Health Council of the Netherlands

Cortisone

Evaluation of the effects on reproduction, recommendation for classification

2013/27

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Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Cortisone*
Uw kenmerk : DGV/MBO/U-932542
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Geachte minister,

Graag bied ik u hierbij het advies aan over de effecten van cortison 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 Gezondheidsraad.

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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Cortisone

Evaluation of the effects on reproduction,
recommendation for classification

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. 2013/27, The Hague, November 15, 2013

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

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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Contents

Samenvatting

In het voorliggende advies heeft de Gezondheidsraad cortison onder de loep genomen. Cortison is een synthetisch steroïd hormoon (corticosteroïde). Het wordt gebruikt als geneesmiddel voor de behandeling van bijnierschorshormoon-insufficiëntie en voor onderdrukking van ontstekingsreacties (aspecifiek anti-inflammatoir effect) en van (auto-)immuunprocessen. 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 (GBBS) van de raad, hierna aangeduid als de commissie, kijkt zowel naar effecten op de vruchtbaarheid van mannen en vrouwen als naar effecten op de ontwikkeling van het nageslacht. Daarnaast worden effecten op de lactatie en via de moedermelk op de zuigeling beoordeeld.

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

- voor effecten op de fertiliteit adviseert de commissie cortison niet te classificeren wegens onvoldoende geschikte gegevens

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

Executive summary

In the present report, the Health Council of the Netherlands reviewed cortisone. Cortisone is a corticosteroid. It is used in the management of adrenocortical insufficiency and as an anti-inflammatory or immunosuppressive agent. This report is part of a series, in which the Health Council evaluates the effects of substances on reproduction, at the 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 (DECOS) 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 cortisone, these recommendations are:

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

Chapter 1

Scope

1.1 Background

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

1.2 Subcommittee and procedure

This document contains the classification of cortisone by the Health Council's Subcommittee on the Classification of Reproduction Toxic Substances, hereafter called the Committee. The members of the Committee are listed in Annex A. The submission letter (in English) to the Minister can be found in Annex B.

In 2013, the President of the Health Council released a draft of the report for public review. The individuals and organizations that commented on the draft report are listed in Annex C. The Committee has taken these comments into account in deciding on the final version of the report.

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

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

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

1.3 Labelling for lactation

The recommendation for classifying substances for effects on or via lactation is also based on Regulation (EC) 1272/2008. The guideline defines that substances which are absorbed by women and have been shown to interfere with lactation or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled. Unlike the classification of substances for fertility and developmental effects, which is based on hazard identification only (largely independent of dosage), the labelling for effects on or via lactation is based on

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 of Medline, starting from 1966 up to November 2011, and by searches on the Internet; an update was performed in TOXNET in January 2013. 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. In addition, handbooks and a collection of most recent reviews were consulted as well as several websites regarding (publications on) toxicology and health. References are divided in literature cited and literature consulted but not cited. Data are described in the text and animal studies with respect to fertility and development are summarized in Annex F. Of each study, the quality of the study (performed according to internationally acknowledged guidelines) and the quality of documentation are considered. In the assessment of the potential reproduction toxic effects of cortisone, 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 preclude assessment of the compound for reproductive toxicity.
- Sufficient data show that no classification for toxic to reproduction is indicated.

1.6 Final remark

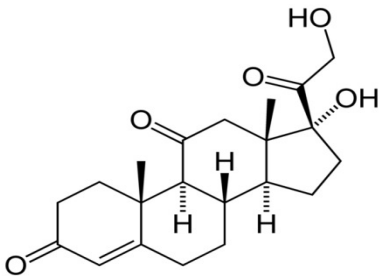
The classification of compounds is based on hazard evaluation (Niesink et al.[28]) only, which is one of a series of elements guiding the risk evaluation process.

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

Cortisone

2.1 Introduction

name	:	cortisone
IUPAC name	:	(8S,9S,10R,13S,14S,17R)-17-hydroxy- 17-(2-hydroxyacetyl)-10,13-dimethyl-1,2,6,7,8,9,12,14,15,16-decahydrocyclopenta[a]phenantrene-3,11-dione
CAS name	:	pregn-4-ene-3,11,20-trione, 17,21-dihydroxy-
CAS registry number	:	53-06-5
EU/EINECS number	:	200-006-5
synonyms	:	17,21-dihydroxypregn-4-ene-3,11,20-trione; 17-hydroxy-11-dehydrocorticosterone; 11-dehydro-17-hydroxycorticosterone; 17α,21-dihydroxy-4-pregnene-3,11,20-trione; 17α,21β-Dihydroxy-4-pregnene-3,11,20-trione; 17α-hydroxy-11-dehydrocorticosterone; Δ^4-pregnene-17α,21-diol-3,11,20-trione
structural formula	:	
molecular weight	:	360.46
chemical formula	:	$C_{21}H_{28}O_5$

use	:	in the Netherlands registered for: replacement therapy of primary and secondary adrenocortical insuffiency; congenital adrenocortical hyperplasia when short duration of action and/or mineralocorticoid mode of action is required; it is orally administered in the form of cortisone acetate tablets at doses of 25-50 mg/day and 15-40 mg/m^2/day, respectively[9]
general toxicity	:	central nervous system: insomnia, nervousness; gastrointestinal: increased appetite, indigestion; dermatologic: hirsutism; endocrine and metabolic: diabetes mellitus; neuromuscular and skeletal: arthralgia; ocular: cataracts, glaucoma; respiratory: epistaxis abdominal distention, acne, alkalosis, amenorrhea, bruising, Cushing's syndrome, delirium, oedema, euphoria, fractures, glucose intolerance, growth suppression, hallucinations, headache, hyperglycaemia, hyperpigmentation, hypersensitivity reactions, hypertension, hypokalaemia, mood swings, muscle wasting, myalgia, nausea, osteoporosis, pancreatitis, peptic ulcer, pituitary-adrenal axis suppression, pseudotumor cerebri, psychoses, seizure, skin atrophy, sodium and water retention, ulcerative oesophagitis, vertigo, vomiting
kinetics	:	cortisone, a biologically inactive glucocorticoid, is reduced in the liver into the active glucocorticoid, hydrocortisone. Both cortisone and hydroxycortisone can be metabolized (further) into hydroxy, dihydroxy and tetrahydroxy derivatives. Hydrocortisone can be dehydrogenized into cortisone. This interconversion is catalyzed by two distinct isozymes of 11ß-hydrosteroid dehydrogenase (11ß-HSD): type 1, 11ß-HSD1, acting principally as a reductase in vivo to generate hydrocortisone; type 2, 11ß-HSD2, acting exclusively as a dehydrogenase to inactivate hydrocortisone to cortisone. The isozymes play a pivotal role in the metabolism of hydrocortisone, tightly controlling the exact concentration of hydrocortisone that is available to bind to the glucocorticoid receptor (11ß-HSD1) and protecting the mineralocorticoid receptor from illicit occupation by hydrocortisone (11ß-HSD2). 11ß-HSD1 is widely distributed in many human tissues, including among others liver and gonad; 11ß-HSD2 is the predominant isozyme in among others placenta and the developing foetus.[39] Normal endogenous plasma concentrations of cortisone and hydrocortisone are 10-20 and 40-300 µg/L, respectively.[25]

2.2 Human studies

Fertility studies

No data are available regarding the effects of exposure to cortisone on human fertility.

Developmental toxicity studies

Data on developmental effects in humans were from case studies only with one exception.

Cleft palate was reported for an infant after maternal intake of high doses of cortisone during the critical process between appearance of the palate shelves and fusion of the palate (total intake during this critical period was 4 grams, i.e. approximately 300 mg/day).[17] Severe multiple malformations were observed in a newborn after cortisone intake during pregnancy (not exceeding 6 mg/day)[43], but whether these malformations were associated with cortisone intake is unknown.

Several healthy children were born after cortisone intake during the first trimester of pregnancy at doses up to 50 mg/day[1] and after cortisone intake during the first, second and third trimester at doses up to 300 mg/day[10]. Out of 25 babies born to women treated with cortisone during pregnancy weeks four to 19 with doses of 25 to 100 mg/day, 21 appeared normal at term. One baby died five days after delivery from coarctation of the aorta, one baby was born with a clubfoot, one baby died three days after delivery (cause of death unknown), and one child developed cataract after 2.5 months.[42]

The Committee notes that these reports described a variety of effects without a clear pattern or dose-response relationship.

In a population-based case-control study including 662 cases of orofacial clefts, 207 conotruncal heart defects, 265 neural tube defects, 165 limb reduction defects and 734 healthy controls, information on medication use from one month before conception through the third month of pregnancy was collected in maternal interviews a few years after delivery. The mothers of five children with orofacial clefts and of one child with a neural tube defect reported cortisone use (one in combination with prednisone), versus none of the control mothers.[6]

2.2.1 *Lactation*

No data are available, both regarding the excretion of cortisone in breast milk and on the effects of exposure to cortisone on lactation and on infants during the lactation period.

Cortisone and hydrocortisone are metabolically interconverted in the human and animal body. Hydrocortisone is a natural component in breast milk, that passes from the maternal bloodstream into milk. In two studies, levels ranging from 0.2 to 33 µg/L were reported. They were derived from 33 samples obtained during postpartum days 1 to >40 from an unspecified number of women and from 75 samples during postpartum months 2 to 12 from four women. Generally, although they decreased during the postpartum period, they varied with time and among individuals.[20,35] In a third study, free cortisol levels in seven women amounted to ca. 17 µg/L on postpartum days 1 and 2 and 7 µg/L on postpartum day 3.[30]

In addition, no data were available on hydrocortisone excretion in breast milk following exogenous exposure to hydrocortisone or cortisone.

2.3 Animal studies

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

The committee notes that in the studies available, cortisone was administered through routes considered less relevant for occupational exposure, viz. subcutaneous, intramuscular and intraperitoneal injection.

2.3.1 Fertility studies

No data are available regarding the effects of exposure to cortisone on fertility in laboratory animals.

2.3.2 Developmental toxicity studies

The most conspicuous developmental toxic effect induced by cortisone is cleft palate.

Fraser (1951) and Fraser and Fainstat (1951) reported that intramuscular injections of cortisone into female mice for three or four days in the middle of the gestational period induced abortion, resorptions, cleft palate and other (not further specified) defects in the offspring. The type of effect and the incidence of cleft palate varied with the stage of pregnancy, the genetic background of the mice used (some strains being more susceptible than others) and the dose. Generally, doses of 5-15 mg/day resulted particularly in abortion and resorptions and doses of 1.25 or 2.5 mg/day in cleft palate. The highest proportion of mice with cleft palate (viz. 79%) was found following a four-day treatment starting on gestational day 10 or 11. No effects, i.e. cleft palates, were observed at doses of 0.625 mg/day and in controls treated with vehicle four days starting on gestational day 11, 12 or 13.[14,15]

The discovery by Fraser and Fainstat[15] that cortisone can cause cleft palate in mice was the start of numerous investigations of the possible mechanisms and aspects of the induction of cleft palate by cortisone (see for review e.g.[16]) and other corticosteroids, thus confirming the findings by Fraser and Fainstat (see e.g.[4,11,13,23,26,32,40,44]).

As to rats, Mosier et al. (1982) did not observe cleft palate following subcutaneous injection of 50 mg cortisone into female Long-Evans rats (n=12)

on gestational day 12 and 13 (incidence: 0/116 vs. 0/154 in six saline-treated controls).[27]

Treating rabbits with intramuscular doses of cortisone of 25 (n=5) or 30 (n=2) mg for four days starting on gestational day 14 (n=4) or 15 (n=3) caused an increased incidence of cleft palate in the treated animals compared to controls (17/35 vs. 0/36).[12] Starting on gestational day 13, Walker (1967) injected intramuscularly New Zealand White rabbits (n=1-5/group) with doses of cortisone of 15, 15, 10 and 10 mg/day, 12, 12, 12 and 12 mg/day, 10, 10, 12 and 12 mg/day, 10, 10, 10 and 10 mg/day, 15, 15 and 10 mg/day, 10, 10 and 12 mg/day, and 15 and 15 mg/day. The corresponding incidences of cleft palate were 9/22, 0/8, 0/10, 2/14, 0/4, 1/7, and 0/15.[41] DeCosta and Abelman (1952) did not report any cleft palate in the offspring of 67 rabbits (of 'mixed strain') treated with intramuscular doses of 15 mg/day for one to 11 days during gestation.[10]

In the above-mentioned studies, also other effects were reported: abortion and resorptions in mice [4,14,15,26,32], statistically significant decreases in mean foetal body and organ weights in rats (accompanied by decreased maternal body weight gains; $p<0.025$)[27], and abortion[10], resorptions[10,12,41] and foetal death in rabbits[12].

Some additional studies reporting other effects are summarized below.

Atkin et al. (1981) investigated the effects of cortisone acetate on calcification and ossification of long bones in mice. Pregnant Sabra mice were injected intramuscularly with 0 or 0.75 mg cortisone acetate (25 mg/kg bw) daily on gestational day 11-19 and the tibial bones of their offspring were examined on postnatal days 1, 3, 5, 10, 15, 20 and 30 (n=168; controls: n=89) . Weight gain of pregnant dams was statistically significantly reduced after treatment with cortisone acetate. Treatment with cortisone acetate induced statistically significantly reduced bone length and width, and an abnormal calcification of cartilage. These effects gradually disappeared with the age of the mice. Statistically significantly thinner metaphyseal and diaphyseal trabeculae were observed after treatment with cortisone acetate during the first two weeks. Additionally, cortisone acetate induced intracellular calcium precipitate formation in chondrocytes throughout the zone of hypertrophic cartilage, and abnormal calcification of the interstitial substance.[2]

Development of the skeleton of foetuses was investigated by Beck et al. (1989) after intramuscular treatment of pregnant CD-1 mice (n=10/group) with cortisone acetate. Doses of 0, 0.15, 0.3, 0. 625 or 1.25 mg were given daily on

gestational day 11-14. Untreated and vehicle (0.85% NaCl)-only control groups were included. Dams were sacrificed at gestational day 18 and foetuses were examined for ossification of cervical centra and abnormalities. Maternal toxicity was not described. Compared to vehicle-treated controls, statistically significant changes were found in the two higher dose groups. They included increases in foetal mortality, frequency of abnormalities (basically cleft palate, but occasionally also kinky tails), frequency of unossified cervical centra and the percentage of foetuses with fewer than seven ossified caudal vertebrae.[3]

The development of the gastrointestinal mucosal barrier of newborns from cortisone-treated rats was investigated by Pang et al. (1985). Sprague-Dawley rats were injected intraperitoneally (number/group not reported) with cortisone acetate (in saline) doses of 0, 200 or 300 mg/kg bw/day from gestational day 17-21. Maternal toxicity was not described. Rats were allowed to deliver. A reduced mean pup body weight was observed (controls: 6.7±0.6 g; low dose: 5.4±0.9 g; high dose: 3.5±0.5 g). Serum cortisol levels in both dams and newborns (dose-dependent) were statistically significantly increased. Compared to control animals, sucrase activity was prematurely induced and lactase and maltase activity were enhanced in the intestinal microvillus membrane of cortisone-treated newborns. Furthermore, binding of the fucose-specific lectin *Ulex Europeus* (UEA) to the microvillus membrane was statistically significantly increased, suggesting an accelerated maturation of the microvillus membrane after cortisone exposure *in utero*.[29]

McDeVitt et al. (1981) investigated the reproduction toxic effects of cortisone using CD-1 albino mice. Mice (n=8/group) were intramuscularly injected with cortisone from gestational day 11-14 at doses of 25, 50, 75, 100 or 125 mg/kg bw/day. An untreated control group and vehicle (saline) only group were included. Necropsy was performed at gestational day 18. In all groups, dams showed lethargy after the second and third administration. Statistically significantly lower maternal weight gains were found in dams exposed to doses of 50 mg/kg and higher. The 75-mg/kg group had a statistically significantly lower percentage of male foetuses while mean foetal weight was reduced in the 50-, 100- and 125-mg/kg groups ($p<0.05$). At doses ≥50 mg/kg/bw day, increases ($p<0.05$) in the mean number of soft tissue and in the mean number of skeletal defects per litter and in the mean percentage of foetuses with soft tissue and in the mean percentage of foetuses with skeletal defects were observed. Soft tissue effects included cleft palate, fifth digit protuberance and cryptorchidism. Skeletal defects included sternebrae effects, split supraoccupital bone or sternebrae and

fused sternebrae. The critical periods reported for cortisone-induced cleft palate are remarkably similar to those required for the production of sternebral, supraoccipital and digital malformations.[24]

Hydrocortisone

Although an evaluation of the reproductive toxic properties of hydrocortisone is beyond the scope of this advice, the Committee notes that parenteral administration of hydrocortisone induced increased incidences of cleft palate in mice[5,18,19,21,22,28,33,34], rats[36] and hamsters[7,8,37,38].

2.3.3 Lactation

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

Hydrocortisone (acetate), administered subcutaneously at 1.5 mg/animal/day to female Wistar rats, once on gestational day 19, once immediately after parturition and once a day during the first 5 days of lactation decreased body weights (315.76±12.61 g; controls: 358.46±16.34 g; not statistically significant) and plasma testosterone concentrations (2.80±0.68 ng/mL; controls: 4.92±0.68 ng/mL; $p<0.05$) and affected contractile response patterns of the seminal vesicle to acetylcholine (viz. an increased sensitivity and a reduced maximum contractile response) in their male offspring at postnatal day 90. Seminal vesicle wet weights did not differ between groups. Organs were not histologically examined.[31]

2.4 Conclusion

Fertility

No human and animal studies were available regarding the effects of exposure to cortisone on fertility.

The Committee proposes not to classify cortisone for fertility due to a lack of appropriate data.

Developmental toxicity

Human data regarding developmental effects consisted of several case reports on a variety of disorders[1,10,17,42,43] and a case-control study showing an association between cortisone use during pregnancy and the occurrence of orofacial clefts[6]. However, the committee concludes that these human data are not sufficient for classification.

In studies in laboratory animals all performed using subcutaneous or intramuscular injection, cortisone induced increases in the incidences of cleft palate in several strains of mice[3,4,11,13-15,23,24,26,32,40,44], in foetal mortality in mice[3] and rabbits[12], in abortion in mice[14,15] and rabbits[10], in the numbers of resorptions in mice[4,14,15,26,32] and rabbits[10,12,41], and in the frequency of soft tissue effects in mice[24] and of skeletal effects in mice[2,3,24] and rats[12] and decreases in foetal body[12,27] and organ[27] weights in rats.

It was generally not reported whether these effects were seen in the presence or absence of maternal toxicity, but the Committee considers that the nature and severity of the effects observed indicate that they occurred independently from maternal toxicity. All studies used routes less relevant to occupational exposure (subcutaneous, intramuscular, intraperitoneal injection). However, the Committee considers these exposure routes relevant for classification of cortisone since systemic exposure will occur via any route of administration of this compound.

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

2.4.1 Lactation

No human or animal data were available on the effects of cortisone on or via lactation. No data were found on endogenous or background levels of cortisone in breast milk or on concentrations in breast milk in women occupationally exposed to cortisone. The Commitee notes that in humans, endogenously produced hydrocortisone can be present in breast milk at levels up to 33 µg/L[20,30,35]. No data were available on hydrocortisone excretion in breast milk following exogenous exposure to hydrocortisone or cortisone. In addition, data to evaluate the potential adverse effects of exposure to hydrocortisone via breast milk on the breastfed infant are lacking.

Following subcutaneous administration of hydrocortisone to female rats on gestational day 19, immediately after parturition and on the first five days of lactation, their 90-day-old male offspring had statistically significantly decreased plasma testosterone levels and deviating cholinomimetic responses of seminal vesicles; seminal vesicle wet weights were not affected.[31] The Committee notes that data on dose-related effects of hydrocortisone on fertility or on reproductive organs are lacking. Therefore, the Committee cannot assess the relevance of these findings on biochemical end points.

Overall, the Committee proposes not labelling cortisone for effects on or via lactation due to a lack of appropriate human and animal data.

Proposed classification for fertility

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

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

Annexes

Annex **A**

The Committee

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

The first draft of the present document was prepared by C.E.F. de Esch MSc, Dr. M.J.W. van den Hoven, and M.M. Tegelenbosch-Schouten MSc from TNO Quality of Life in Zeist.

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 *Cortisone*
Your reference : DGV/MBO/U-932342
Our reference : U-7947/HS/fs/543-Z13
Enclosed : 1
Date : November 15, 2013

Dear Minister,

I hereby submit the advisory report on the effects of cortisone on fertility and on the development of the progeny; it also concerns effects on lactation and on the progeny via lactation. This advisory report is part of an extensive series in which reproduction toxic substances are classified in accordance with European guidelines. This involves substances to which people may be exposed occupationally.

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

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

Yours sincerely,
(signed)
Prof. dr. W.A. van Gool,
President

Annex C

Comments on the public draft

A draft of the present report was released in 2013 for public review. The following organisations and persons have commented on the draft document:

- T.J. Lenz, K. Krajnak. National Institute for Occupational Safety and Health, Cincinnati OH, USA.
- S. Hansen. TIB Chemicals AG, Mannheim, Germany.

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

Annex **D**

Regulation (EC) 1272/2008 of the European Community

3.7 Reproductive toxicity

3.7.1 Definitions and general considerations

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

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

(a) adverse effects on sexual function and fertility;

(b) adverse effects on development of the offspring.

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

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

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

3.7.1.3 Adverse effects on sexual function and fertility

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

3.7.1.4 Adverse effects on development of the offspring

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

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

3.7.2 Classification criteria for substances

3.7.2.1 Hazard categories

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

Table 3.7.1(a) Hazard categories for reproductive toxicants.

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

Table 3.7.1(b) Hazard category for lactation effects.

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

3.7.2.2 Basis of classification

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

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

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

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

3.7.2.3 Weight of evidence

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

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

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

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

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

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

3.7.2.4 Maternal toxicity

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

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

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

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

Maternal mortality:

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

Mating index

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

Fertility index

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

Gestation length

(if allowed to deliver)

Body weight and body weight change:

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

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

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

Food and water consumption (if relevant):

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

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

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

Post-mortem data:

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

3.7.2.5 Animal and experimental data

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

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

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

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

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

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

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

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

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

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

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

3.7.3 Classification criteria for mixtures

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

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

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

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

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

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

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

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

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

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

3.7.4 Hazard Communication

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

Table 3.7.3 Label elements for reproductive toxicity.

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

Annex **E**

Additional considerations to Regulation (EC) 1272/2008

The classification and labelling of substances is performed according to the guidelines of the European Union (Regulation (EC)1272/2008) presented in Annex 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, occurring without reporting the parental or maternal toxicity, may lead to a classification other than category 1B, when the effects occur at dose levels which cause severe toxicity in *general* toxicity studies.
- Clear adverse reproductive effects will not be disregarded on the basis of reversibility per se.

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

* Organisation for Economic Cooperation and Development

Annex **F**

Fertility and developmental toxicity studies

Table 1 Developmental toxicity studies with cortisone in animals.

authors	species	experimental period/ design	dose/route	general toxicity	developmental toxicity
Fawcett et al. (1996)	female CD-1 mice (n=9-11/group)	gd 10-12 4 groups: controls; controls + plasma sampling; sham adrenalectomized, treated; adrenalectomized (with or without plasma sampling), treated mice adrenalectomized at gd 6 gd 10 and 12, blood sampling for corticosterone analysis sacrifice: gd 18	0, 12.5, 25, 50, 100 mg/kg bw/d; sc	not reported	gd 10: decreased corticosterone levels in adrenalectomized group. gd 12: decreased corticosterone levels in sham-adrenalectomized animals vs. controls all treated groups: decreased foetal weights compared to non-sampled controls all groups treated with doses ≥25 mg/kg bw: increased incidence of cleft palate all groups treated with 100 mg/kg bw: increased incidence of intrauterine deaths

Beck et al. (1989)	female CD-1 mice (n=10/group)	gd 11-14; sacrifice: gd 18; foetal skeleton development investigated	0, 0.15, 0.3, 0.625, 1.25 mg cortisone acetate (in 0.85% NaCl); im	not reported	at 0.625 and 1.25 mg sign. changes: increased foetal mortality (8.9±2.6%, 15.3±3.2%, resp.; vehicle controls: 4.6±1.9%) increased frequency of abnormalities (basically cleft palate, occasionally tail kinks) (34.8±4.5%, 66.7±4.5%, resp.; vehicle controls: 0.9±0.9%) increased frequency of unossified cervical centra (20.3±4.7%, 22.7±7.7%, resp.; vehicle controls: 9.2±6.6%) increased percentage of foetuses with fewer than seven ossified caudal vertebrae (51.8±4.7%, 52.3±4.7%, resp.; vehicle controls: 18.1±3.8%)
Piddington et al. (1983)	female CD-1, A/J mice (n not reported)	gd11-14 sacrifice: gd 17	0, 50 (A/J mice), 100 (CD-1 mice) mg/kg bw/d (in DMSO); sc	not reported	A/J mice: 32% resorption; 79% of viable foetuses with cleft palate. CD-1 mice: 44% resorption; 66% of viable foetuses with cleft palate.
Yoneda/Pratt (1982)	female Swiss Webster mice (SWR/NIH) (n not reported)	gd 11 sacrifice: gd 17 3 weeks before mating: normal or vitamin B6-deficient diet; pregnant mice tap water or tap water with vitamin B6	62.5, 125 mg/kg bw cortisone acetate; sc	not reported	6% incidence of cleft palate mice given control diet and tap water and 62.5 mg cortisone acetate 68% incidence of cleft palate in mice given control diet and tap water and 125 mg cortisone acetate
Atkin et al. (1981)	female Sabra mice (n not reported)	gd 11-19; pups examined on pnd 1, 3, 5, 10, 15, 20, 30	0.75 mg cortisone acetate (25 mg/kg bw); im	reduced bw gain of dams	reduced bone length and width, abnormal cartilage calcification, disappearing with age thinner metaphyseal and diaphyseal trabeculae during pnd weeks 1 and 2 intracellular calcium precipitate formation in chondrocytes throughout the zone of hypertrophic cartilage, abnormal calcification of the interstitial substance.

Diewert/Pratt (1981)	female A/J mice (n=5-11/group)	gd 11-14. sacrifice: gd 14-16	100 mg/kg bw/d cortisone acetate (in PBS); sc	not reported	smaller palatal shelves with reductions in extracellular matrix content and in cell number shelf elevation ca. 12 hr delayed, cortisone treatment severely reduced the extent of contact between the palates shelves.
McDeVitt et al. (1981)	female CF-1 albino mice (n= 8/group)	gd11-14 sacrifice: gd 18.	0, 25, 50, 75, 100, 125 mg/kg bw/d cortisone acetate (in saline); im	lethargy after 2nd and 3rd adminis-tration; decreased bw gains at doses ≥50 mg/kg bw ($p<0.05$)	at doses ≥50 mg/kg/bw: increased mean number of soft tissue defects/litter (4.1, 4.0, 4.0, 4.5, resp.; vehicle controls: 0.8; $p<0.05$); increased mean number of skeletal defects/litter (5.8, 9.5, 8.8, 8.7, resp.; vehicle controls: 2.0; $p<0.05$); increased mean percentage of foetuses with soft tissue defects (70.7, 68.3, 77.5, 85.8%, resp.; vehicle controls: 14.0%; $p<0.05$); increased mean percentage of foetuses with skeletal defects (76.7, 87.0, 95.9, 100%, resp.; vehicle controls: 29.5%; $p<0.05$) 75 mg/kg bw: decreased percentage of male foetuses ($p<0.05$). 50, 100, 125 mg/kg bw: decreased mean foetal weights ($p<0.05$) dose-response relationship between cortisone and soft tissue and skeletal defects (incl. cleft palate, split sternebrae).
Vekemans/ Fraser (1979)	female SW, SW/Fr mice (n=3/litter/group)	gd 12 sacrifice; at intervals between gd 14 and 15	50 mg/kg bw cortisone acetate; sc	not reported	delayed shelf movement with 9-10 hr in both strains.
Bedrick/Ladda (1978)	female A/J mice (n not reported)	gd 11-15 sacrifice: gd 18.	100 mg/kg bw/d cortisone acetate (in saline); sc	not reported	increased resorption rate (78% vs. 9% in controls) increased percentage of cleft palate (61% vs. 0%) thinner palatal epithelium in treated animals.

Miller et al. (1977)	female C57BL1/6J (n=6, 15, 19/group)	gd 11-14 effect of changes in diet on cortisone-induced cleft palate investigated.	2.5 mg/d cortisone acetate; im each group received a different diet	not reported	depending on the diet: frequency of cleft palate 18, 42, 8.2% and of resorptions 13.3, 10, 16%
Loevy (1976)	female CD1-mice (n=7-19/group)	gd 11 or 12 after examination of the 1st generation offspring, animals mated at 2 months of age (including cortisone treatment at gd 11 or 12) and the 2nd generation examined as well	5 mg cortisone acetate; injection, site not reported	not reported	cleft palate induced at the same rate in 1st and 2nd generation, with only one small difference: gd 11: decreased incidence of cleft palate in 2nd generation animals from litters without any cleft palate, compared to 2nd generation animals from littermates with at least 1 mouse with cleft palate/litter.
Fraser/Fainstat (1951)	female mice of 5 different strains (n=1-4/group)	4 d during gd 6-20; dams allowed to litter	0, 0.625, 1.25, 2.50, 5, 10 mg/d cortisone acetate; im	no obvious effects	results showed that 2 strains ('S') were relatively more susceptible than the 3 others strains ('LS'); because of small numbers, results were lumped with respect to susceptibility of strains and gestational day(s) treatment started; cleft palate incidence: controls: 0/38 0.625 mg: L: 0/37 (number of females treated: 6); LS: 0/8 (n=1) 1.25+2.5 mg: <gd 10: L: 3/4 (n=4; 2/4 litters resorbed); LS: 8/17 (n=7; 1/7 litters resorbed) gd 10-11: L: 34/43 (79%) (n=11); LS: 14/65 (21.5%) (n=10) gd 12-13: L: 13/44 (29.5%) (n=9); LS: 9/111 (8%) (n=18) gd14-17: L: 7/24 (29%) (n=6); LS: 1/34 (3%) (n=6)

Pang et al. (1985)	female Sprague-Dawley rats (n not reported)	gd 17-21 gastrointestinal mucosal barrier of newborns investigated.	0, 200, 300 mg/kg/ bw cortisone acetate (in saline); ip	not reported	reduced pup bw (controls: 6.7±0.6 g; low dose: 5.4±0.9 g; high dose: 3.5±0.5 g) increased sucrose, lactase, maltase activity in the intestinal microvillus membranes increased binding of the fucose-specific lectin *Ulex Europeus* (UEA) to the microvillus membrane suggesting an accelerated maturation of the microvillus membrane after cortisone exposure in utero
Mosier et al. (1982)	female Long-Evans rats (n=12; controls: n=6)	gd 12 and 13 sacrifice: gd 21	0, 50 mg/d cortisone acetate; sc	sign. decreased bw gain between gd 12 and 21	no effect on number of foetuses/litter and of live foetuses/litter; sign. decreases in foetal bw, absolute brain, heart, liver, adrenal, kidney weights, relative liver, adrenal, kidney weights incidence of omphalocele: 2/321 (controls: 0/348; not sign.) incidence of cleft palate: 0/116 (controls: 0/154)
Walker (1967)	female New Zealand White rabbits (n=1-3/group)	gd 13-16;	mg/kg/d:	not reported	
		gd 13-15;	25, 25, 25, 25		resorbed litters: 3/3
		gd 13-14;	15, 15, 15, 15		resorbed litters: 2/2
		sacrifice: gd 21	15, 15, 10, 10		resorbed litters: 2/5; resorbed foetuses: 1/31 cleft palate: 9/31
			12, 12, 12, 12		resorbed litters: 1/2; resorbed foetuses: 0/8; cleft palate: 0/8
			10, 10, 12, 12		resorbed litters: 1/2; resorbed foetuses: 0/10; cleft palate: 0/10
			10, 10, 10, 10		resorbed litters: 1/3; resorbed foetuses: 1/16; cleft palate: 2/14
			15, 15, 10, 0		resorbed litters: 0/1; resorbed foetuses: 2/4; cleft palate: 0/4

			10, 10, 12, 0	not reported	resorbed litters: 1/3; resorbed foetuses: 6/8; cleft palate: 1/7
			15, 15, 0, 0; cortisone; im		resorbed litters: 0/2; resorbed foetuses: 0/15; cleft palate: 0/15
Fainstat (1954)	female white rabbits (n=7; controls: n=4)	gd 14-17; gd 15-18; sacrifice: gd 25, 28, 29 or 30	0, 25 or 30 mg cortisone acetate; im	not reported	controls: no cleft palate; no mortality 25 mg: resorbed litters: 2/5; dead foetuses: 6/23; cleft palate: 10/23 30 mg: dead foetuses: 3/12; cleft palate: 7/12

bw=body weight; DMSO=dimethylsulfoxide; gd=gestational day(s); hr=hour(s); im: intramuscular; ip=intraperitoneal; n=number; PBS=phosphate-buffered saline; pnd=postnatal day(s); sc: subcutaneous; sign.: statistically significant(ly); wk=week(s)

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