Health Council of the Netherlands

Triamcinolone
Triamcinolone acetonide

Evaluation of the effects on reproduction, recommendation for classification

2013/03

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Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Triamcinolone and Triamcinolone acetonide*
Uw kenmerk : DGV/MBO/U-932542
Ons kenmerk : U-7651/HS/fs/543-N13
Bijlagen : 1
Datum : 5 april 2013

Geachte minister,

Graag bied ik u hierbij het advies aan over de effecten van triamcinolon en triamcinolonacetonide 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. Het is vervolgens getoetst door de Beraadsgroep Gezondheid en omgeving van de raad.

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

Met vriendelijke groet,

prof. dr. W.A. van Gool,
voorzitter

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

to:

the Minister of Social Affairs and Employment

No. 2013/03, The Hague, Aprll 5, 2013

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Preferred citation:
Health Council of the Netherlands. Triamcinolone/Triamcinolone acetonide. The Hague: Health Council of the Netherlands, 2013; publication no. 2013/03.

ISBN: 978-90-5549-946-5

Contents

Samenvatting

In het voorliggende advies heeft de Gezondheidsraad triamcinolon en triamcinolonacetonide onder de loep genomen. Triamcinolon en triamcinolonacetonide zijn glucocorticoide geneesmiddelen en werkzaam als systemische en lokale ontstekingsremmer. 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 naar effecten op de vruchtbaarheid van mannen en vrouwen zowel als 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 triamcinolon komt de commissie tot de volgende aanbevelingen:

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

- voor effecten op of via lactatie adviseert de commissie om triamcinolon niet te kenmerken wegens onvoldoende geschikte gegevens.

Voor triamcinolonacetonide komt de commissie tot de volgende aanbevelingen:

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

Executive summary

In the present report the Health Council of the Netherlands reviewed triamcinolone and triamcinolone acetonide. Triamcinolone and triamcinolone acetonide are glucocorticoid drugs applied for systemic and local anti-inflammatory activity. 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 occupationally exposed. 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. Moreover, 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 triamcinolone, these recommendations are:

- for effects on fertility, the Committee recommends not classifying triamcinolone due to a lack of appropriate data
- for effects on development, the Committee recommends classifying triamcinolone 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 triamcinolone due to a lack of appropriate data.

For triamcinolone acetonide, these recommendations are:

- for effects on fertility, the Committee recommends not classifying triamcinolone acetonide due to a lack of appropriate data
- for effects on development, the Committee recommends classifying triamcinolone acetonide 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 triamcinolone acetonide 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, 1B or 2) and compounds with effects on or via lactation.

1.2 Committee and procedure

This present document contains the classification of triamcinolone and triamcinolone acetonide by the Health Council's Subcommittee on the Classification of Reproduction Toxic Substances. The members of the

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

The classification is based on the evaluation of published human and animal studies concerning adverse effects with respect to fertility and development and 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 C. 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 D).

In 2012, the President of the Health Council released a draft of the report for public review. No comments were received.

1.3 Effects on or via 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 on or via 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 on-line databases XTOXLINE, MEDLINE and CAPLUS, up to January 2011 without a starting date. The final search was performed in PubMed in May 2012. Literature was selected primarily on the basis of the text of the abstracts. Publications cited in the selected articles, but not selected during the primary search, were reviewed if considered appropriate. References are divided in literature cited and literature consulted but not cited.

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

In the assessment of the potential reproduction toxic effects of triamcinolone and triamcinolone acetonide, 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 toxic to reproduction is indicated.

1.6 Final remark

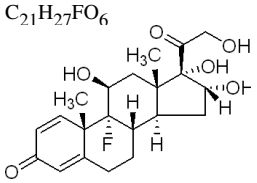
The classification of compounds is based on hazard evaluation only (Niesink et al., 1995[22]), which is one of a series of elements guiding the risk evaluation process. The Committee emphasizes that for derivation of health-based occupational exposure limits these classifications should be placed in 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.

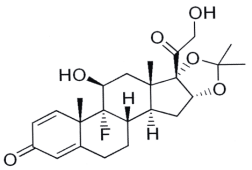
Chapter 2

Triamcinolone and triamcinolone acetonide

2.1 Introduction

The identity and some physicochemical properties of triamcinolone and triamcinolone acetonide are given below.

chemical name	:	triamcinolone
CAS registry number	:	124-94-7
EC/EINECS number	:	204-718-7
IUPAC name	:	(11β,16α)-9-fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione
CAS name	:	pregna-1,4-diene-3,20-dione, 9α-fluoro-11,16,17,21-tetrahydroxy-,11β,16α-
synonyms	:	9α-fluoro-16α-hydroxyprednisolone; 9α-fluoro-11β,16α,17α,21-tetrahydroxy-pregna-1,4-diene-3,20-dione; Δ^1-9α-fluoro-16α-hydroxyhydrocortisone; Δ^1-16α-hydroxy-9α-fluorohydrocortisone; 16α-hydroxy-9α-fluoroprednisolone
colour and physical state	:	fine, white or off-white, crystalline powder
molecular weight	:	394.44
molecular formula	:	$C_{21}H_{27}FO_6$
structural formula	:	
melting point	:	269-271 °C (mp also reported as 260-262.5 °C)
optical rotation	:	$[\alpha]^{25}D = +75°$ (in acetone)
vapour pressure	:	$1x10^{-12}$ Pa (at 25 °C; estimated)
Log $P_{(octanol\text{-}water)}$	:	1.16 (experimental)

solubility	:	80 mg/L water (at 25 °C); 1 g soluble in 70 mL propylene glycol, and less than 20 mL dimethyl sulphoxide; soluble in dimethyl formamide; slightly soluble in alcohol and chloroform
chemical name	:	triamcinolone acetonide
CAS registry number	:	76-25-5
EC/EINECS number	:	200-948-7
IUPAC name (old)	:	9-alpha-fluoro-11-beta,21-dihydroxy-16-alpha,17-alpha-isopropylidene-dioxypregna-1,4-diene-3,20-dione
CAS name	:	pregna-1,4-diene-3,20-dione, 9-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, (11β,16α)-
synonyms	:	(11β,16α)-9-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)] pregna-1,4-diene-3,20-dione; 9α-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone; 9α-fluoro-16α-hydroxyprednisolone acetonide; triamcinolone 16α,17-acetonide; 9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione; 9α-fluoro-16α,17-isopropylidenedioxyprednisolone
colour and physical state	:	white to cream coloured crystalline powder with slight odour
molecular weight	:	434.50
molecular formula	:	$C_{24}H_{31}FO_6$
structural formula	:	
melting point	:	292-294 °C
optical rotation	:	$[\alpha]^{23}D = +109°$ (c=0.75 in chloroform)
vapour pressure	:	1.3×10^{-9} Pa (at 25 °C; estimated)
Log $P_{(octanol\text{-}water)}$	:	2.53 (recommended: see http://logkow.cisti.nrc.ca/logkow/search.html)
solubility	:	practically insoluble in water; very soluble in dehydrated ethanol, chloroform, methanol; slightly soluble in ethanol; sparingly soluble in acetone and ethyl acetate

Data from[5,21]

Triamcinolone and triamcinolone acetonide are glucocorticoid drugs applied for systemic and local anti-inflammatory activity. In the Netherlands, triamcinolone has been registered for oral use (tablets) in humans and triamcinolone acetonide for topical use in humans (ointment/cream; nasal spray; eye drops; suspensions for intramuscular, intra-articular, intrabursal injections) and cats and dogs (lotion; suspensions for intramuscular and subcutaneous injections).[7]

Following intravenous injection of ^{3}H-triamcionolone into dogs, the plasma half-life was about 116 min. The total radioactivity excreted within 72 hours in urine and faeces amounted to approximately 47 and 42%, respectively.[11] Urine analyses revealed the presence of parent compound (20% of the dose injected),

6ß-hydroxytriamcinolone (25%), and a third compound (<5%), which had not been identified but did not appear to be a glucuronide or sulphate conjugate. Without presenting details, Florini et al. stated that a similar pattern of metabolites was found in the urine of one human who received oral unlabeled triamcinolone doses of 96 mg/day for three weeks.[10] Following intravenous injection into rats, the plasma half-life was about 52 min. Measured 40-60 minutes after injection, ^{3}H-triamcinolone was primarily deposited in the muscle, liver, intestine, skin and kidney. The total amount radioactivity excreted within 72 hours in urine and faeces amounted to approximately 26 and 56%, respectively.[11] Hochhaus et al. determined pharmacokinetic parameters of triamcinolone following oral administration to human volunteers. Plasma half-lives were approximately 165 min with maximum concentrations reached after approximately 2 hours.[16]

When [^{14}C-]-triamcinolone acetonide was orally administered to human volunteers, peak plasma levels of triamcinolone acetonide and radioactivity were found within 2 hours of administration. Within 24 hours, approximately 93% and 76% of the parent compound and total radioactivity were eliminated from the plasma, respectively. Most of the radioactivity was excreted in the faeces and urine within 72 and 24 hours, respectively, amounting to 51 and 37%, respectively. Major metabolites identified in plasma, faeces and urine resulted from oxidation at the C6 and C21 positions.[2] In pharmacokinetic studies in animals, generally similar excretion and biotransformation patterns were seen. Hydrolysis of the acetonide moiety resulting in triamcinolone or triamcinolone metabolites was not found to be a significant metabolic pathway.[12,17] When ^{3}[H]-triamcinolone acetonide was injected intramuscularly into female A/J mice, 42%, 30%, and 2% of the administered dose was found 3 hours later at the injection site, in bile and in urine, respectively. After 24 hours, some radioactivity (1.3%) was present at the injection site, while bile/intestinal contents/faeces and urine contained 66% and 15%, respectively. Given to pregnant A/J, C3H, and CBA mice on gestational day 11.5, predominantly parent compound was found in the placentas and embryos 0.5 hour after administration. Concentrations of radioactivity in placentas and embryos of CBA mice were about 40% lower than those in the other two strains. Thereafter, concentrations fell markedly.[37,38]

2.2 Human studies

Fertility studies

Cunningham et al. (1975) investigated the possible ovulation-inhibiting activity of triamcinolone and triamcinolone acetonide in healthy women, aged 22-40, with a history of regular menstrual cycles. A group of six women received daily intramuscular injections of 12.5 mg of triamcinolone diacetate on days 1 and 2 or days 2 and 3 of the menstrual cycle. No menstrual irregularities were observed apart from an ovulation-inhibiting progesterone level (<1.0 ng/mL) in one subject. Another group of 11 women received 25 mg triamcinolone acetonide on day 1 or 2. Of these, seven had plasma progesterone levels <1.0 ng/mL, and six of these seven women had noted changes in the duration of the cycle and intermenstrual or post-menstrual spotting. Daily blood studies in three triamcinolone acetonide-treated subjects revealed that the normal midcycle surge of LH and FSH and the subsequent rise in progesterone were absent in each of these subjects. Using an incidence of 10.7% anovulatory cycles found in 430 cycles of fertile women, aged 22-40, as a control, triamcinolone diacetate did not have an ovulation-inhibiting effect (p=0.8) while triamcinolone acetonide did (p=0.0001).[8] Cunningham et al. (1978) confirmed this ovulation-inhibiting effect of triamcinolone acetonide in a mechanistic follow-up study.[9]

Developmental toxicity studies

Arduini and coworkers (1986) reported a double blind study in ten women at 35 weeks of gestation. One group (n=5) received oral triamcinolone doses of 8 mg at 8:00, 16:00, and 24:00 hour for three consecutive days and the control group received a placebo. Blood cortisol, 17β-estradiol, unconjugated oestriol and ACTH (adrenocortiocotropin hormone) levels were measured every two hours and a 24-hour continuous recording of foetal heart rate beginning at 8:00 was performed on the third day of treatment and three weeks thereafter. At 35 weeks, the number of time periods during which foetuses were active as measured by foetal heart rate after treatment was increased in the treated group (p<0.001) compared to the placebo group, but not at 38 weeks. The placebo group showed similar incidence of activity at weeks 35 and 38. After treatment, a circadian heart rhythm was seen in week 38, but not in week 35, and in the placebo group in weeks 35 and 38. Simultaneously, maternal cortisol (p<0.001), oestriol (p<0.001) and ACTH (p<0.05) levels were reduced in the treated group

compared to the placebo group in week 35, but not in week 38. 17β-Estradiol was not affected. Moreover, a loss of circadian variations of all hormones investigated was found in the treated group in week 35, but not in week 38 or in the placebo group. No differences were observed in infant weight and Apgar scores at birth.[1]

Carmichael and coworkers (2007) reported a population-based case-control study on the possible association between corticosteroid use during pregnancy and orofacial clefts in offspring. The population consisted of deliveries occurring from October 1997 until December 2002 in eight US states. Exposures were assessed by telephone interviews for cases (1,141 with cleft lip ± cleft palate, 628 with cleft palate) and controls (4,143). This yielded mothers of five infants with cleft lip ± cleft palate, mothers of one infant with cleft palate and nine control subjects, who reported triamcinolone use from four weeks before through 12 weeks after conception. In this small study, no clear evidence was seen for an increased risk of cleft lip ± cleft palate (odds ratio 2.0; 95% CI 0.7-6.1) after triamcinolone use.[6]

The Committee notes that it is not clearly indicated in the study whether triamcinolone use included use of triamcinolone or triamcinolone acetonide or both.

Other epidemiological studies as cited in Carmichael et al.[6] with therapeutic use of corticosteroids during pregnancy were available, but none included an adequate group of triamcinolone users and no specific conclusions for triamcinolone were drawn. It is also not clear whether triamcinolone or triamcinolone acetonide or other derivatives were used.

Lactation

There are no studies available regarding the effects of triamcinolone or its acetonide on human lactation. No reports on triamcinolone (acetonide) distribution into human breast milk were found. However, in general, systemic corticosteroids are distributed into breast milk.[21]

2.3 Animal studies

Fertility and developmental toxicity studies in laboratory animals are summarized in Annex E. Generally, no data on effects in maternal animals due to

exposure to triamcinolone or triamcinolone acetonide were given in these studies.

Fertility studies

Triamcinolone

Oral

Selye et al. (1971) investigated the effect of several steroids on gestation in ARS/ Sprague-Dawley rats (see below *Developmental toxicity studies*). Triamcinolone given by gavage at doses of 100 mg/kg bw twice daily on gestational days 2-6 interrupted 8/11 pregnancies indicating preimplantation losses. No such effect was observed at doses of 10 mg/kg bw.[28]

Subcutaneous

Albino female rats (n=6) were given no drug or 0.1 mg/rat/day triamcinolone (ca. 1 mg/kg bw/day) subcutaneously for 15 days. Twenty-four hours after the last injection rats were sacrificed and very limited investigations were made. Relative uterus and ovary weights were significantly decreased ($p<0.01$) in the triamcinolone-treated group. Ovarian alkaline phosphatase activity was significantly decreased ($p<0.01$). Histological investigation of the ovaries revealed no morphological changes.[27]

The Committee notes that in this study, 'triamcinolone' was not further specified. In view of the route of administration and the dose, it could have been triamcinolone acetonide (see developmental toxicity studies below).

Triamcinolone acetonide

Intramuscular injection of daily doses of 4 mg of triamcinolone acetonide into baboons (n=5-8/group) during selected times of the menstrual cycle inhibited ovulation and shortened menstrual cycles.[13]

Developmental toxicity studies

Triamcinolone

Oral

Bishop and coworkers (1985a) investigated the effect of administration of a diet supplemented with soybean oil or soybean oil plus 70 mg triamcinolone to sows (n=38-40) daily for on average the last ten days pre-partum. The 70-mg dose was based on the level of triamcinolone per unit of metabolic weight ($kg^{0.75}$) that had been determined to result in a gluconeogenic response in growing rats and pigs. The triamcinolone treatment had not affected sow weight gains and feed intake during the 28-day lactation period. The colostrum fat content had increased by 21% compared to soybean-supplemented diet.[3]

In a subsequent study (Bishop, 1985b) in which sows (n=6-7) were given the same diet and dose of triamcinolone for the last seven days of gestation, fat percentage of colostrum was not affected. Triamcinolone did not affect the number of stillbirths and the litter size up to 28 days of age, but did increase the piglet weight at birth and at 14 and 28 days of age. After weaning till 165 days of age, no significant effect on body weight of piglets was noted. At weaning (28 days), liver glycogen percentage and serum glucose were not affected, whereas adrenal weight was decreased. In the subsequent study, litter size and birth weight were not affected, nor were liver glycogen percentage and serum glucose level (adrenal weight was not measured). Carcass protein and fat were increased, which did not occur in the first study, although colostrum fat content had increased in the first study.[4]

Gravid sows (n=5-7) were given a standard diet or a diet supplemented with 70 mg/kg bw/day of triamcinolone from gestational day 106 through parturition. One or two pairs of littermate boars were selected from each litter and followed till 30 weeks of age for effects on the gonadotropin-gonadal system and the onset of puberty and post-puberal development. The body weight and testicular volume of the boars were not affected. Although the plasma testosterone concentration was slightly increased at week 16-28 in treated boars, the level at the end of the study was comparable to that in the control group. Plasma cortisol levels were not affected nor were the adrenal weights. Statistically significant differences between treated and control boars with respect to onset and frequency

of mounting and ejaculation indicated that triamcinolone induced acceleration of the development of sexual behaviour and earlier onset of puberty. At sacrifice, weights of testes, epididymides, seminal vesicles, bulbourethral glands and prostate gland were increased ($p<0.10$) in the triamcinolone group. The incidence of cytoplasmic droplets on spermatozoa recovered from the cauda epididymides was similar between treated and control groups, suggesting boars were at a similar level of sexual maturity physiologically at sacrifice.[36]

Walker (1965) administered doses of 0.01 and 0.02 mg triamcinolone diacetate/ day by gavage to A/J mice on gestational days 11-14 and one dose of 0.02 mg on gestational day 14. At gestational day 18, dams were killed. Foetuses were removed and their palate morphology investigated. No palate abnormalities were seen in foetuses of the low-dose (3 litters; 22 foetuses) and the single-dose group (3 litters; 26 foetuses). In the high-dose group (3 litters), 12 foetuses had normal palate morphology while cleft palate was seen in seven.[33]

Selye et al. (1971) investigated the effect of several steroids on gestation in rats. Triamcinolone was given at a dose of 100 mg/kg bw twice daily on gestational days 4-8, 9-13, or 15-19. Cholesterol was given as a negative control at a similar dose and scheme. Eight days after insemination, successful fertilization was checked by a direct inspection of the uterus via a small laparotomy incision. Dams were allowed to give birth. If dams failed to give birth by the end of the 23rd day, they were killed. For the group receiving cholesterol, no pregnancies were interrupted (i.e., total litter aborted or resorbed) when given in any stage of pregnancy. For triamcinolone, all pregnancies were interrupted. A lower dose of 5 mg triamcinolone/kg bw given during gestational days 2-19 induced total abortion/resorption in 4/9 dams.[28]

Subcutaneous

Walker (1971) studied the induction of cleft palate by several anti-inflammatory drugs including triamcinolone in a limitedly described study. Rats were injected subcutaneously with 0.01 to 0.5 mg once daily on gestational days 12-15. No control group was included. Pregnant rats were killed at gestational day 19, and the uterus with foetuses was fixated, the lower jaw of the foetuses was removed and the condition of the palate recorded. At doses of 0.2 and 0.5 mg/day, two pregnant rats died before the end of gestation as did one rat at 0.1 mg/day. At doses of 0.01, 0.05 and 0.1 mg/day, two, eight and four litters could be examined, respectively. The total number of embryos was 27, 95 and 30 at 0.01, 0.05 and

0.1 mg/day with no, three and six embryos resorbed, respectively. Cleft palate was seen in 0, 45 and 80% of foetuses.[35]

Walker (1971) also reported that A/J mice given a single subcutaneous dose of 0.0175 mg/mouse/day on gestational day 11-14 and killed four days after the last injection resulted in five resorptions in seven litters. Cleft palate was found in 44 out of 52 embryos, of which three had a combination of cleft lip-cleft palate. No control group was included.[35]

Intramuscular

Rowland and Hendrickx (1983) compared the relative cleft palate inducing potencies of triamcinolone, triamcinolone acetonide and cortisol in rats. On gestational day 13, which was determined to be the most sensitive day for cleft palate induction by triamcinolone acetonide, pregnant rats (n=10-11) were intramuscularly injected with physiological saline or 10, 20 or 40 mg/kg bw triamcinolone. Dams were killed on gestational day 20 and the number of live foetuses and resorptions were counted. Live foetuses were weighed and examined for external malformations. In the treated groups, there was no statistically significant increase in either the percentage resorptions per litter or the proportion of litters with at least one resorption. Triamcinolone treatment resulted in statistically significantly, dose-relatedly decreased foetal weights at 20 and 40 mg/kg bw. At 10, 20 and 40 mg/kg bw, 45.5, 80 and 91%, respectively, of the litters had cleft palates (controls: 0%) and 7.5, 20 and 34%, respectively of the foetuses (controls: 0%). Foetuses with umbilical hernias were present in triamcinolone-treated groups (not statistically significant), but not in the control group. The ED_{50} (the dose causing cleft palate in 50% of the animals) value was calculated to be 65 mg/kg bw. For triamcinolone acetonide, the ED_{50} was 1.1 mg/kg bw, indicating that the relative cleft palate-inducing potency of triamcinolone acetonide was about 59 times that of triamcinolone.[25]

Walker (1967) exposed New Zealand White rabbits daily to intramuscular doses ranging from 0.01 to 5.0 mg/rabbit on gestational days 13-16 resulting in an increased number of resorbed litters and of cleft palates at doses ≥1.0 and ≥0.10 mg, respectively. American Dutch rabbits given doses from 0.01 to 4.0 mg/rabbit intramuscularly on gestation days 13-16 showed an increased number of resorbed foetuses and cleft palates at doses ≥0.10 and ≥0.30 mg, respectively. All foetuses with cleft palate had both palatine shelves lying in a transverse plane, but separated throughout their length.[34]

Shah (1976) investigated cleft palate induction in hamsters. Mated hamsters (n=3-4) were injected intramuscularly with triamcinolone doses of 0.25, 0.5, 1.0, 2.5 and 5.0 mg in water on gestational day 11. A vehicle control group was included. Dams were killed on gestational day 15 and viable foetuses were weighed, fixated and examined for cleft palate development. Foetal weight was decreased at all doses. The number of live foetuses in the treated groups varied between 25 and 30 (vs. 31 in controls). At doses of 0.25, 0.5, 1.0, 2.5 and 5.0 mg, the percentages of resorptions were 3, 0, 17, 8 and 30, respectively (vs. 0% in controls) and percentages of foetuses with cleft palate 24, 42, 100, 100 and 100, respectively (vs. 0% in controls). The morphology of cleft palate varied with more partial cleft palates and less complete cleft palates at lower doses.[31]

In subsequent studies, Shah (1979, 1980) reported on sequential morphological observations of triamcinolone-induced cleft palate in hamster foetuses. Pregnant hamsters (n=not specified) were given single intramuscular injections of 0 or 4 mg triamcinolone on gestational day 11. Subsequently, dams were killed at two- to four-hour intervals until gestational day 13 and on gestational days 14 and 15 and foetal heads were examined. Normal palatogenesis was completed between gestational days 12 and 13. It was shown that 32 hours after treatment triamcinolone caused basal cell necrosis and delayed differentiation of mesenchymal cells, thereby disrupting the timing of coordinated development of the palatal tissues. The delayed reorientation occurred before any general retardation of foetal growth as indicated by decreased crown-rump length and foetal weight after gestational day 13.[29,30]

Based on the findings in their study that triamcinolone was less potent in inducing cleft palate than triamcinolone acetonide (see above), Rowland and Hendrickx (1983)[25] assumed that the substance administered in the subcutaneous study of Walker (1971)[35] and the intramuscular studies of Walker (1967)[34] and Shah[29-31] was triamcinolone acetonide and not triamcinolone.

Triamcinolone acetonide

Subcutaneous

Walker (1965) injected daily doses of 0.006 mg of triamcinolone acetonide subcutaneously into A/J mice on gestational days 11-14. At gestational day 18, dams were killed. Foetuses were removed and their palate morphology

investigated. There was no increase in the number of litters resorbed but there was a high frequency of cleft palate in the foetuses examined (65%).[33]

Kusagani performed a series of experiments on the occurrence and dose-response relationships of cleft palate, palatal slit and foetal mortality in mice treated with triamcinolone acetonide.

In the first experiment, C57BL/6 and SWV female mice were administered subcutaneously single doses of 0, 1.0, 2.5, 4.0, 5.0 or 7.0 and 0, 1.0, 2.5 or 5.0 mg/kg bw, respectively, at gestational day 12. At gestational day 18, the dams were killed and their uterine contents were examined immediately. In C57BL/6 mice, the number of resorptions/implantations did not significantly differ from the control group. Treatment caused statistically significant dose-related increases in the frequency of cleft palate development in live foetuses (0/209, 0%; 0/81, 0%; 16/119, 13%; 32/113, 28%; 27/82, 33%; 72/103, 70%, respectively) and in palatal slit in live-cleft palate foetuses (12/209, 6%; 25/81, 31%; 36/103, 35%; 36/81, 44%; 34/55, 62%; 21/31, 68%, respectively). In SWV mice, the number of resorptions/implantations (15/213, 7%; 14/143, 10%; 61/220, 28%; 67/170, 39%) and the frequency of cleft palate development in live foetuses (0/198, 0%; 14/129, 11%; 79/159, 50%; 86/103, 83.5%, respectively) were statistically significantly increased, whereas no changes were observed concerning palatal slit development in cleft palate-live foetuses.[19]

In the second experiment, Kusagani transferred blastocysts recovered from the uterus on gestational day 3 of untreated females to the right uterine horn of day 2 pseudopregnant females. Subsequently, these females were given a single subcutaneous injection of triamcinolone acetonide at a dose of 2.5 mg/kg bw, based on the gestational age (day 12) of recipient females. All animals (including untreated females) were killed at gestational day 18. Kusagani concluded that 'in cleft palate induction by triamcinolone acetonide, the effects of uterine environment are more important than those of fetal genotype, whereas in palatal slit occurrence the reverse is true'. The SWV mice were less sensitive to exposure to triamcinolone acetonide than the C57BL/6 mice.[18]

The third experiment was performed with C57BL/6 mice only, and focused on the most sensitive developmental stages during pregnancy. The highest number of resorbed litters ranged around treatment at gestation days 9 (lowest dose, 2.5 mg/kg bw) to 11 (highest dose, 5 mg/kg bw). The frequencies of cleft palate development and palatal slits in cleft-palate live foetuses peaked at around gestation day 12 (in both dose groups).[20]

Intramuscular

Hendrickx et al. (1975) treated bonnet and rhesus monkeys, and baboons intramuscularly at various doses (range: 1-28 mg/kg bw) and at various gestational days (range: day 37-133), depending on the species. Foetuses were delivered by Caesarean section at gestational day 100, near term or naturally. Of each species, also ten untreated control foetuses were included. Effects observed in treated animals included: resorption (rhesus monkey only); intrauterine death (in all species used); malformations in the skeleton (all species), liver (one rhesus monkey), kidneys (one bonnet monkey), thymus (in particular in bonnet and rhesus monkeys) and lymphocytes (in surviving baboon offspring).[15] The Committee noted that no statistical analyses have been performed.

The same research group studied more specifically craniofacial and central nervous system malformations using the same animal species and a comparable study design. Treatment caused increases in prenatal death and stillbirths among bonnet and rhesus monkeys, but not among baboons. Furthermore, multiple cranial and central nervous system malformations were found in all species, although the type of malformations differed somewhat depending on type of species. No statistical analyses have been performed.[14]

Further, this research group reported specifically on craniofacial malformations in rhesus monkeys (n=10/group) following intramuscular injections of triamcinolone acetonide of 10 mg/kg bw at gestational days 23, 25, 27, 29 and 31. Ten untreated pregnant animals served as controls. Offspring were removed by hysterotomy on gestational days 35 and 42 (single mate), and on days 50, 60 and 70 (multiple mate). Examination of rhesus embryos, which were obtained on gestational day 35, did not show gross abnormalities, but histological examination revealed a shortened anlage of the posterior cranial base. Embryos and foetuses obtained on the other gestational days showed craniofacial dysmorphia, encephalocele, malformations in the sphenoid bone, decreased ossification and remodelling on the facial bones, and abnormal position, due to the malformed sphenoid.[23] In addition, on closer examination, Tarara et al. (1988) suggested that the encephalocele may have resulted from a combination of mesenchymal and neural tube malformations.[32]

Walker (1965) injected daily doses of 0.0005-0.5 mg of triamcinolone acetonide intramuscularly into A/J mice on gestational days 11-14 and single doses of 0.05 mg on gestational day 11 and of 0.0125 mg at gestational day 12, 13 or 14.

At gestational day 18, dams were killed. Foetuses were removed and their palate morphology investigated. Doses of 0.025-0.5 mg/day caused (almost) complete resorption. Doses of 0.001-0.125 mg/day caused a dose-dependent increase in frequency of cleft palate ranging from 18 to 100%. No effect was seen at the dose of 0.0005 mg/day. Single doses also induced cleft palates in some foetuses. Occasionally, cleft lip and cleft palate were seen.

129/J, C3H/HeJ, C57BL/6J and DBA/IJ mice were treated similarly on gestational days 11-14 with doses of 0.001-0.025 (129/J mice) or 0.0125 mg/day (other strains). In 129/J mice, there was an increase in the number of resorbed litters at doses ≥0.003 mg/day and in the frequency of cleft palate at doses ≥0.0125 mg/day. The dose of 0.0125 mg/day caused increases in the frequencies of cleft palate in the C3H/HeJ, C57BL/6J and DBA/IJ, a small increase in the number of resorbed foetuses in DBA/IJ mice and almost complete resorption in C57BL/6J mice (no resorptions were seen in C3H/HeJ mice).[33]

Rowland and Hendrickx (1983) gave Sprague-Dawley rats intramuscular injections of 0.125, 0,25 or 0,5 mg/kg bw, daily on gestational days 9-11, 12-14 or 15-17. A vehicle control group was included. Dams were killed on gestational day 20, and foetuses were recovered and prepared for gross and histological examination. No maternal lethality occurred in any of the treated animals. No developmental effects were observed in the groups exposed on gestational days 9-11. In the groups treated on gestational days 12-14, there were dose-related decreases in the percentages of viable foetuses/litter (89%, not statistically significant; 77%, $p \leq 0.05$; 58%, $p \leq 0.01$, respectively; controls: 97%), and increases in the percentages of litters with malformed foetuses (45%, not statistically significant; 80%, $p \leq 0.05$; 100%, $p \leq 0.05$; controls: 9%), and of malformed foetuses/litter (29%, not statistically significant; 61%, $p \leq 0.05$; 84%, $p \leq 0.05$; controls: 2%). The incidences of specific malformations, expressed as percentage of foetuses/litter were: for cleft palate: 23/45 ($p \leq 0.05$), 54/60 ($p \leq 0.05$) and 70/80 ($p \leq 0.05$), vs. 0/0 in controls; for umbilical hernias: 3/9, 20/50 ($p \leq 0.05$) and 58/80 ($p \leq 0.05$), vs. 0/0 in controls; and for undescendent testes: 0/0, 7/12.5 and 28/60 ($p \leq 0.05$), vs. 0/0 in controls. In the gestational days 15-17 groups, only the high-dose group was affected showing decreased percentages of viable foetuses/litter (29% vs. 96% in controls; $p \leq 0.05$), and increased percentages of litters with malformed foetuses (62.5% vs. 0% in controls; $p \leq 0.05$) and of malformed foetuses/litter (32% vs. 0% in controls; $p \leq 0.05$). Specific malformations observed were cleft palate in 19% of the foetuses ($p \leq 0.05$) and 50% of the litters (not significant) and hypoplastic thymus in 22% of the foetuses ($p \leq 0.05$) and 37.5% of the litters (not significant).[26]

In another study, Rowland and Hendrickx (1983) compared the relative cleft palate inducing potencies of triamcinolone, triamcinolone acetonide and cortisol in rats. Rats (n=10-11) were intramuscularly injected with physiological saline or 0.5, 2.5 or 5.0 mg/kg bw triamcinolone acetonide on gestational day 13, which was determined to be the most sensitive day for cleft palate induction by triamcinolone acetonide. Dams were killed on gestational day 20 and the number of live foetuses and resorptions were counted. Live foetuses were weighed and examined for external malformations. Treatment did not cause statistically significant increases in either the percentage resorptions per litter or the proportion of litters with at least one resorption. In the groups receiving 2.5 or 5.0 mg/kg, there were increases in the proportion of litters with at least one foetal death (9/10, 90% and 7/9, 78%, respectively; controls: 0/10, 0%; $p<0.05$) and in the mean percentage of dead foetuses per litter (32 and 44%, respectively; controls; 0%; $p<0.05$). Mean foetal weights were statistically significantly decreased in all male dose groups and in the two higher female dose groups. At 0.5, 2.5 and 5.0 mg/kg bw, 50, 100 and 100%, respectively, of the litters had cleft palates (controls: 0%; $p<0.05$ and $p<0.005$) and 21, 79 and 92%, respectively, of the foetuses (controls: 0%; $p<0.005$). In the two higher dose groups, umbilical hernias were observed in all litters and in 94.5 and 82%, respectively, of the foetuses. Triamcinolone acetonide was found to be a more potent cleft palate inducer than triamcinolone (see above).[25]

Rotschild et al. (1997) studied the effects of triamcinolone acetonide in the airways and lungs of rat foetuses. Sprague-Dawley rats (n=3-5/group) received intramuscular injections of doses of 0.6 mg/kg bw/day on gestational day 12-14. Non-treated pregnant controls were included. Foetuses were removed on gestational days 15, 17, 18 and 21, and underwent gross and histological examination. On lung tissue, morphometric analysis was performed. Statistically significantly reduced maternal weight gain, foetal weight, placental weight and amniotic fluid weight were observed in the treated groups compared to controls. There was no significant difference in litter size between the groups. Cleft palate was found to be increased in the exposed foetuses pooled from gestational day 18 and 20 (69/80 vs.1/100 in controls). Regarding pulmonary airways, the investigators found profound pulmonary hypoplasia in treated groups, which was accompanied by diminished number of intermediate airways, increased number of peripheral saccules and increased differentiation.[24]

Lactation

No studies were found regarding the effects of triamcinolone or triamcinolone acetonide on or via lactation in laboratory animals.

2.4 Conclusion

Triamcinolone

Triamcinolone did not have an ovulation-inhibiting effect when given intramuscularly to six women during the first three days of the menstrual cycle.[8]

In rats, oral administration on gestational days 2-6 caused preimplantation loss.[28]

Overall, the Committee proposes not to classify triamcinolone for effects on fertility due to the absence of information on effects following relevant routes.

Both human and animal data were available to evaluate the developmental toxicity of triamcinolone.

In a small double blind study, oral treatment in week 35 of pregnancy resulted in transient effects on foetal activity and circadian heart rhythm but did not affect infant weight and Apgar scores at birth.[1]

In a small population-based case-control study investigating use of triamcinolone and cleft lip ± cleft palate, no clear evidence was found for an increased risk.[6] However, it was not clear whether triamcinolone use included use of triamcinolone or triamcinolone acetonide or both.

Oral administration to sows for the last 10 days pre-partum, did not affect pregnancy outcome or piglets[3,4], when given from gestational day 106 through parturition, triamcinolone induced an acceleration of development of sexual behaviour and an earlier onset of puberty in their male offspring.[36] In laboratory animals, oral administration of triamcinolone caused interruption of pregnancies (postimplantation loss) in rats[28] and an increased number of foetuses with cleft palate in a limited study in mice[33]. The latter finding was supported by the results of an intramuscular rat study. It was not reported whether effects were seen in the presence or absence of maternal toxicity.

Overall, the Committee concludes that the human data are not sufficient for classification. The Committee is further of the opinion that the effects observed in laboratory animals occurred independent of any maternal toxicity. Therefore, based on the effects observed in laboratory animals, the Committee proposes to

classify triamcinolone for developmental effects in category 1B (*presumed human reproductive toxicant*).

There were no human or animal data on effects on or via lactation of triamcinolone. Therefore, the Committee proposes not labelling triamcinolone for effects on or via lactation because of a lack of data.

Proposed classification for fertility

Lack of appropriate data precludes the assessment of triamcinolone for effects on fertility.

Proposed classification for developmental toxicity

Category 1B, H360D.

Proposed labelling for effects on or via lactation

Lack of appropriate data precludes the assessment of triamcinolone for effects on or via lactation.

Triamcinolone acetonide

Triamcinolone acetonide had an ovulation-inhibiting effect in 7/11 women when given intramuscularly during one of the first two days of the menstrual cycle.[8]

Intramuscular injection into baboons during selected times of the menstrual cycle inhibited ovulation and shortened menstrual cycles.[13]

Overall, the Committee proposes not to classify triamcinolone acetonide for effects on fertility due to a lack of appropriate human and animal data.

In a small population-based case-control study investigating use of triamcinolone and cleft lip ± cleft palate, no clear evidence was found for an increased risk.[6] However, it was not clear whether triamcinolone use included use of triamcinolone or triamcinolone acetonide or both.

In laboratory animals, viz, monkeys[14,15,23,32], rats[24-26] and mice[18-20,33], triamcinolone acetonide induced high rates of cleft palate. It was generally not reported whether this effect was seen in the presence or absence of maternal toxicity, but the Committee is of the opinion that this occurred independent of maternal toxicity. All the studies used routes (subcutaneous and intramuscular

injection) less relevant to occupational exposure. Kinetic studies showed that triamcinolone acetonide is systemically absorbed following oral administration to human volunteers.[2] In addition, triamcinolone caused developmental effects following oral administration (see afore). Based on these findings, the Committee assumes that occupational exposure to triamcinolone acetonide could lead to internal exposures.

Overall, based on the effects observed in laboratory animals, the Committee proposes to classify triamcinolone acetonide for developmental effects in category 1B (*presumed human reproductive toxicant*).

There were no human or animal data on effects on or via lactation of triamcinolone acetonide.

Therefore, the Committee proposes not labelling triamcinolone acetonide for effects on or via lactation because of a lack of data.

Proposed classification for fertility

Lack of appropriate data precludes the assessment of triamcinolone acetonide for effects on fertility.

Proposed classification for developmental toxicity

Category 1B, H360D.

Proposed labelling for effects on or via lactation

Lack of appropriate data precludes the assessment of triamcinolone acetonide for effects on or via lactation.

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

Annexes

Annex **A**

The Committee

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The first draft of this report was prepared by Dr. H. Barendse from the Regulatory Affairs Department of Wil Research Europe BV (Den Bosch, the Netherlands), 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 *Triamcinolone and triamcinolone acetonide*
Your reference	:	DGV/MBO/U-932342
Our reference	:	U-7651/HS/fs/543-N13
Enclosed	:	1
Date	:	April 5, 2013

Dear Minister,

I hereby submit the advisory report on the effects of triamcinolone and triamcinolone acetonide 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 reproductive toxic substances are classified in accordance with European guidelines. This involves substances to which people can be exposed while pursuing their occupation.

The advisory report was prepared by the a permanent committee of the Health Council of the Netherlands, the Subcommittee on the Classification of Reproduction Toxic Compounds. The advisory report was subsequently 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. W.A. van Gool,
President

Annex **C**

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

developmental 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

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

calculation 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 for effects 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 lactation
Category 1A r eproductive 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 **D**

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 B. 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 B, 3.7.2.2.1.)
- adverse effects in a reproductive study, reported without information on 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 **E**

Fertility and developmental toxicity studies in animals

Table 1 Fertility studies in laboratory animals with triamcinolone.

authors	species	experimental period/design	dose/route	general toxicity	effects on reproductive organs/ effects on reproduction
Sarkar, 1967	female rats albino (n=6/group)	15 d; sacrifice 24 h after last injection; histological investigation of ovaries; determination of uterine and ovary weight, ovarian tissue alkaline phosphatase activity	0, 0.1 mg/rat/d; sc	not reported	no histological change of ovary; decreased uterine weight, ovary weight and ovarian tissue alkaline phosphatase activity ($p<0.01$)

d=day(s); h=hour(s); n=number; sc=subcutaneous

Table 2.1 Developmental toxicity studies in animals with triamcinolone: oral.

authors	species	experimental period/ design	dose/route	general toxicity	developmental toxicity
Selye, 1971	Sprague-Dawley rats (n=9-11/ group)	gd 2-6, 4-8, 9-13, 15-19	100 mg/kg bw (controls: cholesterol: 100 mg/kg bw); twice daily; gavage	not reported	number of interrupted pregnancies 8/11, 10/10, 11/11, 9/9 at gd 2-6, 4-8, 9-13 or 15-19, resp., vs. none in controls

Selye, 1971	Sprague-Dawley rats (n=9)	gd 2-19	5 mg/kg bw (controls: cholesterol: 100 mg/kg bw);twice daily; gavage	not reported	number of interrupted pregnancies 4/9 vs. none in controls
Selye, 1971	Sprague-Dawley rats (n=5)	gd 2-6	10 mg/kg bw (controls: cholesterol: 100 mg/kg bw); twice daily	not reported	no interrupted
Bishop, 1985a	Yorkshire x Hampshire pigs (n=38-40/group)	last 10 d pre-partum examintions: bw, food intake sows (26/group); protein (13/group), fat (26/group) content colostrum; growing of piglets followed till 165 d old; % liver glycogen, serum glucose, adrenal weight, carcass fat and protein at 28 d (1 male/ litter)	0, 70 mg/d; soybean-supplemented diet	sow weight gain, feed intake not affected during 28-d lactation; colostrum fat content increased by 21%	no effect on number of stillbirths, litter size up to 28 d of age; increase of piglet weight at birth, 14, 28 d of age; after weaning till 165 d of age no effect on bw of piglets; decreased adrenal weight; increased serum glucose; % liver glycogen, and carcass fat and protein not affected
Bishop, 1985b	Yorkshire x Hampshire pigs (n=6-7/ group)	last 7 d pre-partum examinations: fat content colostrum (5/ group); carbohydrate, fat. protein metabolism in piglets at birth, 6, 12, 24, 48 h of age (1/litter/ time point)	0, 70 mg/d; soybean-supplemented diet	colostrum fat content not affected	litter size, birth weight not affected; % liver glycogen, serum glucose level not affected; increased carcass protein and fat
Zavos, 1988	Yorkshire x Hampshire pigs (n=5-7/ group)	from gd 106 through parturition; one or two pairs of littermate boars (closest to the mean pig weight of the litter) from each litter followed till 30 wk of age; examinations: bw, plasma testosterone, cortisol; sexual performance parameters	0, 70 mg/kg bw; standard diet	not reported	bw, testicular volume not affected; slightly increased plasma testosterone concentrations at wk 16-28, terminal levels not affected; plasma cortisol levels, adrenal weights not affected ; increased percentage of boars with ejaculate containing spermatozoa ($p<0.05$) at an earlier point in time ($p<0.01$); earlier and higher mounting activity ($p<0.10$), more ejaculates ($p<0.05$), a greater number of ejaculates ($p<0.001$) and ejaculation at an earlier age; comparable semen volumes, increased sperm concentrations at each time point ($p<0.10$); increased testes, epididymides, seminal vesicles, bulbourethral glands, prostate gland ($p<0.10$) weights; no effect on incidence of cytoplasmic droplets on spermatozoa recovered from the cauda epididymides

bw=body weight; d=day(s); gd=gestational day(s); n=number; wk=week(s)

Table 2.2 Developmental toxicity studies in laboratory animals with triamcinolone: subcutaneous.

authors	species	experimental period/design	dose/route	general toxicity	developmental toxicity
Walker, 1971	Holtzman rats (n=2-4/group)	gd 12-15; sacrifice gd 19	0.01, 0.05, 0.1, 0.2, 0.5 mg/rat/d[a]	mortality in dams: 0, 0, 1, 2, 2 at 0.01, 0.05, 0.1, 0.2, 0.5 mg, resp; no dams left at 0.2 and 0.5 mg	number of resorptions 0, 3, 6 and percentage of embryos with cleft palate 0, 45, 80% at 0.01, 0.05 and 0.1 mg, resp
Walker, 1971	A/J mice (n=7)	gd 11-14; sacrifice gd 18	0.0175 mg/rat/d[a]	not reported	5 embryos resorbed; 44/52 embryos with cleft palate (85%); of these 3 had cleft lip-cleft palate

[a] According to Rowland and Hendrikx (1983) not triamcinolone, but triamcinolone acetonide was used here.
bw=body weight; d=day(s); gd=gestational day(s); n=number

Table 2.3 Developmental toxicity studies in laboratory animals with triamcinolone: intramuscular

authors	species	experimental period/design	dose/route	general toxicity	developmental toxicity
Walker, 1967	New Zealand white rabbits (n=1-8/group)	gd 13-16; sacrifice gd 21	0.01, 0.1, 0.25, 0.3, 0.5, 0.75, 1.0, 2.0, 5.0 mg/rabbit/d[a]	not reported	number of resorbed litters: 0/8, 0/3, 0/4, 0/1, 0/3, 0/2, 2/7, 3/3, 1/1 at 0.01, 0.1, 0.25, 0.3, 0.5, 0.75, 1.0, 2.0, 5.0 mg, resp; number of resorbed foetuses: 1, 0, 0, 0, 3, 2, 6 at 0.01, 0.1, 0.25, 0.3, 0.5, 0.75, 1.0 mg, resp; number of cleft palate in live foetuses: 0/55, 4/23, 4/28, 0/4, 2/11, 4/14, 17/32 at 0.01, 0.1, 0.25, 0.3, 0.5, 0.75, 1.0 mg, resp
Walker, 1967	American Dutch rabbits (n=2-7/group)	gd 13-16; sacrifice gd 21	0.01, 0.1, 0.2, 0.3, 0.6, 1.0, 2.0, 4.0 mg/rabbit/d[a]	not reported	no resorbed litters; number of resorbed foetuses: 1, 5, 8, 4, 5, 12, 5, 32 at 0.01, 0.1, 0.2, 0.3, 0.6, 1.0, 2.0, 4.0 mg, resp; number of cleft palate in live foetuses: 0/16, 0/32, 1/27, 11/24, 5/9, 4/4, 5/5, 0/0 at 0.01, 0.1, 0.2, 0.3, 0.6, 1.0, 2.0, 4.0 mg, resp
Shah, 1976	Golden Syrian hamsters (n=3-4/group)	gd 11; sacrifice gd 15; foetuses weighed, investigated for cleft palate	0, 0.25, 0.5, 1.0, 2.5, 5.0 mg/hamster	not reported	at all doses: decreased foetal weight, increased % cleft palate; at 5.0 mg: reduced number of live foetuses; at ≥1.0 mg: increased % resorptions; dose-related increased number of complete cleft palates; the number of partial cleft palates increased at the 3 lower doses and then decreased at the 2 highest doses

Shah, 1979, 1980	Golden Syrian hamsters (n=3-4/group)	gd 11; sacrifice in 2-4 h intervals until gd 13 and on gd 14 +15; foetuses weighed, measured, investigated for cleft palate (n=17-38/time point)	0, 4 mg/ hamster	not reported	32 h after treatment: basal cell necrosis and delayed differentiation of mesenchymal cells, thereby disrupting the timing of coordinated development of the palatal tissues; delayed reorientation before any general retardation of foetal growth as indicated by crown-rump length and foetal weight ($p<0.001$ after gd 13)
Rowland/ Hendrickx, 1983	Sprague-Dawley rats (n=10-11)	gd 13; sacrifice gd 20; examinations: number of live, dead foetuses, resorptions; foetal weight; sex; external malformations	0, 10, 20, 40 mg/kg bw	not reported	no increase in % of resorptions per litter or proportion of litters with at least one resorption; increased % litters/foetuses with cleft palate (dose-related; all partial clefts) and umbilical hernias (not statistically significant) at all doses; decreased foetal weight at 20 and 40 mg/kg bw

[a] According to Rowland and Hendrikx (1983) not triamcinolone, but triamcinolone acetonide was used here.
bw=body weight; d=day(s); gd=gestational day(s); h=hour(s); n=number

Table 3 Fertility studies in laboratory animals with triamcinolone acetonide.

authors	species	experimental period/design	dose/route	general toxicity	effects on reproductive organs/ effects on reproduction
Hagino, 1972	baboons (n=5-8/ group)	during 2 d preceding the expected time of ovulation (cycle d 12-14); or for 2 d during the early cycle of follicle development; or on d 1 and 3 of menstruation; or on d 1 of menstruation; or on d 1 and 3 of menstruation, for 2-7 consecutive cycles	0, 4 mg/ baboon/d; im	not reported	inhibition of ovulation shortening of menstrual cycles

d=day(s); h=hour(s); im=intramuscular; n=number

Table 4.1 Developmental toxicity studies in laboratory animals with triamcinolone acetonide: subcutaneous.

authors	species	experimental period/design	dose	general toxicity	developmental toxicity
Kusanagi, 1983a	C57BL/6 mice (n=10-16/group; controls: n=29); female SWV mice (n=11-16/group; controls n=15)	gd 12; sacrifice gd 18	C57BL/6: 0, 1.0, 2.5, 4.0, 5.0, 7.0 mg/kg bw SWV: 0, 1.0, 2.5, 5.0 mg/kg bw	not reported	C57BL/6 mice (in order of increasing dose): number of resorbed litters/implants: 41/250 (16.4%, control), 10/91 (11.1%), 12/131 (9.2%), 13/126 (10.3%), 14/96 (14.6%), 21/124 (16.9%); cleft palate in live foetuses: 0/209 (0%, control), 0/81 (0%), 16/119 (13.4%), 32/113 (28.3%), 27/82 (32.9%), 72/103 (69.9%); palatal slit in live foetuses with cleft palate: 12/209 (5.7%), 25/81 (30.9%), 36/103 (35.0%), 36/81 (44.4%), 34/55 (61.8%), 21/31 (67.7%). SWV mice (in order of increasing dose): number of resorbed litters/implants: 15/213 (7.0%, control), 14/143 (9.8%), 61/220 (27.7%), 67/170 (39.4%); cleft palate in live foetuses: 0/198 (0%, control), 14/129 (10.9%), 79/159 (49.7%), 86/103 (83.5%); palatal slit in live foetuses with cleft palate: 0/198 (0%, control), 0/115 (0%), 0/80 (0%), 0/17 (0%). SWV mice differed in response of palatal slit development in live foetuses with cleft palate.
Kusanagi, 1983b	C57BL/6 mice (n=14 or 16; female SWV mice (n=15 or 16)	at gd 3 blastocysts were recovered from the uterus, and transferred surgically to the uterus of day 2 pseudopregnant females (from the same or other species); these females were treated on gd 12 based on the gestational age of recipient females; sacrifice gd 18	0, 2.5 mg/kg bw	not reported	C57BL/6 → C57BL/6 transfer: number of resorbed litters/implants: 8/60 (13.3%) vs. 3/31 in controls (9.7%); cleft palate in live foetuses: 3/52 (5.8%) vs. 0/28 (0%); palatal slit in live foetuses with cleft palate: 21/49 (42.9%) vs. 6/28 (21.4%) C57BL/6 → SWV transfer: number of resorbed litters/implants: 25/70 (35.7%) vs. 16/48 (33.3%); cleft palate in live foetuses: 7/45 (15.6%) vs. 0/32 (0%); palatal slit in live foetuses with cleft palate: 6/38 (15.8%) vs. 0/32 (0%) SWV → SWV transfer: number of resorbed litters/implants: 30/74 (40.5%) vs. 22/56 (39.3%); cleft palate in live foetuses: 17/44 (38.6%) vs. 0/34 (0%); palatal slit in live foetuses with cleft palate: 0/27 (0%) vs. 0/34 (0% SWV → C57BL/6 transfer: number of resorbed litters/implants: 6/54 (11/1%) vs. 4/53 (7.5%); cleft palate in live foetuses: 2/48 (4.2%) vs. 0/49 (0%; palatal slit in live foetuses with cleft palate: 0/46 (0%) vs. 0/49 (0%)

Kusanagi, 1984	C57BL/6 mice (n=14-16 (controls: n=29)	on single days during gd 6-15; sacrifice gd 18	gd 9: 0, 2.5, 5.0, 10.0, 15.0 mg/kg bw; gd 6-15: 0, 2.5, 5.0 mg/kg bw.	not reported	gd 9 (in order of increasing dose): number of resorbed litters/implants: 41/250 (16.4%), 19/128 (14.8%), 12/123 (9.8%), 41/126 (32.5%), 69/140 (49.3%); cleft palate in live foetuses: 0/209 (0%), 1/109 (0.9%), 6/111 (5.4%), 11/85 (12.9%), 10.71 (14.1%); palatal slit in live foetuses with cleft palate: 12/209 (5.7%), 22/108 (20.4%), 41/105 (39.0%), 34/74 (46.0%), 27/61 (44.3%). Kusanagi showed that the number of resorptions/implants was highest when treatment took place at gd 8-11, and that the frequency of cleft palates and palatal slits was highest at gd 12-13.

bw=body weight; d=day(s); gd=gestational day(s); n=number

Table 4.2 Developmental toxicity studies in laboratory animals with triamcinolone acetonide: subcutaneous.

authors	species	experimental period/design	dose	general toxicity	developmental toxicity
Hendrickx, 1975	bonnet monkeys (*Macaca radiate*) (n=5) rhesus monkeys (*Macaca mulatta*) (n=10) baboons (*Papio cynocephalus*) (n=6) controls: n=10/species	1 or 4 consecutive d on: bonnet: gd 41–44 (bonnet m.); rhesus gd 37-48 baboon: gd 50-133 delivery at gd 100 (near term, or naturally)	bonnet: 15-20 mg/kg bw rhesus: 3-28, or 3-19 mg/kg bw baboon: 1-14 mg/kg bw	not reported	effects observed included: resorption (rhesus monkey only), intrauterine death (all species), and malformations (all species); type of malformations: cleft palate in 1 bonnet monkey; choanal atresia and mandibular overbite in a baboon; hyperextension of the knee, medial rotation of the hind limbs in 2 bonnet monkeys; depression of the sternum toward spine in 1 baboon; syndactyly, hypoplasia and cutaneous webbing in digits in 1 rhesus monkey; alterations in facial development in 3 bonnet monkeys and 8 rhesus monkeys; malformations in the liver in 1 rhesus monkey; renal malformations in 1 bonnet monkey; growth retardation in all 3 species; pronounced malformation in the thymus in all bonnet monkeys, most rhesus monkeys (13/17), and 2 baboons (2/6); deficiency in both total and subpopulations of lymphocytes in surviving baboons offspring (animals demonstrated persistent lymphopenia); no statistical analyses performed.

Hendrickx, 1980	bonnet monkeys (*Macaca radiata*) (n=15) rhesus monkeys (*Macaca mulatta*) (n=18) baboons (*Papio cynocephalus*) (n=6) controls: n=10 (bonnet) or 14 (rhesus and baboon)	single or multiple-day treatment between gd 21-43; foetuses of bonnet, rhesus monkeys delivered by Caesarean section or naturally; sacrifice remaining offspring: 18-30 mo; foetuses of baboons delivered by Caesarean section at gd 100±2; gross and histopathology examination restricted to craniofacial and cns malformations	5-20 mg/ kg bw	not reported	major malformations: bonnet monkeys (single vs. multiple-day treatment): craniofacial dysmorphia, 60 vs. 100%; aplasia cutis congenital, 60 vs. 20%; cranium bifidum occultum, 80 vs. 30%; cranium bifidum, 20 vs. 70%; arched palate, 0 vs. 50%; cleft palate, 0 vs. 30%; meningocele, 20 vs. 70%; encephalocele, 0 vs. 0%; occipital lobe hypoplasia, 40 vs. 20%; cerebellar hypoplasia, 20 vs. 40%; hydrocephalus, 0 vs. 30%; midbrain beaking, 40 vs. 20%; growth retardation, 0 vs. 40%; rhesus monkeys (single vs. multiple-day treatment): craniofacial dysmorphia, 100 vs. 100%; aplasia cutis congenital, 25 vs. 7%; cranium bifidum occultum, 50 vs. 14%; cranium bifidum, 50 vs. 86%; arched palate, 75 vs. 64%; cleft palate, 0 vs. 14%; meningocele, 50 vs. 36%; encephalocele, 0 vs. 50%; occipital lobe hypoplasia, 100 vs. 29%; cerebellar hypoplasia, 50 vs. 71%; hydrocephalus, 50 vs. 43%; midbrain beaking, 50 vs. 57%; growth retardation, 0 vs. 43%; baboons (multiple-day treatments, 5 or 10 mg/kg bw, respectively): craniofacial dysmorphia, 100 vs. 100%; aplasia cutis congenita, 33 vs. 0%; cranium bidifum occultum, 33 vs.0%; cranium bificum, 0 vs. 100%; arched palate, 33 vs. 50%; cleft palate, 0 vs. 0%; meningocele, 0 vs. 50%; encephalocele, 0 vs. 50%; occipital lobe hypoplasia, 100 vs. 50%; cerebellar hypoplasia, 100 vs. 100%; hydrocephalus, 0 vs. 50%; midbrian beaking, 0 vs. 0%; growth retardation, 100%; prenatal death and stillbirths tripled in bonnet monkeys, doubled in rhesus monkeys, not changed in baboons.

Parker, 1983	rhesus monkeys (*Macaca mulatta*) (n=10; controls: n=10)	gd 23, 25, 27, 29, 31; offspring recovered by hysterotomy at gd 35 and 42 (single mate), and 50, 60, and 70 (multiple mate); embryos and foetuses: gross and histological examination restricted to craniofacial and cns malformations	0, 10 mg/ kg bw	not reported	gross observations:
					gd 35 (n=2): no exposure related malformations observed;
					gd 42/43 (n=2): craniofacial dysmorphia; occipital encephalocele; subcutaneous oedema; low-set ears (1 animal); appendicular malformations (1 animal);
					gd 50 (n=2): craniofacial dysmorphia; occipital encephalocele; subcutaneous oedema; low-set ears; exophtalmia; arched or cleft palate (1 animal);
					gd 60(n=2): craniofacial dysmorphia; occipital encephalocele; subcutaneous oedema; low-set ears; appendicular malformations (1 animal);
					gd 70 (n=2): craniofacial dysmorphia; occipital encephalocele; low-set ears; exophtalmia; arched or cleft palate

					major histological major findings: gd 35: shortened parachordal mesenchymal condensation; increased cephalic flexure in the brain; gd 42/43, 50, 60, 70: abnormal parachordal cartilage morphology; thin, underdeveloped sphenoid; shortening of the posterior cranial base, decreased cranial base angle; decreased ossification and remodelling in the facial bones, and abnormal position due to the malformed sphenoid
Rowland, Hendrickx 1983	Sprague-Dawley rats (n=9-11/ group)	gd 9-11, gd 12-14, or gd 15-17; sacrifice gd 20	0, 0.125, 0.25, 0.5 mg/kg bw	no maternal lethality observed	effects on prenatal development (in order of increasing exposure level): gd 9-11: viable foetuses/litters: 96, 97, 89, 83%; litters with malformed foetuses: 0, 0, 0, 14%; malformed foetuses/litter: 0, 0, 0, 2%; gd 12-14: viable foetuses/litters: 97, 89, 77, 58%; litters with malformed foetuses: 9, 45, 80 ($p<0.05$), 100% ($p<0.05$); malformed foetuses/litter: 2, 29, 61 ($p<0.05$), 84% ($p<0.05$); gd 15-17: viable foetuses/litters: 98, 96, 100, 92%($p<0.05$); litters with malformed foetuses: 0, 0, 0, 63% ($p<0.05$); malformed foetuses/litter: 0, 0, 0, 32%($p<0.05$); incidence of specific malformations (percentage of foetuses/litter with): gd 9-11: no malformations observed; gd 12-14 (in order of increasing dose): cleft palate: 0/0, 23/45 ($p<0.05$), 54/60 ($p<0.05$), 70/80 ($p<0.05$); umbilical hernias: 0/0, 3/9, 20/50 ($p<0.05$), 58/80 ($p<0.05$); undescended testes: 0/0, 0/0, 7/13, 28/60 ($p<0.05$); hypoplastic thymus: 0/0, 0/0, 0/0, 0/0; gd 15-17 (0.5 mg/kg bw): cleft palate: 19/50 ($p<0.05$); umbilical hernias: 0/0; undescended testes: 0/0; hypoplastic thymus: 22/38 ($p<0.05$); no malformations observed in groups given the other doses.
Rotschild, 1997	Sprague-Dawley rats (n=3-5/ group	gd 12-14; sacrifice on gd 15, 17, 18, 21; lung tissue of foetuses examined by morphometry	0, 0.6 mg/kg bw	reduced maternal weight gain, placental weight, amniotic fluid weight ($p<0.05$)	general findings: significantly increased number of foetuses with cleft palates (69/80 in treated pooled gd 18 and 21 vs. 1/100 in controls; no effect on litter size morphometry findings (data of GD 21; control vs. treatment): mean linear intercept (µm): 58.8±1.0 vs. 50.3±2.0 (p=0.04); mean chord length of saccules (µm): 9.9±0.4 vs. 12.6±0.7 (p=0.009); volume density of saccular air(proportions): 17.7±0.4 vs. 25.1±1.7 (p=0.007); volume density of saccular wall: 66.8±1.2 vs. 57.1±1.73 (p = 0.002); volume density of bronchial air: 2.0±0.2 vs. 4.0±1.0 (p=0.1); volume density of bronchial wall: 4.1±0.5 vs. 6.0±1.0 (p=0.11); volume density of non-parenchyma tissue: 9.4±0.7 vs. 7.7±1.0 (p=0.18);

		peripheral airway count higher in treated animals compared to controls ($p<0.001$); significantly reduced pole to pole length ($p<0.05$); histological lung tissue examination: profound pulmonary hypoplasia, accompanied by diminished intermediate airways numbers, increased peripheral saccules numbers, increased cell differentiation.

bw=body weight; cns=central nervous system; d=day(s); gd=gestational day(s); mo=month(s); n=number

Health Council of the Netherlands

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