Health Council of the Netherlands

Chlorpromazine

Evaluation of the effects on reproduction, recommendation for classification

2015/14

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Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Chlorpromazine*
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Geachte minister,

Graag bied ik u hierbij het advies aan over de effecten van chloorpromazine op de vruchtbaarheid en het nageslacht; het betreft ook effecten op de lactatie en via de moedermelk op de zuigeling. Dit advies maakt deel uit van een uitgebreide reeks waarin voor de voortplanting giftige stoffen worden geclassificeerd volgens richtlijnen van de Europese Unie. Het gaat om stoffen waaraan mensen tijdens de beroepsuitoefening kunnen worden blootgesteld.

Dit advies is opgesteld door een vaste commissie van de Gezondheidsraad, de Subcommissie Classificatie reproductietoxische stoffen van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen. Het is vervolgens getoetst door de Beraadsgroep Gezondheid en omgeving van de Gezondheidsraad.

Ik heb dit advies vandaag ter kennisname toegezonden aan de minister van Volksgezondheid, Welzijn en Sport en, eveneens ter kennisname, aan de staatssecretaris van Infrastructuur en Milieu.

Met vriendelijke groet,

prof. dr. J.L. Severens,
vicevoorzitter

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Chlorpromazine

Evaluation of the effects on reproduction,
recommendation for classification

Committee on the Classification of Reproduction Toxic Substances
of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2015/14, The Hague, May 20, 2015

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

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Contents

Samenvatting

In het voorliggende advies heeft de Gezondheidsraad chloorpromazine onder de loep genomen. In Nederland kan chloorpromazine worden voorgeschreven als middel tegen misselijkheid en braken als andere middelen zijn gecontra-indiceerd, als palliatieve sedatie ter bestrijding van delirium, dyspneu en onrust en ter bestrijding van hardnekkige hik. Dit advies past in een reeks adviezen waarin de Gezondheidsraad op verzoek van de minister van Sociale Zaken en Werkgelegenheid de effecten van stoffen op de voortplanting beoordeelt. Het gaat vooral om stoffen waaraan mensen tijdens de beroepsuitoefening kunnen worden blootgesteld. De Subcommissie Classificatie reproductietoxische stoffen van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen van de raad, hierna aangeduid als de commissie, kijkt zowel naar effecten op de vruchtbaarheid van mannen en vrouwen als naar effecten op de ontwikkeling van het nageslacht. Daarnaast worden effecten op de lactatie en via de moedermelk op de zuigeling beoordeeld.

Op basis van Verordening (EG) 1272/2008 van de Europese Unie doet de commissie een voorstel voor classificatie. Voor chloorpromazine komt de commissie tot de volgende aanbevelingen:

- voor effecten op de fertiliteit adviseert de commissie chloorpromazine te classificeren in categorie 1B (*stoffen waarvan verondersteld wordt dat zij toxisch zijn voor de menselijke voortplanting*) en te kenmerken met H360F (*kan de vruchtbaarheid schaden*)

- voor effecten op de ontwikkeling adviseert de commissie chloorpromazine te classificeren in categorie 1B (*stoffen waarvan verondersteld wordt dat zij toxisch zijn voor de menselijke voortplanting*) en te kenmerken met H360D (*kan het ongeboren kind schaden*)
- voor effecten op en tijdens lactatie adviseert de commissie om chloorpromazine niet te kenmerken wegens onvoldoende geschikte gegevens.

Executive summary

In the present report the Health Council of the Netherlands reviewed chlorpromazine. In the Netherlands, chlorpromazine may be prescribed in the management of nausea and vomiting in case other medicines are contraindicated, in palliative sedation for the relief of delirium, dyspnoea and restlessness, and in the treatment of intractable hiccups. This report is part of a series, in which the Health Council evaluates the effects of substances on reproduction, at request of the Minister of Social Affairs and Employment. It mainly concerns substances to which man can be exposed occupationally. The Subcommittee on the Classification of Reproduction Toxic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee, evaluates the effects on male and female fertility and on the development of the progeny. Furthermore, the Committee considers the effects of a substance on lactation and on the progeny via lactation.

The Committee recommends classification according to Regulation (EC) 1272/ 2008 of the European Union. For chlorpromazine, these recommendations are:

- for effects on fertility, the Committee recommends classifying chlorpromazine in category 1B (*presumed human reproductive toxicant*) and labelling with H360F (*may damage fertility*)
- for effects on development, the Committee recommends classifying chlorpromazine in category 1B (*presumed human reproductive toxicant*) and labelling with H360D (*may damage the unborn child*)

- for effects on or via lactation, the Committee recommends not labelling chlorpromazine due to a lack of appropriate data.

Chapter 1

Scope

1.1 Background

As a result of the Dutch regulation on registration of compounds toxic to reproduction that came into force on 1 April 1995, the Minister of Social Affairs and Employment requested the Health Council of the Netherlands to classify compounds toxic to reproduction. This classification is performed by the Health Council's Subcommittee on the Classification of reproduction toxic substances of the Dutch Expert Committee on Occupational Safety (DECOS). The classification is performed according to European Union Regulation (EC) 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. The CLP guideline is based on the Globally Harmonised System of Classification and Labelling of Chemicals (GHS). The Subcommittee's advice on the classification will be applied by the Ministry of Social Affairs and Employment to extend the existing list of compounds classified as reproductive toxicant (category 1A and 1B and 2) or compound with effects on or via lactation.

1.2 Committee and procedure

This document contains the classification of chlorpromazine by the Health Council's Subcommittee on the Classification of Reproduction Toxic Substances, hereafter called the Committee. The members of the Committee are

listed in Annex A. The submission letter (in English) to the Minister can be found in Annex B.

In 2014, the President of the Health Council released a draft of the report for public review. The individuals and organizations that commented on the draft report are listed in Annex C. The Committee has taken these comments into account in deciding on the final version of the report. The comments received, and the replies by the Committee, can be found on the website of the Health Council.

The classification is based on the evaluation of published human and animal studies concerning adverse effects with respect to fertility and development as well as lactation of the above mentioned compound.

Classification for reproduction (fertility (F) and development (D)):	
Category 1	Known or presumed human reproductive toxicant (H360(F/D))
Category 1A	Known human reproductive toxicant
Category 1B	Presumed human reproductive toxicant
Category 2	Suspected human reproductive toxicant (H361(f/d))
No classification for effects on fertility or development	
Classification for lactation:	
	Effects on or via lactation (H362)
	No labelling for lactation

The classification and labelling of substances is performed according to the guidelines of the European Union (Regulation (EC) 1272/2008) presented in Annex D. The classification of compounds is ultimately dependent on an integrated assessment of the nature of all parental and developmental effects observed, their specificity and adversity and the dosages at which the various effects occur. The guideline necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the regulation, the committee has agreed upon a number of additional considerations (see Annex E).

1.3 Labelling for lactation

The recommendation for classifying substances for effects on or via lactation is also based on Regulation (EC) 1272/2008. The guideline defines that substances which are absorbed by women and have been shown to interfere with lactation or which may be present (including metabolites) in breast milk in amounts

sufficient to cause concern for the health of a breastfed child, shall be classified and labelled. Unlike the classification of substances for fertility and developmental effects, which is based on hazard identification only (largely independent of dosage), the labelling for effects on or via lactation is based on a risk characterization and therefore, it also includes consideration of the level of exposure of the breastfed child.

Consequently, a substance should be labelled for effects during lactation when it is likely that the substance would be present in breast milk at potentially toxic levels. The Committee considers a concentration of a compound as potentially toxic to the breastfed child when this concentration exceeds the exposure limit for the general population, e.g. the acceptable daily intake (ADI).

1.4 Data

Literature searches were conducted in the online databases TOXLINE, MEDLINE and CAPLUS, up to and including January 2012 without a starting date; an update was performed in TOXNET in April 2014. Publications cited in the selected articles, but not retrieved during the primary search, were reviewed if considered appropriate. In addition, handbooks and most recent reviews were consulted. References are divided in literature cited and literature consulted but not cited.

The committee describes both human and animal studies in the text. The animal data are described in more detail in Annex F as well. Of each study the quality of the study design (performed according to internationally acknowledged guidelines) and the quality of documentation are considered.

In the assessment of the potential reproduction toxic effects of chlorpromazine, the Committee also used data on adverse effects related to its application as a therapeutic agent.

1.5 Presentation of conclusions

The classification is given with key effects, species and references specified. In case a substance is not classified as toxic to reproduction, one of two reasons is given:

- lack of appropriate data precludes assessment of the compound for reproductive toxicity
- sufficient data show that no classification for reproductive toxicity is indicated.

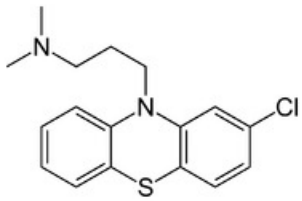
1.6 Final remark

The classification of compounds is based on hazard evaluation only (Niesink et al., 1995)[46], which is one of a series of elements guiding the risk evaluation process. The Committee emphasizes that for derivation of health-based occupational exposure limits these classifications should be placed in a wider context. For a comprehensive risk evaluation, hazard evaluation should be combined with dose-response assessment, human risk characterization, human exposure assessment and recommendations of other organizations.

Chapter 2

Chlorpromazine

2.1 Introduction

name	:	chlorpromazine
CAS number	:	50-53-3
CAS registry name	:	10H-phenothiazine-10-propanamine, 2-chloro-N,N-dimethyl-
synonyms	:	chloropromazine; 2-chloropromazine; 2-chloro-10-[3-(dimethylamino)propyl]- phenothiazine; 2-chloro-10[3'-(dimethylamino)propyl]phenothiazine; N-(3-dimethylaminopropyl)-3-chlorophenothiazine
colour and physical state	:	oily liquid; white crystalline solid
molecular weight	:	318.6
molecular formula	:	$C_{17}H_{19}ClN_2S$
structural formula	:	
melting point	:	approximately 60 °C
boiling point	:	200-205 °C (at 0.1 KPa)
vapour pressure	:	$0.7x10^{-3}$ Pa (at 25 °C; estimated)
Log $P_{octanol/water}$	:	5.35 (recommended value)[58]

solubility	:	practically insoluble in water (2.6 mg/L; at 24 °C); very soluble in ethanol, ether, benzene and chloroform; soluble in dilute hydrochloric acid
use	:	in human medicine, for the treatment of both acute and chronic psychoses including schizophrenia, organic-induced psychoses and manic-depressive illness; it has also been used in the first trimester of pregnancy to control nausea and vomiting and to control depressions and/or psychotic behaviour as well as during labour and delivery; routes of administration are oral, rectal, intramuscular or intravenous. in veterinary medicine, as an antiemetic, a pre-anaesthetic or a muscle relaxant. In the Netherlands, chlorpromazine-containing medicines are not registered for use in human or veterinary medicine nowadays[14]; it is available, as a suppository, on prescription at pharmacists in the management of nausea and vomiting in case other medicines are contraindicated, in palliative sedation for the relief of delirium, dyspnoea and restlessness and in the treatment of intractable hiccups.[15]
general toxicity	:	oral LD50 values were 135 and 210 mg/kg bw in mice and rats, respectively; intravenous LD50 values 20, 23-46, 16 and 30 mg/kg bw in mice, rats, rabbits and dogs, respectively; intraperitoneal LD50 values 115-136 mg/kg bw and 71 mg/kg bw in mice and rats, respectively[33]
mechanism	:	Chlorpromazine is a phenothiazine derivative and acts as an effective antagonist on different postsynaptic receptors (e.g. dopamine receptors, serotonin receptors, histamine receptors, α1- and α2-adrenergic receptors and on M1 and M2 muscarinic acetylcholine receptors).
kinetics	:	Chlorpromazine is highly lipophilic and rapidly binds to plasma protein after administration; it is rapidly distributed throughout the body and highest concentrations of this drug are found in organs that need a high supply of blood (e.g. brain, lung etc.). It is metabolized mainly in the liver by cytochrome-P450 family enzymes, usually CYP2D6. The major metabolic pathways of the drugs are hydroxylation and conjugation with glucuronic acid. Due to its high lipophilicity, high membrane- and protein binding, the elimination half-life of chlorpromazine is 16-30 hours. Approximately 10-12 metabolites are generated by the hepatic pathway, which may be detected in the urine for several months after discontinuation of use.[33] Considerably longer plasma elimination half-lives (rapid phase: 1.46 days; slow phase: 3.19 days) were described in an infant whose mother was treated with chlorpromazine the last trimester of pregnancy.[45]

Data from HSDB[44], unless otherwise noted.

2.2 Human studies

2.2.1 Fertility studies

Giarola et al. studied 54 patients treated with chlorpromazine (100-600 mg) or meprobamates daily for several months and reported persisting amenorrhoea in 74% of the patients while 59% of the patients showed anovulation.[22]

Similar effects were also reported by Whitelaw[72] and Sulman et al.[65]

2.2.2 Developmental toxicity studies

Numerous studies evaluated the use of chlorpromazine in obstetrics to relieve pain in labour (e.g.[1,11-13,16,26,27,30,35,41,42,47,59,60]). In the majority of the studies however, chlorpromazine was used in combination with one or more other drugs, no untreated control groups were included, and effects on newborn were described in general terms. In combination with the exposure period, i.e. a few hours just before and during parturition, the Committee considers these studies of little relevance in assessing the developmental toxic effects of chlorpromazine and will not present them here in further detail.

A prospective survey was described by Rumeau-Rouquette et al., which included 12,764 women in 12 University hospitals in Paris. Four out of 57 women exposed to chlorpromazine during the first three months of pregnancy gave birth to malformed infants: syndactyly; microcephaly, clubfoot/hand, muscular abdominal aplasia (also exposed to acetylpromazine); endocardial fibroelastosis, brachymesophalangy, clinodactyly (also exposed to pipamazine); and microcephaly (also exposed to promethazine). However, the study did not take into account confounders such as concomitant medical conditions and concurrent medication, alcohol or smoking.[55]

Farkas and Farkas performed a prospective study which included 906 women who had hyperemesis gravidarum in the first trimester of pregnancy and delivered between September 1, 1963 and August 31, 1968 in a hospital in Cluj, Romania. In the group of 152 women hospitalized and treated with chlorpromazine alone, three gave birth to infants with (not specified) malformations (2%), whereas no malformed infants were seen in a similarly treated group of 102 ambulatory patients. The malformation rates in the group of

906 patients and in the group of 84 ambulatory patients receiving a placebo were 3.9 and 2.4%, respectively.[20]

Sobel et al. found 52 records of women who were treated with chlorpromazine during pregnancy and delivered in eight different New York State mental hospitals from 1949 through 1958. In four cases, foetal damage (miscarriage, stillbirth, developmental delay) occurred after treatment with chlorpromazine (100-400 mg/day during gestation), the prevalence (8%) being comparable with foetal damage (7%) found in a control group of 202 non-treated women. However, babies from three women who were treated with 500-600 mg chlorpromazine daily in the later part of pregnancy were born with respiratory distress and cyanosis and required oxygen over a sustained period. One of the babies died. No respiratory distress was observed in the 49 cases treated with a lower concentration of chlorpromazine.[64]

Ayd reported on 27 women treated with chlorpromazine pre-pregnancy, at the time of conception and during gestation (n=16) or starting some time after the first trimester (n=11). All women delivered full-term healthy babies with normal birth weights. Nine of the infants were breast-fed for varying lengths of time with no apparent adverse effects. In addition, no intellectual or behavioural problems were reported during follow-up periods up to 7 years.[3]

In order to study the effects of psychotropic drugs on infant behaviour, Auerbach et al. recruited 54 women during the last trimester of pregnancy in the period 1973-1977. Four of these women received chlorpromazine alone. The behaviour of their infants was assessed at postnatal days 3 (n=2) and 14 (n=4) using the Brazelton Neonatal Behavioral Assessment Scale. At postnatal day 3, behavioral signs including hypertonia and startles were observed in one infant. At postnatal day 14, mild or extreme hypertonia was seen in all four infants, as well as poor motor maturity in two, tremulousness in one, and startles in one infant. According to Auerbach et al., it was not clear whether these effects should be interpreted as symptoms of neonatal abstinence or withdrawal or as extrapyramidal signs associated with drug toxicity, or whether exposure via breast milk could have been involved.[2]

Several cases of infants from mothers treated during (a part of) their pregnancy with chlorpromazine mostly in combination with other drugs or other kinds of therapy were reported.[4,7,18,19,24,28,40,43,45,48,49,66] These reports described a variety of effects among which neurological effects, including extrapyramidal

symptoms, and intestinal effects and one stillbirth with malformations. In one of these cases, severe neurological depression slowly abating during the first nine postnatal days was accompanied by steadily decreasing plasma chlorpromazine levels.[45]

Kris and Carmichael reported on 12 women receiving chlorpromazine before, during and after pregnancy or during and after pregnancy. No infant born showed signs of abnormality at birth, and all infants (aged five to 16 months at the time of publication) showed normal behaviour and development.[37] In a subsequent report, Kris stated that over a period of ten years 52 children were born to mothers maintained on psychopharmacotherapy (probably chlorpromazine) throughout pregnancy, parturition and postpartum. They all seemed normal at the time of birth and no indications of the presence of any problems of behaviour or any emotional or mental disturbances were seen during the mostly undefined follow-up period.[36]

2.2.3 Lactation

Kris et al. reported normal development of seven breast-fed infants whose mothers received chlorpromazine (50-150 mg/day) during pregnancy and postnatally.[37]

Blacker et al. measured levels of chlorpromazine in plasma 30, 60, 90 and 180 minutes and in milk 60, 120 and 180 minutes following administration of 1,200 mg to one woman hospitalized four days postpartum. Peak levels amounted to 750 µg/L (at 90 minutes) and 290 µg/L (at 120 minutes) in plasma and milk, respectively. During the 18-day treatment period in hospital, she breast-fed her infant without effects on its growth, activity or development. Blacker et al. estimated that the mother's dose of 1,200 mg (20 mg/kg bw) would have resulted in a dose of 3 µg/kg bw in the child. They stated that they could not detect chlorpromazine in blood or in breast milk of other patients following oral doses of 600 mg.[9]

Ayd reported on 27 pregnant women treated with chlorpromazine) prior to and during pregnancy or starting some time after the first trimester. All women delivered full-term healthy babies with normal birth weights. Nine of the infants were breast-fed for varying lengths of time with no apparent adverse effects. No intellectual or behavioural problems were reported during follow-up periods up to 7 years.[3]

Uhlir and Ryznar examined breast milk of 15 patients. Metabolites of chlorpromazine were found in one to four fractions of 27 samples from 12 patients. Uhlir and Ryznar stated that the daily dose of chlorpromazine should exceed 200 mg in order to enter into the breast milk.[67]

Vorherr presented breast milk levels of 300 µg/L and stated that the percentage of administered dose in breast milk was 0.07%/day. No more details were given.[69]

Using a modified gas chromatographic method, Wiles et al. measured chlorpromazine in samples of breast milk from four mothers (concentrations ranged from 7-98 µg/L), two of whom breast-fed their babies. One of these infants was found drowsy and lethargic after ingestion of chlorpromazine in the breast milk (92 µg/L), whereas the other infant (concentration in breast milk of 7 µg/L) showed no effects.[73]

Ohkubo et al. developed a high-performance liquid chromatographic (HPLC) assay for the determination of chlorpromazine in serum and blood and used the method in four patients receiving oral chlorpromazine doses of 40, 100, 120 or 2 00 mg. In the patient receiving 40 mg, the concentration in milk was 5.5 µg/L, while no results were reported for the other patients. Levels in plasma were 5.0, 7.5 and 12.0 µg/L at 100, 120 and 200 mg, respectively; no results were available for the patient receiving 40 mg. The limit of detection of the method was 0.5 µg/L.[50]

Yoshida et al. used a HPLC method to determine, amongst others, chlorpromazine concentrations in maternal milk and plasma and an enzyme immunoassay for concentrations in maternal plasma, urine and milk and in infant's plasma and urine. Twelve women were monitored, one woman receiving daily doses of 50 mg chlorpromazine alone during eight weeks breast-feeding, three women receiving doses of 200-600 mg during six to nine weeks breast-feeding in combination with haloperidol, and eight haloperidol or trifluoperazine. Using HPLC, concentrations of chlorpromazine up to 271 µg/L were measured and with the immunoassay, that presumably included metabolites as well, up to 568 µg/L. In a total of four urine and three plasma samples obtained from two infants, chlorpromazine (plus metabolites) levels were ≤1,4 µg/L and ≤0.7 µg/L, respectively.

Repeated clinical and developmental assessments of the breast-fed infants carried out up to 30 months of age showed a decline in developmental scores from the first to second assessment at 12-18 months in three infants from mothers treated with both chlorpromazine and haloperidol. No effects were observed in the other infants, among which one from a mother treated with

chlorpromazine alone, or at other ages (1-4 months, 5-11 months, 19-30 months).[75]

The Committee notes that the more recent studies[50,73,75] used more sensitive and specific methods for the determination of chlorpromazine in plasma, urine and breast milk.

2.3 Animal studies

Fertility and developmental toxicity studies in laboratory animals are summarized in Annex F.

2.3.1 Fertility studies

Oral administration

Saigo et al. administered oral (gavage) doses of chlorpromazine of 0, 12.5, 25, 50 or 100 mg/kg bw/day to male and female Sprague-Dawley rats (n=10 and 17-25, respectively) for nine weeks prior to mating and evaluated the effects for over three generations. One third of the pregnant rats was sacrificed on gestational day 14, one third on gestational day 21, while the remaining one third was allowed to deliver.

Maternal toxicity observed included generally dose-dependent decreases in body weight gain, water and food consumption, sedation and inhibited spontaneous locomotion, and at 100 mg/kg bw/day blepharitis (starting after about four to six weeks of treatment). At 12.5 and 25 mg/kg bw/day the body weight gain was decreased in the final third of the treatment period. At 50 and 100 mg/kg bw/day the body weight gain was decreased from the beginning of treatment onwards. Statistics were not reported.

In the groups receiving 50 and 100 mg/kg bw, oestrus cycles were 5-13 days, compared with 4-10 days prior to administration and at 12.5 mg/kg bw and 4-11 days at 25 mg/kg bw. The percentages of females inseminated were 100, 86 and 84% at 0, 50 and 100 mg/kg bw, respectively, and of females being pregnant 94, 81, 72 and 57%* at 0, 25, 50 and 100 mg/kg bw, respectively (*$p<0.05$). At gestational day 14 or 21, post-mortem gross observations did not reveal external uterine or ovarian abnormalities.

In the groups which were allowed to litter, treatment did not affect pregnancy length.[56]

Yokoya treated groups of ten-week-old male and female Sprague-Dawley rats (n=10-22/sex/group) with oral (gavage) doses of chlorpromazine of 0, 12.5, 25, 50 or 100 mg/kg bw/day for two weeks prior to mating. Half of the pregnant mothers were sacrificed on gestational day 14 while the remaining dams were allowed to deliver (F1 generation). The male and remaining female F0 rats were sacrificed at 14 and 20 weeks of age, respectively. Maternal toxicity included dose-related decreases in body weight gain and food consumption, sedation and inhibited spontaneous locomotion. Supporting data for these statements were not reported.

The percentages of females inseminated were 100 and 82% at 0 and 100 mg/kg bw, respectively (difference not statistically significant), and of females being pregnant 95, 75, 72*, 71* and 61%* at 0, 12.5, 25, 50 and 100 mg/kg bw, respectively (*$p<0.05$). At autopsy of male animals treated with 100 mg/kg bw/day, relative weights of pituitary and prostate glands were 6-10% and of adrenals more than 10% higher than those of controls; in females, relative weights of ovaries and adrenals were more than 10% and 6-10% higher and those of pituitary gland and uterus more than 6% lower compared to controls. No effect of chlorpromazine was found on gestation length and delivery.[74]

Izumi et al. administered oral (gavage) doses of chlorpromazine of 0, 3, 10 or 30 mg/kg bw/day to female Crl:CD(SD) rats (n=10/group) for two or four weeks. Animals were sacrificed after the treatment period. During the two-week treatment period, no mortality or changes in body weight (gain) or food consumption were observed. At 10 and 30 mg/kg bw, ptosis was observed and at 30 mg/kg bw, decreased locomotor activity, prone position and lachrymation.

At 10 and 30 mg/kg bw, all animals had irregular oestrus cycles compared to 0/10 in controls ($p<0.01$). At necropsy, there were no gross pathological changes. No changes were observed in the absolute ovary and pituitary weights but uterus weights were decreased at 30 mg/kg bw ($p<0.01$). Microscopic examinations revealed the presence of large atretic follicles in 0, 1, 2 and 6 animals and of alveolar hyperplasia of the mammary gland in 0, 1, 1 and 5 animals, respectively.

When treated for four weeks, results for mortality, clinical signs, body weight, food consumption and gross pathology were similar to those in the two-week study.

At 30 mg/kg bw/day, 10/10 animals had irregular oestrus cycles compared to 3/10, 0/10 and 7/10 at 0, 3 and 10 mg/kg bw/day, respectively. Weights of ovaries and uterus were statistically significantly decreased at 10 and 30 mg/kg bw, those of the pituitary at 30 mg/kg bw. Microscopic examinations revealed the presence

of large atretic follicles in 0, 0, 3 and 3 animals and of alveolar hyperplasia of the mammary gland in 0, 0, 2 and 7 animals, respectively.[32]

Izumi et al. also administered oral (gavage) doses of chlorpromazine of 0, 3, 10 or 30 mg/kg bw/day to female Crl:CD(SD) rats (n=10/group) from two weeks before mating through gestational day 6. Animals were sacrificed at gestational day 13. During the experimental period, no mortality occurred. Decreased motor activity and ptosis were seen at 10 and 30 mg/kg bw and at 30 mg/kg bw, respectively. Body weight gains were affected during the treatment period in the highest dose group; at gestational day 13, body weights were decreased ($p<0.05$) in the two higher dose groups.

All animals treated with 10 or 30 mg/kg bw/day had irregular oestrus cycles compared to 1/10 in the control group. At 30 mg/kg bw, a fertility index of 70% (vs. 89% in controls; not statistically significant) and a prolonged mean copulatory interval of 7.1 days (vs. 2.3 days; $p<0.05$) were observed. Treatment did not affect the mean numbers of corpora lutea and implantations and the mean percentages pre-implantation loss.[32]

Hoekstra et al. treated female Charles River CD rats with oral (gavage) doses of chlorpromazine of 4 mg/kg bw/day for one day or of 45 mg/kg bw/day for seven or 14 days. Vehicle served as a control. No data on general toxicity were presented. After a single dose of chlorpromazine, ovulation was blocked in pro-oestrus rats, which was reversed by coitus. After multiple dosing, the inhibition of ovulation was increased. Again, the ovulation inhibition was reversed by coitus.[31]

Saillenfait and Vannier did not observe effects on gestation length in pregnant Sprague-Dawley rats (number not reported) receiving daily oral (gavage) doses of chlorpromazine of 20 mg/kg bw from gestational day 6 to 20, when compared to vehicle. Treatment did not affect maternal body weight.[57]

Hafs et al. treated male goats (mixed breeding: Saanen and Togenburg; n=3/group) with daily oral doses of chlorpromazine of 0 or 90 mg for eight weeks. Chlorpromazine treatment did not affect body weight gains. There were no statistically significant effects on semen characteristics. At post-mortem examinations of the testes, epididymides, seminal vesicles, thyroid glands and pituitary glands, no effects on their weights or histological changes were observed.[23]

Subcutaneous administration

Bhargava and Jaitly found that in female albino mice (n=12), the average duration of the oestrus cycle during a ten-day treatment with subcutaneous doses of chlorpromazine of 10 mg/kg bw was increased when compared to the duration before treatment. No data were presented on general toxicity but it was stated that experiments were repeated with lower doses in case a dose proved to be fatal or significantly reduced body weight.[8]

Intramuscular administration

Banik et al. treated four-day cyclic female Sprague-Dawley rats (n=7-23/group) one day before the expected pro-oestrus and on the day of pro-oestrus with chlorpromazine (0 or 4 mg/kg bw) intramuscularly. No data on general toxicity were presented. Chlorpromazine given at the day of pro-oestrus blocked ovulation. Ovulation could be induced in rats treated with chlorpromazine after injection with human chorionic gonadotropin.[5]

Lescoat and Chambon measured the effect of chlorpromazine on pituitary concentrations of gonadotropin and prolactin in pregnant rats. Pregnant female rats were injected intramuscularly with 0 or 10 mg chlorpromazine/kg bw every eight hours during 72 hours from gestational day 1 to 4. No data on general toxicity were presented. Chlorpromazine induced decreases in luteinizing hormone from gestational day 0 to 3, decreases in follicle-stimulating hormone from gestational day 1 to 3 and increases in prolactin from gestational day 1 to 4.[39]

Hafs et al. treated male goats (mixed breeding: Saanen and Togenburg; n=3/group) with daily intramuscular doses of chlorpromazine of 0 and 90 mg for eight weeks. Chlorpromazine treatment caused tranquilization in 2/3 goats. There was no effect on body weight gain. Of the semen characteristics examined, semen volume was increased (p=0.08) and sperm motility decreased (p=0.04). Post-mortem examination of the testes, epididymides, seminal vesicles, thyroid glands and pituitary glands did not reveal organ weight or histological changes.[23]

Land injected five ewes per group intramuscularly with 0 or 10 mg chlorpromazine/kg bw twice daily for six different three-day periods during the oestrus cycle. Apart from an increase (by about 9%) at treatment days 3-5 and a decrease (by about 9%) at treatment days 12-14, body weights did not differ

between groups. Results indicated that the ovulation rate was not depressed by any of the treatments. Treatment during the luteal phase of the cycle raised the subsequent mean ovulation rate slightly (2.70 versus 2.27 eggs).[38]

2.3.2 *Developmental toxicity studies*

Oral administration

Saigo et al. administered chlorpromazine (0, 12.5, 25, 50, 100 mg/kg bw/day) daily by gavage to both male and female Sprague-Dawley rats (n=10 and n=17-25, respectively) for nine weeks prior to mating and evaluated the effects for over three generations. Maternal toxicity observed included a generally dose-dependently decreased body weight gain, decreased water and food consumption, accompanied by sedation and inhibited spontaneous locomotion, and at 100 mg/kg bw/day blepharitis (starting after about four to six weeks of treatment). At 12.5 and 25 mg/kg bw/day the body weight gain was decreased in the final third of the treatment period. At 50 and 100 mg/kg bw/day the body weight gain was decreased from the beginning of treatment onwards. Statistics were not reported.

In the animals sacrificed at gestational days 14 and 21, statistically significant decreases were seen in the number of live foetuses/litter at 100 mg/kg bw and at 12.5, 25 and 100 mg/kg bw, respectively, and in the average foetal weights at 25, 50 and 100 mg/kg bw in both groups.

In the groups allowed to litter, statistically significant decreases were noted with respect to the numbers of live pups/litter (at 100 mg/kg bw), the average pup weights at 48 hours (at 25, 50, 100 mg/kg bw) and the percentages of live pups at postnatal day 22 (at 50, 100 mg/kg bw). Especially the weights of the pups of the two higher dose groups did not reach those of the controls during the lactation period. At postnatal week 10, average body weights and oestrus cycle lengths did not differ between groups. No abnormal behaviour was noted, and no visible external abnormalities were seen upon gross observations.

When F1 males and females were allowed to mate for an F2 generation, the percentages of females inseminated or being pregnant did not differ between groups. At sacrifice at gestational day 14, the numbers of live foetuses/litter in F1 groups from exposed parents were not different from those in the controls but average foetal weights were statistically significantly decreased in the groups from parents treated with 12.5, 25 and 100 mg/kg bw. There were no uterine or ovarian abnormalities upon gross observations. In the groups that were allowed to deliver, there were no differences between groups with respect to gestation

length, number of live pups/litter, average pup weight at 48 hours (apart from those descendant from F0 rats treated with 12.5 mg/kg bw) and pup survival at day 22. F2 pups descendant from treated F0 rats gained more weight up to weaning than controls. Gross observations of the F2 pups did not reveal abnormalities.

Recording of wet weights of major organs of F0 and F1 rats showed effects at 100 mg/kg bw only, including increased weights of the liver, kidney, adrenal, pituitary, testis and prostate in males and kidney, adrenal gland and ovary in females, and decreased weights of the pituitary and the uterus in females.[56]

Yokoya et al. treated both male and female Sprague-Dawley rats of the F0 generation (n=10-22/sex/group) daily with chlorpromazine (0, 12.5, 25, 50, 100 mg/kg bw/day) by gavage two weeks prior to mating. The effects of chlorpromazine administered in the F0 generation were evaluated on developmental parameters over three generations. Maternal toxicity included dose-related decreases in body weight gain and food consumption, sedation and inhibited spontaneous locomotion. Supporting data for these statements were not reported.

No effect of chlorpromazine was found on gestation length and delivery. The survival of foetuses and pups, and the live foetal and pup weights decreased dose-dependently in F0 rats receiving at doses ≥25 mg/kg bw. In the F1 rats, the number of live foetuses decreased after exposure of the F0 rats to 50 and 100 mg/kg bw/day chlorpromazine. No effect was observed on the number of live F2 pups, but the average pup weight was statistically significantly increased after exposure of the F0 rats to more than 12.5 mg/kg/day chlorpromazine.[74]

Izumi et al. did not observe effects on mean numbers of live and dead embryos and on mean percentages of postimplantation loss in female Crl:CD(SD) rats (n=10/group) given oral (gavage) doses of chlorpromazine of 0, 3, 10 or 30 mg/kg bw/day from two weeks before mating through gestational day 6 (see 2.3.1 Fertility studies).[32]

Beall et al. administered daily oral (gavage) doses of chlorpromazine of 0, 5, 25 or 35 mg/kg bw to pregnant rats (n=19-24/group, CAW; CFE (SD) spf strain) on days 6 through 15 after mating. On gestational day 21, foetuses were removed and examined for gross, visceral and skeletal abnormalities. Three dams of the high-dose group died during the study.

Treatment did not affect the number of implantations. At 25 and 35 mg/kg bw/day, statistically significant increases in the percentages of dams with

resorptions (45% and 63%, respectively; controls: 17%) and in the percentages of resorptions (7% and 20%, respectively; controls: 2%) were found. At 35 mg/kg bw/day, the average litter size was decreased (10.5±1.0 vs. 13.6±0.4 in controls; $p<0.05$). Apart from one foetus in the low-dose group showing absence of the tail and lumbar vertical malformations, no gross, skeletal or visceral abnormalities were seen.[6]

Saillenfait and Vannier administered oral (gavage) doses of chlorpromazine of 0 or 20 mg/kg bw to pregnant Sprague-Dawley rats (number not reported) received daily from gestational day 6 to 20. Dams were weighed regularly up to postnatal day 21. At parturition, litters were examined for litter size, sex distribution, weight and number of dead or malformed offspring. Within 15 hours after birth, all treated litters were cross-fostered to control females. At postnatal day 21, litters were weaned and littermates were separated and housed by sex until completion of the study at postnatal day 84. During the postnatal period, offspring (12 litters/group) was examined for physical landmarks, neuromotor development and behaviour.

Treatment did not cause statistically significant effects on maternal body weights, litter size, sex distribution within litters, offspring mortality or externally visible malformations. No statistically significant effects of chlorpromazine on parental body weights, litter size, sex distribution within litters, offspring mortality, external examination or physical offspring development or postweaning neurobehavioural tests were observed. However in preweaning behavioural tests, i.e. negative geotaxis (at postnatal days 8, 10, 12), swimming development (at postnatal day 6, 8, 10, 12) and surface righting reflex (at postnatal days 3 to 6), the only changes observed were statistically significantly better performances (compared to controls) in the surface righting reflex test at postnatal day 6 and in swimming development test at postnatal days 6 and 8.[57]

Druga et al. treated female rats (n=5; Wistar/H-Riop) with single oral doses of 0 or 3.7×10^{-4} M/kg bw (119 mg/kg bw) of chlorpromazine, on gestational day 13, 14 or 15. On gestational day 21, females were sacrificed and resorptions, live and dead foetuses, foetal weight and external malformations were recorded. Data on maternal toxicity were not presented. Treatment caused higher foetal mortality ($p<0.05$) and decreased foetal weights ($p<0.05$). There was no effect on the femur index (length: thickness) or the number of foetuses with cleft palate and micromelia.[17]

Robertson et al. treated female CD rats (n=20/group) with oral (gavage) doses of chlorpromazine of 0, 1, 3 or 9 mg/kg bw/day from gestational day 6 to 15. One half of the dams was sacrificed at gestational day 21 for uterine content and foetal examinations. The other half was allowed to litter for offspring growth, morphologic and reflex development and reproductive performance evaluations. Maternal toxicity was limited to the dams receiving 9 mg/kg bw/day, and consisted of decreased activity two to four hours after dosing and a statistically significant decrease in maternal weight gain.

No treatment-related effects were observed on the number of implants, resorptions, live and dead foetuses per litter, foetal weight and external, visceral, and skeletal abnormalities. In addition, no effects were found on gestation length, number of live and dead pups at birth, pup weights, organ weights, physical and reflex development of the pups and histomorphologic and morphometric examinations of their brains. In the post-weaning period there were significant increases in open field activity and decreases in latency time in male offspring at 3 and 9 mg/kg bw compared to the pooled controls. Mating performance of offspring prenatally exposed to chlorpromazine was unaffected.[53]

Ordy et al. administered oral (gavage) doses of 0, 4 and 16 mg/kg bw to female inbred C57BL/10 mice (n=20/group) throughout pregnancy. There was no effect on dam body weight gains but the high dose produced statistically significant decreases in activity in an open field test one to five hours after administration. Treatment caused statistically significant increases in the number of days between mating and birth (22.35, 23.85, 28.80 days, respectively) and statistically significant decreases in mean litter sizes (8.0, 7.9, 5.8, respectively) and mean litter weights (1.41, 1.33, 1.17 g, respectively).[51]

In a second study, Ordy et al. evaluated the effects of prenatally administered doses of chlorpromazine on pregnancy and behaviour of the dams, hepatocellular alterations in relation to mortality, postnatal survival and changes in behaviour of the offspring in female inbred C57BL/10 mice. Groups of 30 to 56 mice were treated with oral (gavage) doses of chlorpromazine of 0, 4 and 16 mg/kg bw from six days after mating until birth. Maternal effects included dose-related increases in the number of days between mating and birth, decreases in body weight gains and reduced activity in open field behaviour. The changes in duration between mating and birth and in body weight gain were observed at the highest dose (both $p<0.001$). The reduced activity in open field behaviour had the same p-value, though whether that applies to both doses, or to the highest one, was not mentioned.

Treatment induced decreases in mean litter sizes (7.6±0.32, 6.8±0.33, 5.8±0.30 ($p<0.001$), respectively) and mean litter weights (1.41±0.01 g, 1.36±0.02 g, 1.22±0.02 g ($p<0.001$), respectively) and increases in percentages of mortality at birth (1.5±0.14%, 3.4±0.23% ($p<0.001$), 11.9±0.33% ($p<0.0001$). Effects of chlorpromazine on offspring behaviour included: fewer avoidances in shock-elicted escape-avoidance learning, less traversing of squares in open field exploration, longer open field latencies and fewer wheel revolutions than the placebo offspring. Chlorpromazine also affected liver enzyme levels in the offspring (viz. increases in leucine aminopeptidase activities, decreases in alkaline phosphatase activities and depletion of glycogen). The percentage of postnatal survival at 60 days was lower after prenatal treatment with chlorpromazine and was lowest in the female offspring, independent of cross-fostering.[52]

Intraperitoneal administration

Singh et al. treated pregnant CF rats (n=5-9) intraperitoneally with single doses of chlorpromazine of 100 mg/kg bw on gestational day 14. On gestational days 16, 17, 18, 19 and 20, foetuses were collected by Caesarean section and examined for abnormalities. No data on maternal toxicity were presented.

Chlorpromazine treatment caused intrauterine growth retardation, increased foetal mortality (19-30%; controls (vehicle): 0-3%), increased percentages of malformed foetuses (91-98%; controls: 0-4%) and a delay of one to three days in the ossification of the centres of the long bones of the extremities, scapulae, ilium and skull bones. No ossification of the ischium and pubis was observed at gestational day 20. Although no abnormal ossification was found in the sternebrae, only 6.5% of the treated foetuses showed all six sternebrae as compared with 98% of the controls.[61-63]

Furukawa et al. injected single intraperitoneal doses of chlorpromazine of 0, 50 and 100 mg/kg bw into Wistar Hannover Gallas rats (n=16-22/group) at gestational day 14. Animals were sacrificed at gestational day 14.5, 15, 17 and 21 for foetal and histopathological placental examinations. Decreased body weight gain (based on the body weight at gestational day 14) was seen at 50 mg/kg bw during gestational day 15 to 18 ($p<0.01$ or $p<0.05$) and at 100 mg/kg bw during gestational day 15 to 21 ($p<0.01$ at all timepoints). Clinical signs such as prone position, hypothermia, loss or decrease of locomotor activity, vaginal haemorrhage, eye discharge and incontinence of urine were seen

disappearing by gestational day 17 at 50 mg/kg bw and by gestational day 19 at 100 mg/kg bw at the latest.

On gestational day 17, the percentages of dams with complete foetal resorptions was 20% and on gestational day 21, 20% and 44% at 50 mg/kg bw and 100 mg/kg bw, respectively. In the other groups, there were no litters with complete resorption. Reduced weights of embryos/foetuses were observed at 5 0 mg/kg bw at gestational days 15 and 17 and at 100 mg/kg bw at gestational days 15-21, and of placentas 50 mg/kg bw at gestational days 17 and at 100 mg/kg bw at gestational days 14.5-21. No external malformations were seen following macroscopic examinations of foetuses at gestational day 21, Histological placental examination showed tropoblast apoptosis in the labyrinth zone, leading to labyrinth zone hypoplasia, and glycogen cell apoptosis in the basal zone, ultimately leading to metrial gland apoptosis.[21]

Subcutaneous administration

Hironaka et al. administered daily subcutaneous doses of chlorpromazine of 0, 8 or 16 mg/kg bw to Sprague-Dawley rats (n=13/group) from gestational days 17 to day 21. At the day of parturition, the total number of offspring, including the number of dead, were recorded. Generally, five male and five female pups/litter were randomly selected and allowed to be reared by nontreated foster mothers. Pup body weights were recorded regularly. At weaning (postnatal day 21), male offspring was randomly selected for a learning experiment (lever press; light-dark discrimination) initiated at five weeks of age. No data on maternal toxicity were presented.

No differences in the number of offspring per dam were observed. Treatment resulted in statistically significant decreases in male pup body weights at birth in both dose groups and in statistically significantly increased pup mortality at birth and during the lactation period in the high-dose group. There was no effect on the acquisition of lever press responses and on the original discrimination learning. However, reversal learning acquisition was impaired.[29]

Umemura et al. evaluated the effects of chlorpromazine on spontaneous motor activity level and learning behaviour of light-dark discrimination in the offspring of female Jcl:SD rats (n=9-11 rats/group) subcutaneously treated with 2 mg/kg bw/day (once daily) or with 8 mg/kg bw/day (twice daily 4 mg/kg bw) from gestational day 17 through postnatal day 21. Vehicle served as control. In the maternal animals, sedation, slowed motion and eye-closing were observed during treatment with doses of 2 and 8 mg/kg bw. At 8 mg/kg bw/day, nursing

behaviour was absent because of cataleptic manifestations. At this high dose, the mean maternal body weights and water and food intakes tended to be lower than at 2 or 0 mg/kg bw/day, but there were no statistically significant differences among groups.

At 8 mg/kg bw/day, mortality of pups during lactation was statistically significantly increased and pup weights were statistically significantly lower on postnatal day 14 and 21. No influence of the treatment was observed on the activity level at six to seven weeks of age and on learning behaviours of the continuous food reinforcement and light-dark discrimination. In some offspring from treated females, the reversal learning of the light-dark discrimination was impaired.[68]

West et al. treated pregnant Crl:CD(SD)BR rats (n=28) subcutaneously with 0 or 1 mg chlorpromazine/kg bw on gestational days 14, 16, and 18. An olfactory discrimination test was performed in pups on postnatal day 9 and 10. Treatment did not affect maternal body weights or food and water consumption. Chlorpromazine treatment slowed the response toward the dam but did not affect the response to the empty goal box. This may indicate a possible deficit in olfactory discrimination.[71]

Intramuscular administration

Hannah et al. treated pregnant Long-Evans hooded rats with intramuscular injections of chlorpromazine doses of 0 and 15 mg/kg bw/day from gestational day 18 onwards. In postnatal week 1, 3 and 24, whole litters were euthanized (3 litters/time point) and concentrations of noradrenaline, dopamine and serotonin in the cerebellum and hippocampus were determined. Data on maternal toxicity were not presented.

At postnatal week 1, increased levels of dopamine and serotonin were found in both brain regions while at postnatal week 24, all three monoamines were decreased in the cerebellum and increased in the hippocampus.[25]

Walker et al. intramuscularly injected single doses of 50 mg chlorpromazine/kg bw into pregnant mice (A/J and C3H strains) on gestational day 14. Mice were killed on gestational day 17 and the foetuses were evaluated for foetal palate morphology. Following treatment, dams were heavily sedated for more than nine to often more than 18 hours (probably depending on the tranquilizer tested).

Retardation of foetal development (presence of a heartbeat, but morphological rating equivalent to a younger foetus) was encountered in high

frequency after treatment with chlorpromazine in A/J mice only. Treatment caused cleft lip with cleft palate in foetuses of the A/J strain (13%) only (spontaneous incidence in the A/J strain: 6-16.7%[34,54]). Isolated cleft palate was found in 21.3% of foetuses of the A/J strain and in 3.2% of foetuses of the C3H strain (spontaneous incidences: 0.25%-1%[34,54] and <1%[10], respectively).[70]

2.3.3 *Lactation*

No relevant experimental animal data were available on the effects of chlorpromazine on or via lactation.

2.4 Conclusion

2.4.1 *Fertility*

The Committee concludes that the human data are not sufficient for classification of chlorpromazine for effects on fertility.[22,65,72] Based on the findings in oral studies in rats[5,31,32,56,74] the Committee proposes to classify chlorpromazine for effects on fertility in Category 1B (*presumed human reproductive toxicant*). This is supported by findings in a subcutaneous study in mice[8] and an intramuscular study in rats[5].

2.4.2 *Developmental toxicity*

The Committee concludes that the human data are not sufficient for classification of chlorpromazine for effects on development.[3,4,7,18-20,24,28,36,37,40,43,45,48,49,55,64,66] Based on the developmental toxicity found in oral studies in rats and mice[6,17,51-53,56,57,74] that was considered to be independent of maternal toxicity, the Committee proposes to classify chlorpromazine for effects on development in category 1B (*presumed human reproductive toxicant*). This conclusion is supported by findings in intraperitoneal[21,61-63] and subcutaneous[29,68,71] studies.

2.4.3 *Lactation*

No studies were found regarding the effects of chlorpromazine on or via lactation in animals.

Following oral administration to lactating women, chlorpromazine was found in breast milk.[3,9,50,67,69,73,75] However, there was insufficient information on the relation between these levels and the possible adverse effects in infants. In

addition, there is no information about a safe/acceptable daily intake of chlorpromazine. Therefore, the Committee cannot calculate a safe level for chlorpromazine in human breast milk.

The Committee proposes not labelling chlorpromazine for effects on or via lactation due to a lack of appropriate human and animal data.

Proposed classification for fertility

Category 1B, H360F.

Proposed classification for developmental toxicity

Category 1B, H360D.

Proposed labelling for effects on and via lactation

Lack of appropriate human and animal data precludes assessment of chlorpromazine for effects on or via lactation.

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A	The Committee
B	The submission letter (in English)
C	Comments on the public draft
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E	Additional considerations to Regulation (EC) 1272/2008
F	Fertility and developmental toxicity studies

Annexes

Annex **A**

The Committee

- A.H. Piersma, *Chairman*
  Professor of Reproductive and Developmental Toxicology, Utrecht University, Utrecht and National Institute of Public Health and the Environment, Bilthoven
- D. Lindhout
  Professor of Medical Genetics; Paediatrician (not practising), Clinical Geneticist, University Medical Centre, Utrecht
- N. Roeleveld
  Reproductive Epidemiologist, Radboud university medical center, Nijmegen
- J.G. Theuns-van Vliet
  Reproductive Toxicologist, TNO Triskelion BV, Zeist
- D.H. Waalkens-Berendsen
  Reproductive Toxicologist, Zeist
- P.J.J.M. Weterings
  Toxicologist, Weterings Consultancy BV, Rosmalen
- A.S.A.M. van der Burght, *Scientific Secretary*
  Health Council of the Netherlands, Den Haag
- J.T.J. Stouten, *Scientific Secretary till June 1, 2014*
  Health Council of the Netherlands, Den Haag
- P.W. van Vliet, *Scientific Secretary from June 1, 2014*
  Health Council of the Netherlands, Den Haag

The first draft of the present document was prepared by D.H. Waalkens-Berendsen and M.J.W. van de Hoven (TNO Quality of Life, Zeist) by contract with the Ministry of Social Affairs and Employment.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **B**

The submission letter (in English)

Subject : Submission of the advisory report *Chlorpromazine*
Your reference : DGV/BMO/U-932542
Our reference : U-8379/EvV/fs/543-E15
Enclosure(s) : 1
Date : 20 May, 2015

Dear Minister,

I hereby submit the advisory report on the effects of *Chlorpromazine* on fertility and on the development of the progeny; it also concerns effects on lactation and on the progeny via lactation.

This advisory report is part of an extensive series in which reproduction toxic substances are classified in accordance with European guidelines. This involves substances to which people may be exposed occupationally.

The advisory report was prepared by a permanent committee of the Health Council of the Netherlands, the Subcommittee on the Classification of Reproduction Toxic Substances of the Dutch Expert Committee on Occupational Safety (DECOS). The advisory report was consequently reviewed by the Health Council's Standing Committee on Health and the Environment.

Today I sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their information.

Yours sincerely,
(signed)
Prof. dr. J.L. Severens,
Vice President

Annex C

Comments on the public draft

A draft of the present report was released in 2014 for public review. The following organization and persons have commented on the draft document:

- T.J. Lentz, PhD, J. O'Callaghan, PhD, National Institute for Occupational Safety and Health (NIOSH), Cincinnati, OH, USA

The comments received, and the reply by the Committee can be found on the website of the Health Council.

Annex **D**

Regulation (EC) 1272/2008 of the European Community

3.7 Reproductive toxicity

3.7.1 Definitions and general considerations

3.7.1.1 Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. The definitions presented below are adapted from those agreed as working definitions in IPCS/EHC Document No 225, Principles for Evaluating Health Risks to Reproduction Associated with Exposure to Chemicals. For classification purposes, the known induction of genetically based heritable effects in the offspring is addressed in Germ Cell Mutagenicity (section 3.5), since in the present classification system it is considered more appropriate to address such effects under the separate hazard class of germ cell mutagenicity.

In this classification system, reproductive toxicity is subdivided under two main headings:

(a) adverse effects on sexual function and fertility;

(b) adverse effects on development of the offspring.

Some reproductive toxic effects cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity. Nonetheless, substances with these effects, or mixtures containing them, shall be classified as reproductive toxicants.

3.7.1.2 For the purpose of classification the hazard class Reproductive Toxicity is differentiated into:

- adverse effects
  - on sexual function and fertility, or
  - on development;
- effects on or via lactation.

3.7.1.3 Adverse effects on sexual function and fertility

Any effect of substances that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

3.7.1.4 Adverse effects on development of the offspring

Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

3.7.1.5 Adverse effects on or via lactation are also included in reproductive toxicity, but for classification purposes, such effects are treated separately (see Table 3.7.1 (b)). This is because it is desirable to be able to classify substances specifically for an adverse effect on lactation so that a specific hazard warning about this effect can be provided for lactating mothers.

3.7.2 Classification criteria for substances

3.7.2.1 Hazard categories

3.7.2.1.1 For the purpose of classification for reproductive toxicity, substances are allocated to one of two categories. Within each category, effects on sexual function and fertility, and on development, are considered separately. In addition, effects on lactation are allocated to a separate hazard category.

Table 3.7.1(a) Hazard categories for reproductive toxicants.

Categories		Criteria
CATEGORY 1		Known or presumed human reproductive toxicant Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).
	Category 1A	Known human reproductive toxicant The classification of a substance in Category 1A is largely based on evidence from humans.
	Category 1B	Presumed human reproductive toxicant The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.
CATEGORY 2		Suspected human reproductive toxicant Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

Table 3.7.1(b) Hazard category for lactation effects.

EFFECTS ON OR VIA LACTATION
Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the: (a) human evidence indicating a hazard to babies during the lactation period; and/or (b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or (c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

3.7.2.2 Basis of classification

3.7.2.2.1 Classification is made on the basis of the appropriate criteria, outlined above, and an assessment of the total weight of evidence (see 1.1.1). Classification as a reproductive toxicant is intended to be used for substances which have an intrinsic, specific property to produce an adverse effect on reproduction and substances shall not be so classified if such an effect is produced solely as a non-specific secondary consequence of other toxic effects.

The classification of a substance is derived from the hazard categories in the following order of precedence: Category 1A, Category 1B, Category 2 and the additional Category for effects on or via lactation. If a substance meets the criteria for classification into both of the main categories (for example Category 1B for effects on sexual function and fertility and also Category 2 for development) then both hazard differentiations shall be communicated by the respective hazard statements. Classification in the additional category for effects on or via lactation will be considered irrespective of a classification into Category 1A, Category 1B or Category 2.

3.7.2.2.2 In the evaluation of toxic effects on the developing offspring, it is important to consider the possible influence of maternal toxicity (see section 3.7.2.4).

3.7.2.2.3 For human evidence to provide the primary basis for a Category 1A classification there must be reliable evidence of an adverse effect on reproduction in humans. Evidence used for classification shall ideally be from well conducted epidemiological studies which include the use of appropriate controls, balanced assessment, and due consideration of bias or confounding factors. Less rigorous data from studies in humans shall be supplemented with adequate data from studies in experimental animals and classification in Category 1B shall be considered.

3.7.2.3 Weight of evidence

3.7.2.3.1 Classification as a reproductive toxicant is made on the basis of an assessment of the total weight of evidence, see section 1.1.1. This means that all available information that bears on the determination of reproductive toxicity is considered together, such as epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs. Evaluation of substances chemically related to the substance under study may also be included, particularly when information on the substance is scarce. The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, the presence of maternal toxicity in experimental animal studies, level of statistical significance for inter-group differences, number of endpoints affected, relevance of route of administration to humans and freedom from bias. Both positive and negative results are assembled together into a weight of evidence determination. A single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification (see also 3.7.2.2.3).

3.7.2.3.2 Toxicokinetic studies in animals and humans, site of action and mechanism or mode of action study results may provide relevant information which reduces or increases concerns about the hazard to human health. If it is conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified.

3.7.2.3.3 If, in some reproductive toxicity studies in experimental animals the only effects recorded are considered to be of low or minimal toxicological significance, classification may not necessarily be the outcome. These effects include small changes in semen parameters or in the incidence of spontaneous defects in the foetus, small changes in the proportions of common foetal variants such as are observed in skeletal examinations, or in foetal weights, or small differences in postnatal developmental assessments.

3.7.2.3.4 Data from animal studies ideally shall provide clear evidence of specific reproductive toxicity in the absence of other systemic toxic effects. However, if developmental toxicity occurs together with other toxic effects in the dam, the potential influence of the generalised adverse effects shall be assessed to the extent possible. The preferred approach is to consider adverse effects in the embryo/foetus first, and then evaluate maternal toxicity, along with any other factors which are likely to have influenced these effects, as part of the weight of evidence. In general, developmental effects that are observed at maternally toxic doses shall not be automatically discounted. Discounting devel-

opmental effects that are observed at maternally toxic doses can only be done on a case-by-case basis when a causal relationship is established or refuted.

3.7.2.3.5 If appropriate information is available it is important to try to determine whether developmental toxicity is due to a specific maternally mediated mechanism or to a non-specific secondary mechanism, like maternal stress and the disruption of homeostasis. Generally, the presence of maternal toxicity shall not be used to negate findings of embryo/foetal effects, unless it can be clearly demonstrated that the effects are secondary non-specific effects. This is especially the case when the effects in the offspring are significant, e.g. irreversible effects such as structural malformations. In some situations it can be assumed that reproductive toxicity is due to a secondary consequence of maternal toxicity and discount the effects, if the substance is so toxic that dams fail to thrive and there is severe inanition, they are incapable of nursing pups; or they are prostrate or dying.

3.7.2.4 Maternal toxicity

3.7.2.4.1 Development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms. In the interpretation of the developmental outcome to decide classification for developmental effects it is important to consider the possible influence of maternal toxicity. This is a complex issue because of uncertainties surrounding the relationship between maternal toxicity and developmental outcome. Expert judgement and a weight of evidence approach, using all available studies, shall be used to determine the degree of influence that shall be attributed to maternal toxicity when interpreting the criteria for classification for developmental effects. The adverse effects in the embryo/foetus shall be first considered, and then maternal toxicity, along with any other factors which are likely to have influenced these effects, as weight of evidence, to help reach a conclusion about classification.

3.7.2.4.2 Based on pragmatic observation, maternal toxicity may, depending on severity, influence development via non-specific secondary mechanisms, producing effects such as depressed foetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited number of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification shall be considered where there is a significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies.

3.7.2.4.3 Classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1. However, when a substance is so toxic that maternal death or severe inanition results, or the dams are prostrate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects. Classification is not necessarily the outcome in the case of minor developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification when seen in association with maternal toxicity.

3.7.2.4.4 Some of the end points used to assess maternal effects are provided below. Data on these end points, if available, need to be evaluated in light of their statistical or biological significance and dose response relationship.

Maternal mortality:

an increased incidence of mortality among the treated dams over the controls shall be considered evidence of maternal toxicity if the increase occurs in a dose-related manner and can be attributed to the systemic toxicity of the test material. Maternal mortality greater than 10 % is considered excessive and the data for that dose level shall not normally be considered for further evaluation.

Mating index

(no. animals with seminal plugs or sperm/no. mated × 100) (*)

Fertility index

(no. animals with implants/no. of matings × 100)

Gestation length

(if allowed to deliver)

Body weight and body weight change:

Consideration of the maternal body weight change and/or adjusted (corrected) maternal body weight shall be included in the evaluation of maternal toxicity whenever such data are available. The calcula-

* () It is recognised that the Mating index and the Fertility index can also be affected by the male.

tion of an adjusted (corrected) mean maternal body weight change, which is the difference between the initial and terminal body weight minus the gravid uterine weight (or alternatively, the sum of the weights of the foetuses), may indicate whether the effect is maternal or intrauterine. In rabbits, the body weight gain may not be useful indicators of maternal toxicity because of normal fluctuations in body weight during pregnancy.

Food and water consumption (if relevant):

The observation of a significant decrease in the average food or water consumption in treated dams compared to the control group is useful in evaluating maternal toxicity, particularly when the test material is administered in the diet or drinking water. Changes in food or water consumption need to be evaluated in conjunction with maternal body weights when determining if the effects noted are reflective of maternal toxicity or more simply, unpalatability of the test material in feed or water.

Clinical evaluations (including clinical signs, markers, haematology and clinical chemistry studies):

The observation of increased incidence of significant clinical signs of toxicity in treated dams relative to the control group is useful in evaluating maternal toxicity. If this is to be used as the basis for the assessment of maternal toxicity, the types, incidence, degree and duration of clinical signs shall be reported in the study. Clinical signs of maternal intoxication include: coma, prostration, hyperactivity, loss of righting reflex, ataxia, or laboured breathing.

Post-mortem data:

Increased incidence and/or severity of post-mortem findings may be indicative of maternal toxicity. This can include gross or microscopic pathological findings or organ weight data, including absolute organ weight, organ-to-body weight ratio, or organ-to-brain weight ratio. When supported by findings of adverse histopathological effects in the affected organ(s), the observation of a significant change in the average weight of suspected target organ(s) of treated dams, compared to those in the control group, may be considered evidence of maternal toxicity.

3.7.2.5 Animal and experimental data

3.7.2.5.1 A number of internationally accepted test methods are available; these include methods for developmental toxicity testing (e.g. OECD Test Guideline 414), and methods for one or two-generation toxicity testing (e.g. OECD Test Guidelines 415, 416).

3.7.2.5.2 Results obtained from Screening Tests (e.g. OECD Guidelines 421 — Reproduction/ Developmental Toxicity Screening Test, and 422 — Combined Repeated Dose Toxicity Study with

Reproduction/Development Toxicity Screening Test) can also be used to justify classification, although it is recognised that the quality of this evidence is less reliable than that obtained through full studies.

3.7.2.5.3 Adverse effects or changes, seen in short- or long-term repeated dose toxicity studies, which are judged likely to impair reproductive function and which occur in the absence of significant generalised toxicity, may be used as a basis for classification, e.g. histopathological changes in the gonads.

3.7.2.5.4 Evidence from in vitro assays, or non-mammalian tests, and from analogous substances using structure-activity relationship (SAR), can contribute to the procedure for classification. In all cases of this nature, expert judgement must be used to assess the adequacy of the data. Inadequate data shall not be used as a primary support for classification.

3.7.2.5.5 It is preferable that animal studies are conducted using appropriate routes of administration which relate to the potential route of human exposure. However, in practice, reproductive toxicity studies are commonly conducted using the oral route, and such studies will normally be suitable for evaluating the hazardous properties of the substance with respect to reproductive toxicity. However, if it can be conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals shall not be classified.

3.7.2.5.6 Studies involving routes of administration such as intravenous or intraperitoneal injection, which result in exposure of the reproductive organs to unrealistically high levels of the test substance, or elicit local damage to the reproductive organs, including irritation, must be interpreted with extreme caution and on their own are not normally the basis for classification.

3.7.2.5.7 There is general agreement about the concept of a limit dose, above which the production of an adverse effect is considered to be outside the criteria which lead to classification, but not regarding the inclusion within the criteria of a specific dose as a limit dose. However, some guidelines for test methods, specify a limit dose, others qualify the limit dose with a statement that higher doses may be necessary if anticipated human exposure is sufficiently high that an adequate margin of exposure is not achieved. Also, due to species differences in toxicokinetics, establishing a specific limit dose may not be adequate for situations where humans are more sensitive than the animal model.

3.7.2.5.8 In principle, adverse effects on reproduction seen only at very high dose levels in animal studies (for example doses that induce prostration, severe inappetence, excessive mortality) would

not normally lead to classification, unless other information is available, e.g. toxicokinetics information indicating that humans may be more susceptible than animals, to suggest that classification is appropriate. Please also refer to the section on maternal toxicity (3.7.2.4) for further guidance in this area.

3.7.2.5.9 However, specification of the actual 'limit dose' will depend upon the test method that has been employed to provide the test results, e.g. in the OECD Test Guideline for repeated dose toxicity studies by the oral route, an upper dose of 1 000 mg/kg has been recommended as a limit dose, unless expected human response indicates the need for a higher dose level.

3.7.3 Classification criteria for mixtures

3.7.3.1 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

3.7.3.1.1 The mixture shall be classified as a reproductive toxicant when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 reproductive toxicant and is present at or above the appropriate generic concentration limit as shown in Table 3.7.2 for Category 1A, Category 1B and Category 2 respectively.

3.7.3.1.2 The mixture shall be classified for effects on or via lactation when at least one ingredient has been classified for effects on or via lactation and is present at or above the appropriate generic concentration limit as shown in Table 3.7.2 for the additional category for effects on or via lactation.

Table 3.7.2 Generic concentration limits of ingredients of a mixture classified as reproduction toxicants or foreffects on or via lactation that trigger classification of the mixture.

Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:			
	Category 1A reproductive toxicant	Category 1B reproductive toxicant	Category 2 reproductive toxicant	Additional category for effects on or via l actation
Category 1A reproductive toxicant	≥ 0,3 % [Note 1]			
Category 1B reproductive toxicant		≥ 0,3 % [Note 1]		
Category 2 reproductive toxicant			≥ 3,0 % [Note 1]	
Additional category for effects on or via lactation				≥ 0,3 % [Note 1]

Note The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).
Note 1 If a Category 1 or Category 2 reproductive toxicant or a substance classified for effects on or via lactation is present in the mixture as an ingredient at a concentration above 0,1 %, a SDS shall be available for the mixture upon request.

3.7.3.2 Classification of mixtures when data are available for the complete mixture

3.7.3.2.1 Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients of the mixture. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual components. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of reproduction test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

3.7.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles

3.7.3.3.1 Subject to paragraph 3.7.3.2.1, where the mixture itself has not been tested to determine its reproductive toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

3.7.4 Hazard Communication

3.7.4.1 Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.7.3

Table 3.7.3 Label elements for reproductive toxicity.

Classification	Category 1A or Category 1B	Category 2	Additional category for effects on or via lactation
GHS Pictograms			No pictogram
Signal Word	Danger	Warning	No signal word
Hazard Statement	H360: May damage fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H361: Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H362: May cause harm to breast-fed children.
Precautionary Statement Prevention	P201 P202 P281	P201 P202 P281	P201 P260 P263 P264 P270
Precautionary Statement Response	P308 + P313	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405	
Precautionary Statement Disposal	P501	P501	

Annex **E**

Additional considerations to Regulation (EC) 1272/2008

The classification and labelling of substances is performed according to the guidelines of the European Union (Regulation (EC)1272/2008) presented in Annex D. The classification of compounds is ultimately dependent on an integrated assessment of the nature of all parental and developmental effects observed, their specificity and adversity, and the dosages at which the various effects occur. The guideline necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the regulation, the Committee has agreed upon a number of additional considerations:

- If there is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility or subsequent developmental toxic effects in the offspring, the compound will be classified in category 1A, irrespective of the general toxic effects (see Annex D, 3.7.2.2.1.).
- Adverse effects in a reproductive study, occurring without reporting the parental or maternal toxicity, may lead to a classification other than category 1B, when the effects occur at dose levels which cause severe toxicity in *general* toxicity studies.
- Clear adverse reproductive effects will not be disregarded on the basis of reversibility per se.

- The Committee does not only use guideline studies (studies performed according to OECD* standard protocols) for the classification of compounds, but non-guideline studies are taken into consideration as well.

* Organisation for Economic Cooperation and Development.

Annex **F**

Fertility and developmental toxicity studies

Table 1 Fertility effects with chlorpromazine in animals: oral administration.

authors	species	experimental period/design	dose	general toxicity	effects on reproductive organs/ effects on reproduction
Saigo (1990)	Sprague-Dawley rats (males: n=10/ group; females: n=17-25/ group)	male and female rats treated 9 wk prior to mating; 1/3 of pregnant rats sacrificed at gd 14, 1/3 at gd 21, 1/3 allowed to deliver	0, 12.5, 25, 50, 100 mg/kg bw/d; gavage	generally dose-dependently decreased bw gain, decreased water, food consumption; after every chlorpromazine administration: animals sedated, spontaneous locomotion inhibited, symptoms persisting for up to several hr with dose-dependent intensity and duration; after the 2nd wk of administration: the durations of the symptoms following administration shortened slightly; at 100 mg/ kg bw/d, about 4-6 wk after the beginning of the treatment: blepharitis in 25% of the animals (more severe in males than in females). At 12.5 and 25 mg/kg bw/day the body weight gain was decreased in the final third of the treatment period. At 50 and 100 mg/kg bw/day the body weight gain was decreased	oestrus cycle length: 4-10 d, 4-11 d, 5-13 d, 5-13 d at 12.5, 25, 50, 100 mg/kg bw/d, resp.; 4-10 d prior to treatment number of females inseminated (%): 100, 100, 94, 86, 84, at 0, 12.5, 25, 50, 100 mg/kg bw, resp. number of females pregnant (%): 94, 95, 81, 72, 57*, resp. no effect on gestation length post-mortem gross examination at gd 14 or 21: no external uterine or ovarian abnormalities

				from the beginning of treatment onwards. Statistics were not reported.	
Yokoya (1990)	Sprague-Dawley rats (males: n=10/group; females: n=19-22/group)	male and female rats treated 2 wk before mating; 1/2 of pregnant rats sacrificed at gd 14, 1/2 allowed to deliver	0, 12.5, 25, 50, 100 mg/kg bw/d; gavage	dose-relatedly decreased bw gain, decreased water, food consumption; marked decreased bw gain in males at 100 mg/kg bw/d; about 5-10 min after administration: spontaneous locomotion of all chlorpromazine-treated groups inhibited, animals sedated, symptoms persisting from 30 min to several hr with dose-dependent intensity and duration; Supporting data for these statements were not reported. Post-mortem examination at wk 14 (males) and wk 20 (females): at 100 mg/kg bw/d: increased male and female liver, kidney wt (>10%)	number of females inseminated (%): 100, 100, 90, 90, 82, resp. number of females pregnant (%): 95, 75, 72*, 71*, 61*, resp. no effect on gestation length post-mortem examination at wk 14 (males) and wk 20 (females): at 100 mg/kg bw/d: increased male adrenal, pituitary, prostate gland wt (>10%); increased female adrenal gland, ovary wt (>10%); decreased female pituitary, uterus wt (>6%)
Izumi et al. (2009)	female Crl:CD(SD) rats (n=10/group)	2 wk	0, 3, 10, 30 mg/kg bw/d; gavage	no mortality or changes in bw (gain) or food consumption; at 10 and 30 mg/kg bw: ptosis; at 30 mg/kg bw: decreased locomotor activity, prone position, lachrymation	number of animals with irregular oestrus cycle: 0, 1, 9**, 10**, resp. post-mortem examinations: mean uterus wt (mg): 396±164, 487±159, 323±100, 230±45**, resp.; no effect on absolute ovary and pituitary wt; no gross pathological changes; microscopically: large atretic follicles in 0, 1, 2, 6 animals, resp.; alveolar mammary gland hyperplasia in 0, 1, 1, 5 animals, resp.
Izumi et al. (2009)	female Crl:CD(SD) rats (n=10/group)	4 wk	0, 3, 10, 30 mg/kg bw/d; gavage	no mortality or changes in bw (gain) or food consumption; at 10 and 30 mg/kg bw: ptosis; at 30 mg/kg bw: decreased locomotor activity, prone position, lachrymation	number of animals with irregular oestrus cycle: 3, 0, 7, 10**, resp. post-mortem examinations: mean ovary wt (mg): 78.0±11.7, 71.8±6.7, 64.1±7.3**, 58.9±12.7**, resp.; mean pituitary wt (mg): 11.5±0.8, 11.6±1.1, 9.6±1.8**, 9.2±1.3**, resp.; mean uterus wt (mg): 384±159, 367±132, 279±42**, 272±50**, resp.; no gross pathological changes; microscopically: large atretic follicles in 0, 0, 3, 3 animals,

					resp.; alveolar mammary gland hyperplasia in 0, 0, 2, 7 animals, resp.
Izumi et al. (2009)	female Crl:CD(SD) rats (n=10/ group	2 wk before mating through gd 6 sacrifice: gd 13	0, 3, 10, 30 mg/kg bw/d; gavage	no mortality; during treatment: decreased bw gain at 30 mg/kg bw; at gd 13 at 10 and 30 mg/ kg bw: decreased bw* decreased motor activity and ptosis at 10 and 30 mg/kg bw and at 30 mg/kg bw, resp.	number of animals with irregular oestrus cycle: 1, 1, 10**, 10**, resp.; fertility index (%): 89, 100, 90, 70, resp.; copulatory interval (d): 2.2, 3.0, 2.0, 7.1*, resp.; no effect on mean numbers of corpora lutea, mean number of implantations, mean percentages preimplantation loss
Hoekstra et al. (1984)	female CD rats n=3/ group)	1 (day of pro-oestrus) , 7 or 14 d; females mated after last day of dosing	0, 4 mg/kg bw, for 1 d; 0, 45 mg/kg bw/d for 7 or 14 d; gavage	no effect on bw	After a single injection ovulation was blocked in pro-oestrus rats, which was reversed by coitus. After multiple dosing, the inhibition of ovulation was increased. Again, the ovulation inhibition was reversed by coitus
Hafs/Williams (1964)	male goats (mixed breeding: Saanen and Togenburg; n=3/group)	8 wk semen collected at 2-wk intervals, 5 times before treatment, 5 times during treatment	0, 90 mg/kg bw/d; spansules	no effect on bw or heart rate (measured 30 min after administration); no signs of lethargy or paralysis	no effect on pH of fresh sperm, semen/ejaculate, sperm motility, % motile sperm, sperm/mL semen, total sperm/ ejaculate, motile sperm/ ejaculate post-mortem examinations: no organ wt or macro/microscopic changes in testes, epididymides, seminal vesicles, thyroid glands, pituitary glands

bw=body weight; d=day(s); gd=gestational day(s); wk=week(s); wt=weight(s); *: $p<0.05$; **: $p<0.001$.

Table 2 Fertility effects with chlorpromazine in animals: parental administration.

authors	species	experimental period/design	dose	general toxicity	effects on reproductive organs/effects on reproduction
Bhargava/ Jaitly (1964)	female albino mice (n=12)	10 d vaginal smears recorded for 10 d before treatment and during treatment	10 mg/kg bw/d; sc	no effect on bw	average duration of oestrus cycle before treatment (d): 4.58±0.76 average duration of oestrus cycle during treatment (d): 8.44±2.4**
Banik/Herr (1968)	female Sprague-Dawley rats (n=7-23/ group)	the day before, the day of expected pro-oestrus.	0, 4 mg/kg bw; im	not reported	Inhibition of ovulation and no alteration of the estrogenic effects
Lescoat/ Chambon (1983)	female Wistar rats (n=unknown)	3 times/d; gd 0-3; sacrifice at gd 1, 2, 3, or 4; pituitary concentrations of FSH, LH, prolactine measured	0, 30 mg/kg bw/d; im	not reported	FSH: statistically significantly lower on gd 1, 2, 3 compared to controls LH: statistically significantly on gd 1, 2, 3, 4 prolactine: statistically significantly higher at on gd 1, 2, 3, 4
Hafs/Williams (1964)	male goats (mixed breeding: Saanen and Togenburg; n=3/group)	8 wk semen collected at 2-wk intervals, 5 times before treatment, 5 times during treatment	0, 90 mg/kg bw/d; im	no effect on bw gain; slight lethargy in 3/3; limb paralysis in 2/3 (starting after about 2 wk of treatment)	average semen volume: 2.0 vs. 1.6 in controls (p=0.08); average sperm/mL fresh semen (x10^9): 1.65 vs. 2.13 (p=0.04) no effect on pH of fresh sperm, sperm motility, % motile sperm, total sperm/ ejaculate, motile sperm/ejaculate post-mortem examinations: no organ wt or macro/microscopic changes in testes, epididymides, thyroid glands, pituitary glands
Land (1973)	Finn-Dorset ewes (n=5/ group)	2 times/d; 6 different 3-d periods of oestrus cycle	0, 20 mg/kg bw/d; im	increased bw (by about 9%) at treatment d 3-5; decreased bw (by about 9%) at treatment d12-14	bw (kg): d 0-2: 61.05; d 3-5: 65.25; d 6-8: 61.15; d 9-11: 60.15; d 12-14: 55.15; d 15-17: 60.55; controls: 60.16 ovulation (CL): d 0-2: 2.20; d 3-5: 2.60; d 6-8: 2.80; d 9-11: 2.60; d 12-14: 2.80; d 15-17: 2.20; controls: 2.27 oestrus cycle length (d): d 0-2: 16.9; d 3-5: 17.7; d 6-8: 17.5; d 9-11: 17.7; d 12-14: 18.7; d 15-17: 17.8; controls: 17.4

bw=body weight; d=day(s); FSH=follicle-stimulating hormone; gestational day(s); im=intramuscular(ly); LH=luteinizing hormone; pnd=postnatal day(s); sc=subcutaneous(ly); wk=week(s); wt=weight(s); *: p<0.05; **: p<0.001.

Table 3 Developmental toxicity studies with chlorpromazine in animals: oral (gavage) administration.

authors	species	experimental period/design	dose	general toxicity	developmental toxicity
Saigo (1990)	Sprague-Dawley rats (males: n=10/group; females: n=17-25/group)	male and female rats treated 9 wk prior to mating; 1/3 of pregnant rats sacrificed at gd 14, 1/3 at gd 21, 1/3 allowed to deliver F1 pups which were either sacrificed after weaning or mated at pnw 10 to obtain an F2 generation	0, 12.5, 25, 50, 100 mg/kg bw/d	generally dose-dependently decreased bw gain, decreased water, food consumption; after every chlorpromazine administration: animals sedated, spontaneous locomotion inhibited, symptoms persisting for up to several hr with dose-dependent intensity and duration; after the 2nd wk of administration: the durations of the symptoms following administration shortened slightly; at 100 mg/kg bw/d, about 4-6 wk after the beginning of the treatment: blepharitis in 25% of the animals (more severe in males than in females). At 12.5 and 25 mg/kg bw/day the body weight gain was decreased in the final third of the treatment period. At 50 and 100 mg/kg bw/day the body weight gain was decreased from the beginning of treatment onwards. Statistics were not reported	sacrifice at gd 14: mean number of live foetuses/litter: 12.2±1.2, 11.5±0.8, 13.2±1.2, 12.0±1.0, 9.7±0.8*, at 0, 12.5, 25, 50, 100 mg/kg bw/d, resp.; average live foetal wt (g): 2.68±0.02, 2.65±0.03, 2.48±0.02*, 2.39±0.05**, 2.12±0.04** sacrifice at gd 21: mean number of live foetuses/litter: 12.7±0.2, 11.7±0.1*, 10.8±0.1*, 12.2±0.4, 9.3±1.3*, resp.; average live foetal wt (g): 5.03±0.03, 5.34±0.04**, 5.21±0.05*, 4.94±0.17, 3.84±0.26**, resp. F1 generation: mean number of live pups/litter: 13.0±0.9, 12.0±0.6, 11.3±0.9, 11.4±0.9, 9.0±0.9*, resp.; average pup wt at 48 hr (g): 6.38±0.05, 6.42±0.03, 6.04±0.04*, 5.65±0.36*, 5.48±0.36*, resp.; pup survival at pnd 22 (%): 94, 96, 100, 80*, 81*, resp. at pnw 10: no effect on oestrus cycle length, average bw; no abnormal behaviour seen; no visible external abnormalities upon gross observations. mating F1: no effect on percentages of females inseminated or being pregnant sacrifice at gd 14: no effects on mean number of live foetuses/litter; average live foetal wt (g): 2.56±0.01, 2.48±0.03*, 2.46±0.02*, 2.45±0.05**, 2.23±0.06* no uterine, ovarian abnormalities upon gross observations F2 generation: no effect on gestation length, mean number of live pups/

					litter, average pup wt at 48 hr; pup survival at pnd 22; F2 pups descendant from treated F0 rats gained more weight up to weaning than controls; no visible abnormalities upon gross observations recording of wet organ wt of F0 and F1 rats: only effects at 100 mg/kg bw/d: increases in wt of the liver, kidney, adrenal, pituitary, testis, prostate in males, in kidney, adrenal gland, ovary in females, decreases in wt of pituitary, the uterus in females
Yokoya (1990)	Sprague-Dawley rats (n=10-22/ sex/ group)	male and female rats treated 2 wk before mating; 1/2 of pregnant rats sacrificed at gd 14, 1/2 allowed to deliver	0, 12.5, 25, 50, 100 mg/kg bw/d	dose-relatedly decreased bw gain, decreased water, food consumption; marked decreased bw gain in males at 100 mg/kg bw/d; about 5-10 min after administration: spontaneous locomotion of all chlorpromazine-treated groups inhibited, animals sedated, symptoms persisting from 30 min to several hr with dose-dependent intensity and duration; Supporting data for these statements were not reported. Post-mortem examination at wk 14 (males) and wk 20 (females): at 100 mg/kg bw/d: males: increased adrenal, pituitary, prostate gland wt (>10%); females: increased ovary wt (>10%), decreased pituitary, uterus wt (>6%)	sacrifice at gd 14: mean number of live foetuses/ litter: 12.4±0.7, 9.1±0.7*, 9.9±0.7*, 8.8±0.5*, 8.0±0.7*, at 0, 12.5, 25, 50, 100 mg/kg bw/d, resp.; average live foetal wt (g): 2.72±0.02, 2.62±0.01*, 2.30±0.03**, 1.98±0.08**, 2.04±0.05** F1 generation: mean number of live pups/ litter: 12.4±0.8, 9.7±0.7*, 8.8±1.1*, 8.3±1.0*, 8.0±1.0*, resp.; average pup wt (g) at 48 hr, males: 6.85±0.05, 6.10±0.14*, 6.17±0.36*, 5.12±0.54*, 5.07±0.84*, resp.; females: 6.83±0.06, 6.05±0.13*, 5.95±0.32*, 5.16±0.45*, 5.05±0.65*, resp.; at pnd 7, males: 14.83±0.58, 13.46±0.65, 11.34±0.71*, 10.64±0.84*, 10.34±0.71*, resp.; females: 14.80±0.67, 13.47±0.56, 11.40±0.86*, 10.08±0.72*, 10.28±0.54*, resp.; at pnd 14, males: 25.32±0.84, 24.68±0.73, 23.04±0.56, 22.35±0.93*, 23.45±1.30, resp.; females: 24.06±0.75, 23.34±0.64, 22.67±0.36, 22.36±0.83*, 23.06±0.93*, resp.; at pnd 21, males: 42.34±1.04,

37.65±0.81*, 32.46±1.32*, 30.03±2.34*, 30.18±2.65*, resp.; females: 41.06±1.10, 36.64±0.94*, 32.00±1.06*, 29.18±1.84*, 29.07±2.03*, resp.
pup survival at pnd 22 (%): 99, 93, 75*, 58**, 46**, resp.
mating F1:
no effect on percentages of females inseminated or being pregnant
sacrifice at gd 14:
mean number of live foetuses/ litter: 11.6±0.5, 11.6±0.8, 10.0±1.1, 10.0±0.3*, 10.01±0.3*, resp.; average live foetal wt (g): 2.61±0.02, 2.58±0.04, 2.52±0.02*, 2.64±0.08, 2.43±0.06*
no effect on F1 male and female wet organ wt at post-mortem examinations at wk 3, 12 (males), 18 (females)
F2 generation:
no effect on gestation length, mean number of live pups/ litter; average pup wt (g) at 48 hr, males: 5.73±0.08, 7.14±0.29*, 6.39±0.15*, 6.77±0.21*, 7.17±0.27*, resp.; females: 5.89±0.06, 6.93±0.18*, 6.41±0.34*, 6.59±0.68*, 7.03±0.34*, resp.; at pnd 7, males: 14.87±0.23, 16.10±0.38*, 16.14±0.86*, 10.52±0.75*, 18.36±0.53*, resp.; females: 14.79±0.41, 16.00±0.44*, 16.08±0.76*, 16.50±0.87*, 18.19±0.44*, resp.; at pnd 14, males: 23.15±0.92, 28.94±0.64*, 27.77±0.73*, 27.61±0.32*, 30.23±0.51, resp.; females: 23.26±0.93, 28.89±0.56*, 27.75±0.74, 27.56±0.81*, 30.33±0.56*, resp.; at pnd 21, males: 34.14±0.10, 42.63±0.84*, 22.34±1.34*, 41.07±1.46*, 45.89±1.63*, resp.; females: 33.04±0.11, 41.52±0.65*, 41.36±1.36*, 40.84±0.96*, 44.08±1.34*,

					resp. pup survival at pnd 22 (%): 100, 89, 100, 68**, 50**, resp. no effect on F2 male and female wet organ wt at post-mortem examinations at pnw 3
Izumi et al. (2009)	female Crl:CD(SD) rats (n=10/ group	2 wk before mating through gd 6 sacrifice: gd 13	0, 3, 10, 30 mg/kg bw/d	no mortality; during treatment: decreased bw gain at 30 mg/kg bw; at gd 13 at 10 and 30 mg/kg bw: decreased bw* decreased motor activity and ptosis at 10 and 30 mg/kg bw and at 30 mg/kg bw, resp.	no effect on mean numbers of live and dead embryos, on mean percentages of postimplantation loss
Beall (1970)	female CAW;CFE(SD) spf rats (n=19-24/group)	gd 6-15 gd 21: foetuses removed and examined for gross, visceral and skeletal abnormalities	0, 5, 25, 35 mg/kg bw/d	not reported, but mortality in 3/22 dams at 35 mg/kg bw/d	number of dams with resorptions: 4 (17%), 7 (37%), 9 (45%)*, 12 (63%)**, at 0, 5, 25, 35 mg/kg bw/d, resp.; number of resorptions: 6 (1.8%), 13 (6%), 17 (7%)**, 51 (20%)**, resp.; mean litter size: 13.6±0.4, 11.5±0.8, 13.3±0.5, 10.5±1.0* no effect on the number of implantations mean foetal bw (g): 5.36±0.03, 5.16±0.06**, 5.05±0.03**, 5.32±0.03, resp. number of abnormal foetuses: 0, 1 (with absence of tail, 3 posterior lumbar vertebrae; split ossification centre first lumbar vertebra; prematurely fused second lumbar arch), 0, 0, resp.
Saillenfait/ Vannier (1988)	female Sprague-Dawley rats (n=31/group)	gd 6-20 at parturition, litters examined: litter size, sex distribution, number of dead or malformed offspring; 15 hr after birth, all treated litters were cross-fostered to control females; offspring observed for physical landmarks	0, 20 mg/kg bw/d	no effect on maternal bw	no effect on gestation length, litter size, litter sex distribution, mortality mean offspring wt (g): preweaning: pnd 1: 6.2±0.14, 6.2±0.16 at 0, 20 mg/kg bw, resp.; pnd 3: 7.8±0.25, 8.5±0.17*, resp.; pnd 6: 11.6±0.41, 12.7±0.30*; pnd 9: 16.2±0.54, 18.2±0.54, resp.; pnd 12: 21.9±0.79, 23.2±0.52*, resp.; pnd 15: 26.3±0.76, 28.3±0.67, resp.; pnd 18: 31.1±1.04, resp.; pnd 21: 38.0±1.30, 43.2±1.04*, resp.; postweaning: pnd 28: 66±2.2, 73±1.8*, resp., pnd 35:

		(pinna detachment, incisor eruption, eye opening), behaviour: pre-weaning: surface righting reflex, swimming development (angle assessment, limb usage), negative geotaxis, open field (ambulation, rearing); post-weaning: rotarod, open field (ambulation, rearing), pupillary reflex, water maze (learning, retention), nocturnal activity, auditory startle reflex; in males only, neurohistology and measurement of chatecholamine (noradrenaline, dopamine) and DNA concentrations; sacrifice: males: pnw 9, 11 or 12, females: pnw 9	111±3.5, 120±2.7*, resp.; pnd 42: 166±3.4, 166±3.7, resp.; pnd 49: 217±4.0, 222±3.8, resp.; pnd 56: 268±5.0, 275±4.1, resp.; pnd 63: 304±6.2,309±5.1, resp. no malformations upon external examination no effect on physical landmarks pre-weaning behavioural testing: surface righting reflex (% of pups righted <2 s): pnd 3: trial1: 37, 40, resp., trial 2: 41, 45, resp.; pnd 4: trail 1: 59, 68, resp., trial 2: 71, 70, resp.; pnd 5: trial 1: 77, 89, resp., trial 2: 79, 90, resp.; pnd 6: trial 1: 93, 99**, resp., trial 2: 94, 100**, resp.; swimming development: angle assessment: pnd 6: 1.2±0.09, 1.3±0.06*, resp.; pnd 8: 2.5±0.09, 3.4±0.10**, resp.; pnd 10: 3.8±0.09, 3.7±0.10, resp.; pnd 12: 4.3±0.08, 4.5±0.06*, resp.; no effect on limb usage no effect on negative geotaxis no effect on open field performance on pnd 18 post-weaning behavioural testing: rotarod test on pnd 22 (s) males: trial1: 81±62, 63±64, resp.; trial 2: 96±66, 82±70*, resp.; trial 3: 119±71, 107±73, resp.; trial 4: 131±67, 102±73, resp.; no effect in females; open field performance: ambulation: pnd 35: males: 13.9±5.5, 14.6±7.3, resp. ; females: 17.8±6.0, 20.4±6.3*, resp.; no effect on rearing in males and females on pnd 35, on rearing or ambulation in males (females not tested) on pnd 56 compared to controls, lower** nocturnal activity no effect on pupillary reflex, water maze performance, auditory startle response DNA (µg/g brain): 973±59,

					DNA (µg/g brain): 973±59, 467±51**, resp.; no effect on cathecholamine concentrations no histological brain changes
Druga et al. (1980)	female Wistar/ H-Riop rats (n≥5/group)	gd 13, 14 or 15 sacrifice: gd 21 for foetal examinations	0, 119 mg/kg bw	not reported	treatment on gd 14: foetal mortality (%): 7.6±0.9, 24.5±7.9**, at 0, 119 mg/kg bw, resp.; mean foetal wt (g): 3.5±0.06, 3.2±.10**, resp. (no data concerning treatment on gd 13 or 15) no effect on femur-index value (length: thickness), on incidence of foetuses with cleft palate or micromelia at treatment on gd 13, 14 or 15
Robertson et al. (1980)	female Charles River CD rats (n=20/group)	gd 6-15 ½ of pregnant animals sacrificed at gd 21 for foetal examinations; other ½ allowed to deliver ; on gd 1, treated animals cross-fostered with controls; ½ of the offspring selected for physical landmarks (pinna detachment, lower incision eruption, hair growth, eye opening, vaginal canalization, testis descent), behavioural testing (surface righting reflex, horizontal movement, auditory startle reflex, open field activity, rotarod), reproductive performance; other ½ sacrificed at pnw	0, 1, 3, 9 mg/ kg bw/d; 2 control groups included	at 9 mg/kg bw: decreased activity 2-4 hr after dosing; statistically significantly decreased bw gain	sacrifice at gd 21: no effect on total number of implantations, resorptions, live and dead foetuses /litter, on foetal weights; no external, visceral, skeletal abnormalities. F1 generation: no effect on gestation length pre-weaning: pnd 1: average pup wt/litter (g): 6.5, 6.5, 6.2, 6.1**, 6.2** at 0, 0, 1, 3, 9 mg/kg bw, resp.; no effect on sex distribution, number of live and dead pups, number of live pups/litter pnd 7, 14, 21: no effect on number of live pups, number of dead pups during d 2-7, 8-14, 15-21, resp., average pup wt/litter postweaning: no effect on average male and female bw on pnd 21, 42, 84, 105; mean bw gain (g): pnd 21-42: females: 115±1.5, 111±1.7*, 112±1.6, 110±1.8* at 0 (pooled), 1, 3, 9 mg/kg bw, resp.; males: 156±2.1, 151±1.6, 149±1.5, 142±2.6*, resp.; pnd 42-84: females: 116±1.6, 109±1.8, 108±1.5, 116±1.7, resp.; males: 255±3.1, 254±3.0, 245±3.5*, 251±3.3*, resp.; pnd 21-105: females: 228±2.7, 229±3.2, 226±4.3, 227±3.7; males: 440±5.1, 450±6.4, 424±7.2, 423±6.3, resp.

		15 or 16 for weighing organs and, in control and high-dose animals, histological brain examination			pnw 3: decreased*** latency time at 3, 9 mg/kg bw; pnw 7: increased*** open-field activity at 9 mg/kg bw; pnw 13: increased*** open-field activity at 3 mg/kg bw; decreased*** latency time at 9 mg/kg bw; no effect on physical development, righting and auditory startle reflex, reproductive performance no effect on organ wt, no histomorphologic and morphometric changes in brains
Ordy et al. (1963)	female inbred C57BL/10 mice (n=20/group; controls: n=40)	6 d after mating until delivery	0, 4, 16 mg/kg bw/d	no effect on bw gain; at 16 mg/kg bw, decreased activity in an open field test ($p<0.001$) 1-5 hr after administration	mean d between mating and birth: 22.35, 23.85, 28.80*** at 0, 4, 16 mg/kg bw/d, resp.; mean litter size: 8.0, 7.9, 5.8*, resp. ; mean litter wt (g): 1.41, 1.33, 1.17****
Ordy et al. (1966)	female inbred C57BL/10 mice (n=30-56/ group)	6 d after mating until delivery after delivery, offspring cross-fostered examinations: leucine aminopeptidase, alkaline phosphatase activity, glycogen in liver homogenates at birth and pnd 75; open-field exploration, locomotor activity (not at pnd 20), shock-elicited escape-avoidance conditioning at pnd 20 and 60; hexobarbital-induced loss of righting reflex at pnd 30 and 60 (at 4 mg/kg bw only)	0, 4, 16 mg/kg bw/d	mean bw gain (g): 15.1±0.48, 13.4±0.57, 10.3±0.52*** at 0, 4, 16 mg/kg bw, resp.; mean duration between mating and birth (d): 22.7±0.64, 25.4±1.3, 30.8±1.3***, resp.; impaired open-field behaviour*** (whether statistical result applies to both doses or to the highest one, not mentioned)	mortality at birth (%): 1.5±0.14, 3.4±0.23****, 11.9±***** at 0, 4, 16 mg/kg bw, resp.; mean litter size: 7.6±0.32, 6.8±0.33, 5.8±0.30, resp.; mean litter wt (g): 1.41±0.01, 1.36±0.02, 1.22±0.02****, resp.; mortality at pnd 60: 35% in control offspring, 49% in treated offspring**; no differences in sex ratio of postnatal mortality between offspring from untreated mothers raised by untreated mothers (males: 47%, females: 53%) or raised by treated mothers (males: 47%, females: 53%); differences in sex ratio of postnatal mortality in offspring from treated mothers raised by untreated mothers (males: 33%, females: 67%)** or raised by treated mothers (males: 38%, females: 62%)*; in liver homogenates: at birth: increased leucine aminopeptidase activity**, decreased alkaline phosphatase activity** at 16 mg/kg bw, decreased glycogen** at 4 and

				16 mg/kg bw; at pnd 75: increased leucine aminopeptidase activity**, increased alkaline phosphatase activity** (glycogen not determined); hexobarbital-induced loss of righting reflex: differences in duration of hexobarbital action at pnd 30 and 60 between treated and control offspring**, between pnd 30 and pnd 60 test replication**, between males and females** behavioural tests: (generally dose-related) fewer avoidances in shock-elicted escape-avoidance learning, less traversing of squares in open field exploration, longer open field latencies and fewer wheel revolutions in treated offspring

bw=body weight(s); d=day(s); hr=hour(s); pnd=postnatal day(s); pnw=postnatal week(s); wk=week(s); wt=weight(s); *=p<0.05; **=p<0.01; ***=p<0.005; ****=p<0.001; *****=p<0.0001.

Table 4 Developmental toxicity studies with chlorpromazine in animals: parental administration

authors	species	experimental period/design	dose/route	general toxicity	developmental toxicity
Singh et al. (1978, 1978, 1979)	female CF rats (n=5-9; controls n=3-4);	gd 14 sacrifice: gd 16, 17, 18,19, 20 for foetal skeletal examinations	0, 100 mg/kg bw; ip	not described	foetal mortality: 19-30% in treated groups vs. 0-3% in controls; no. of malformations: 91-98% in treated groups vs. 0-4% in controls; foetal wt, crown-rump length, tail length decreased**** in treated groups at all time points of sacrifice; delayed ossification (by 1-3 d) of long bones of extremities, scapulae, ilium, skull bones; no ossification of ischium, pubis; decreased number/ range of ossified vertebral bodies and arches
Furukawa et al. (2014)	female Wistar Hannover Gallas rats (n=16-22/ group)	gd 14 sacrifice: gd 14.5, 15, 17, 21 for foetal and histological placental examinations	0, 50, 100 mg/ kg bw; ip	based on bw at gd 14, decreased bw gain during gd 15-18 and gd 15-21 at 50 and 100 mg/kg bw, resp.; clinical signs: prone position, hypothermia, loss/decrease of locomotor activity, vaginal haemorrhage, eye discharge, incontinence of urine, disappearing by gestational day 17 at 50 mg/kg bw and by gestational day 19 at 100 mg/ kg bw at the latest	gd 14.5: no litters with completed resorptions; no effect on number living foetuses/litter (as mean of individual litter values), % foetal mortality, mean foetal wt (as mean of individual litter values); mean placental wt (g) (as mean of individual litter values): 0.243±0.035, 0.208±0.028, 0.199±0.035*, at 0, 50, 100 mg/kg bw, resp. gd 15: no litters with completed resorptions; no effect on number living foetuses/litter, % foetal mortality, mean foetal wt (g): 0.268 ± 0.021, 0.229 ± 0.022*, 0.177 ± 0.004**, resp.; mean placental wt (g): 0.229 ± 0.038, 0.187 ± 0.032, 0.147 ± 0.026*, resp. gd 17: no effect on number living foetuses/litter, % foetal mortality, % litters with completed resorptions: 0, 20, 20, resp.; mean foetal wt (g): 0.770 ± 0.023, 0.553 ± 0.065**, 0.517 ± 0.066**, resp.; mean placental wt (g): 0.317 ± 0.018, 0.254 ± 0.022*, 0.228 ± 0.034**, resp.

					gd 19: no effect on number living foetuses/litter, % foetal mortality, mean foetal wt, % litters with completed resorptions: 0, 20, 44, resp.; mean placental wt (g): 0.449 ± 0.035, 0.434 ± 0.035, 0.375 ± 0.031*, resp. histopathology: tropoblast apoptosis in the labyrinth zone, leading to labyrinth zone hypoplasia; glycogen cell apoptosis in the basal zone, ultimately leading to metrial gland apoptosis
Umemura et al. (1983)	female Jcl:SD rats (n=9-11/ group)	gd 17-pnd 21 sacrifice: pnd 22: dams, female offspring, part of male offspring behavioural testing in selected male offspring at pnw 5 (learning), 6-7 (motor activity), 15 (learning)	0, 2 mg/kg bw/d (once daily); 8 mg/ kg bw/d (twice daily 4 mg/kg bw); sc	sedation, slowed motion, eye-closing in dams of both dosing groups; no nursing behaviour in many dams of the high-dose group due to cataleptic manifestations; mean bw at 8 mg/kg bw tended to be lower than at 2 or 0 mg/kg bw, but no statistically significant difference among groups; low water and food intake at 8 mg/kg bw	no effect on mean litter size; male, female mean pup wt at birth; mortality at birth: 1 (0.8%), 5 (4%), 9 (7%), 16 (12%) at 0 (untreated), 0 (vehicle), 2 mg/kg bw, 4 mg/kg bw, resp. pnd 14: mean pup wt (g), male: 31.6±1.5, 33.1±2.9, 31.7±2.2, 29.7±3.5*, resp.; female: 31.6±1.3, 32.0±2.8, 31.1±2.4, 28.8±2.7, resp. pnd 21: mortality (pnd1-21): 0, 0, 2 (2%), 22 (20%)*; mean pup wt (g), male: 53.4±2.3, 54.9±3.9, 53.6±3.7, 48.5±5.8*, resp.; female: 52.8±2.2, 52.8±3.9, 51.7±4.1, 47.7±4.0*, resp. pnw 5: no effect on lever pressing (continuous food reinforcement), light-dark discrimination learning, impaired reversal discrimination learning at 2 and 8 mg/kg bw pnw 6-7: no effect on motor activity pnw 15: no effect on lever pressing, light-dark discrimination learning, impaired reversal discrimination learning at 8 mg/kg bw

Hironaka et al. (1988)	female Sprague Dawley rats (n=13-14/ group)	gd 17-21 at parturition, pups from treated mothers transferred to non-treated mothers; behavioural testing started at pnw 5	0, 8, 16 mg/kg bw/d; sc	not reported.	no effect on mean litter size; total number of deaths at birth: 2, 10, 25** at 0, 8, 16 mg/kg bw, resp.; total number of deaths during lactation period: 0, 18, 60**, resp.; mean pup wt at birth (g): male: 6.4±0.3, 5.9±0.4*, 5.4±0.3*, resp.; female: 6.1 ±0.4, 5.3±1.2, 5.1±0.3, resp.; no effect on mean male and female pup bw at pnd 21 pnw 5: retarded reversal learning acquisition; no effect on acquisition of lever press responses and on original discrimination learning
West et al. (1986)	female Crl:CD(SD)BR rats (n=6/ group; controls: n=14).	gd 14, 16, 18 olfactory discrimination test performed in pups on pnd 9 and 10	0, 1 mg/kg bw/d; sc	no effect on maternal bw, food and water consumption	no effect on pup bw, litter size, sex ratio decreased response toward dams; no effect on response to the empty goalbox
Hannah et al. (1987)	female Long-Evans rats (n=9 /group)	gd 18-pnd 21 sacrifice of whole litters (n=3/sample time point) at pnw 1, 3 and 24 for examination of monoamine levels in cerebellum and hippocampus	15 mg/kg bw/ d; im	not reported	pnw 1: increased levels of dopamine* and serotonin** in cerebellum and hippocampus pnw 21: no effect on monoamine levels pnw 24: decreased levels of noradrenaline*, dopamine*, serotonin* in cerebellum; increased levels of noradrenaline*, dopamine*, serotonin* in hippocampus
Walker/ Patterson (1974)	female A/J (n=21), C3H (n=6) mice	gd 14 sacrifice: gd 17; foetal palate morphology evaluated	50 mg/kg bw; im	heavily sedation for 9-18 hr	A/J mice: number of foetuses resorbing: 51; number of foetuses retarded (heart beating, but morphological rating equivalent to a younger foetus): 39; number of foetuses maturing (heart beating, morphological rating consistent with chronological age): 61; foetuses with cleft lip and cleft palate occurring together: 13%; foetuses with isolated cleft palate: 21%

		C3H mice: number of foetuses resorbing: 4; number of foetuses retarded (heart beating, but morphological rating equivalent to a younger foetus): 0; number of foetuses maturing (heart beating, but morphological rating consistent with chronological age): 31; foetuses with cleft lip and cleft palate occurring together: 0%; foetuses with isolated cleft palate: 3%

bw=body weight(s); d=day(s); gd=gestational day(s); hr=hour(s); im=intramuscular; ip=intraperitoneal; pnd=postnatal day(s); pnw=postnatal week(s); sc=subcutaneous; wk=week(s); wt=weight(s); *=p<0.05; **=p<0.01; ***=p<0.005; ****=p<0.001; *****=p<0.0001.

Health Council of the Netherlands

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