabbit | 5<br>7.5 | Spontaneous abortion | (±) | 5/6 | **< 1**<br>(25 mg/day) |
| | Decreased fetal weight | (-)<br>(±) | 0/3<br>1/1 | Rat<br>Rabbit | 5<br>7.5 | Decreased birthweight | (-) | 1/7 | **< 1**<br>(25 mg/day) |
| | Birth Defects<br>- Congenital malformations | (-)<br>(-) | 0/4<br>0/2 | Rat<br>Rabbit | Up to 40<br>Up to 15 | Birth Defects:<br>- Major malformations | (-) | 0/7 | **<1** (25-28 mg/day) |
| | - Variations | (-)<br>(±) | 0/2<br>1/1 | Rat<br>Rabbit | 12.5<br>7.5 | - Minor | (±) | 2/5 | **<1** (25-28 mg/day) |

Symbols used: **(+)**= presence of effect; **(-)**= absence of effect; **(±)** = effect uncertain; **(?)** = evidence insufficient to draw conclusions; **N.D.**= no data

| Table 8. ANIMAL to HUMAN COMPARISONS (continued) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Endpoints | Animal studies | | | | | Human studies | | | |
| | Adverse Outcomes | Observed effect | N studies reporting effect / N performed | Species | NOEL (mg/kg/day) | Adverse Outcomes | Observed effect | N studies reporting effect / N performed | Dose (mg/kg/day) |
| **Postnatal effects** | Stillbirths | (±) | 1/2 | Rat | 5 | Perinatal death | (-) | 0/5 | < 1 (25 mg/day) |
| | Decreased postnatal survival | (+) | 2/2 | Rat | 3.1 to 5 | | | | |
| | Decreased birthweight (entire gestation exposure) | (+) | 2/2 | Rat | 3.1 to 5 | Decreased birthweight (entire gestation exposure) | (+) ? | 1/2 | < 1 (25 mg/day) |
| | Decreased postnatal weight gain | (+) | 2/2 | Rat | 3.1 to 5 | Postnatal weight gain | N.D. | | |
| | Neurobehavioral effects, sensory-motor (at adolescence, age 2-3 mnths) | (-)? | 0/1 | Rat | 7.4 | Neurobehavioral effects, motor, learning& memory (age 4-6 years) | (-) | 0/2 | < 1 (10 to 80 mg/day) |
| | Developmental delays | N.D. | | | | Developmental delays | N.D. | | |

Symbols used: **(+)**= presence of effect; **(-)**= absence of effect; **(±)** = effect uncertain; **(?)** = evidence insufficient to draw conclusions; **N.D.**= no data