Health Council of the Netherlands

Tellurium

Evaluation of the effects on reproduction, recommendation for classification

2014/07

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Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies *Tellurium*
Uw kenmerk : DGV/MBO/U-932542
Ons kenmerk : U-8075/HS/cn/543-H14
Bijlagen : 1
Datum : 3 april 2014

Geachte minister,

Graag bied ik u hierbij het advies aan over de effecten van tellurium 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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Tellurium

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. 2014/07, The Hague, April 3, 2014

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 tellurium onder de loep genomen. Tellurium wordt gebruikt als additief in koper, ijzer en staal, in gevulcaniseerd rubber, als pigment in glas en keramiek, en in sommige andere applicaties. Dit advies past in een reeks adviezen waarin de Gezondheidsraad op verzoek van de minister van Sociale Zaken en Werkgelegenheid de effecten van stoffen op de voortplanting beoordeelt. Het gaat vooral om stoffen waaraan mensen tijdens de beroepsuitoefening kunnen worden blootgesteld. De Subcommissie Classificatie reproductietoxische stoffen van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen van de raad, hierna aangeduid als de commissie, kijkt zowel naar effecten op de vruchtbaarheid van mannen en vrouwen als naar effecten op de ontwikkeling van het nageslacht. Daarnaast worden effecten op de lactatie en via de moedermelk op de zuigeling beoordeeld.

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

- voor effecten op de fertiliteit adviseert de commissie om tellurium niet te classificeren wegens onvoldoende geschikte gegevens
- voor effecten op de ontwikkeling adviseert de commissie tellurium 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 tijdens of via lactatie adviseert de commissie om tellurium niet te kenmerken wegens onvoldoende geschikte gegevens.

Executive summary

In the present report, the Health Council of the Netherlands reviewed tellurium. Tellurium is used as an additive to copper, iron and steel, in vulcanized rubber, as a colouring agent in glass and ceramics, and in some other applications. 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. Furthermore, the Committee considers the effects of a substance on lactation and on the progeny via lactation.

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

- for effects on fertility, the Committee recommends not classifying tellurium due to a lack of appropriate data
- for effects on development, the Committee recommends classifying tellurium 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 tellurium 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 tellurium 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 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 D. The classification of compounds is ultimately dependent on an integrated assessment of the nature of all parental and developmental effects observed, their specificity and adversity and the dosages at which the various effects occur. The guideline necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the regulation, the Committee has agreed upon a number of additional considerations (see Annex E).

1.3 Labelling for lactation

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

developmental effects, which is based on hazard identification only (largely independent of dosage), the labelling for effects on or via lactation is based on a risk characterization and therefore, it also includes consideration of the level of exposure of the breastfed child.

Consequently, a substance should be labelled for effects 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

For the present evaluation, a review on the toxic effects of tellurium and tellurium compounds by the Health Council's Committee on Updating of Occupational Exposure Limits was available.[9] The last reference concerning reproduction toxic effects cited in there was from 1988. Literature searches were conducted in the online databases XTOXLINE, MEDLINE and CAPLUS, from 1988 up to February 2011. A final search was performed in TOXNET/TOXLINE in November 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 into 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 F as well. Of each study the quality of the study design (performed according to internationally acknowledged guidelines) and the quality of documentation are considered.

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)[16], 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

Tellurium

2.1 Introduction

The identity and some physicochemical properties of tellurium are given below:

name	:	tellurium
CAS registry number	:	13494-80-9
EC/EINECS number	:	236-813-4
synonyms	:	aurum paradoxum; metallum problematum; telloy
colour and physical state	:	grey-white lustrous, brittle, crystalline solid, hexagonal, rhombohedral structure; or dark-grey to brown, amorphous powder with metal characteristics
formula	:	Te
atomic weight	:	127.6
melting point	:	449.5-449.8 °C
boiling point	:	988-989.9 °C
vapour pressure	:	130 Pa at 520 °C
density	:	6.11-6.27 (crystalline)
solubility	:	insoluble in water

use	:	as an alloying additive in steel; as a (minor) additive in copper alloys, in lead alloys, in cast and malleable iron; in the chemical industry as a vulcanizing agent and accelerator in the processing of rubber, and as a component of catalysts for synthetic fibre production; in the production of cadmium-tellurium-based solar cells; in photoreceptor and thermoelectric electronic devices, other thermal cooling devices, as an ingredient in blasting caps, and as a pigment to produce various colours in glass and ceramics[7]; in the past, therapeutically, in the (intramuscular) treatment of syphilis, leprosy, trypanosomiasis (through intramuscular injections), and against excessive sweating[15]

data from [3,9] unless otherwise noted.

So far, 39 tellurium isotopes with atomic masses ranging from 105 to 143 have been discovered; these include eight stable, 16 neutron-deficient and 15 neutron-rich isotopes.[12] Tellurium is a heavy element with chemical properties resembling those of non-metals, such as sulphur, but with more metal-like physical properties. Regarding properties and toxicology, it is similar to selenium, but tellurium is not considered to be a trace element. Biological functions are not yet identified.[15]

The daily intake of tellurium for man was in the 1960s initially estimated to be 600 µg but revised to 100 µg[8]; based on a more recent study, an intake between 1 and 10 µg might be more realistic[14]. 'Background' concentrations of tellurium in blood, saliva and urine are <5 µg/L, <1 µg/L and <0.5 µg/L, respectively.[14]

In human volunteers given metallic tellurium or tetra- or hexavalent tellurium salts, the percentage of intestinal absorption was estimated to be approximately 10 and 25%, respectively, based on cumulative urinary excretion of tellurium in the first four days after administration.[13] In rats and rabbits, intestinal absorption ranges from 10-25 to 40%, respectively.[8,13] Following parenteral administration, tellurium is predominantly excreted in the urine.[8,13] Small amounts (ca. 0.1%) are exhaled presumably as dimethyl telluride which has a characteristic garlic odour.[8]

2.2 Human studies

Fertility studies

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

Developmental toxicity studies

No data are available regarding the effects of exposure to tellurium on development in humans.

Lactation

No data are available regarding the excretion of tellurium in breast milk or the effects of exposure to tellurium on infants during the lactation period.

2.3 Animal studies

Fertility studies

No laboratory animal data are available regarding the effects of exposure to tellurium on fertility.

Developmental toxicity studies

Developmental toxicity studies with tellurium in laboratory animals are summarized in Annex F.

Oral studies

Garro and Pentschew (1964) fed more than 100 pregnant Long-Evans rats diets containing 500, 1,250 or 2,500 ppm of metallic tellurium (based on the data of Duckett and Johnson et al. (see below), these doses could be equal to 30, 75 and 150 mg/kg bw/day). Dams of the two lower dose groups were treated throughout gestation while the high-dose animals were put on a normal diet three to five days before the expected delivery to avoid abortions.

The newborn pups appeared normal although smaller than the controls. Hydrocephalus, that developed immediately after birth, was found in 60-90% and 100% of the pups of the mid- and high-dose groups, respectively, and in a lower, unspecified percentage at the low dose. In all dose groups, 99% of the affected pups died within one month.

Garro and Pentschew stated that the amounts administered were not toxic to the dams tolerating the diets well and behaving normally.[6]

Agnew et al. (1968) found no hydrocephalus in the offspring of Wistar rats (n=4/group) administered dietary amounts of 1,250 and 2,500 ppm of metallic tellurium throughout gestation (based on the data of Duckett and Johnson et al. (see below), these doses could be equal to 75 and 150 mg/kg bw/day).

When given 3,300 ppm (n=10) (approximately 200 mg/kg bw, see afore), hydrocephalus, generally not grossly obvious until postnatal day 4 or 5, was seen in 8/10 litters (allowed to live 19 days or longer after birth) and in 36/77 pups.

Data on maternal toxicity were not presented.[1]

Duckett (1970) fed Wistar rats (n=20/group) 0 or 3,000 ppm (about 180 mg/kg bw/day*) of elemental tellurium in the diet on every gestational day (not further specified). On gestational day 13 and 15, foetuses (number not specified) were removed via the abdominal wall and after closing the abdominal wall again animals were allowed to terminate their pregnancy and give birth. Only the foetuses of tellurium-fed animals, which eventually gave birth to hydrocephalic animals, and foetuses of similar age from the control rats were examined and reported.

The size and appearance of the tellurium and control foetuses were similar. No anomalies were noted in sections of the brains of the tellurium foetuses, stained with haematoxylin-eosin. Electron microscopic examination showed morphological anomalies in the cells in the ependymal layer of the tellurium foetuses, 13- and 15-intrauterine-days old. The ependymal layer of the normal foetal rat resembled that of human, rabbit and chick foetuses. On the ventricular surface of the ependymal cells from tellurium foetuses the normally present microvilli were not present and the number of mitochondria was greatly diminished. Mitochondria were often abnormal, smaller and darker than normal and showed distortion of cristae. The cells in the rest of the telencephalon appeared to be normal.

No data on dams or pups were reported. Duckett only stated that from his experience, the dose given resulted in 50% of the rats giving birth to litters whose every member was hydrocephalic.[4]

Duckett et al. (1971) investigated in a later study the effect of periodical or single dietary dosing on the occurrence of hydrocephalus. Pregnant rats (strain not reported) were given 2,500 ppm (about 150 mg/kg bw/day using a body weight of 250 g) of metallic tellurium in the diet for every gestational day (21 days) and

* Calculated based on 15 g food intake per day containing 45 mg of elemental tellurium and an average body weight of 250 g at the beginning of pregnancy as indicated in Duckett (1970).

12/20 rats gave birth to litters containing an average of eight pups, six of which were hydrocephalic. Subsequently, the same dose was given to three groups of pregnant rats (n=20/group): the first group received tellurium from gestational day 1 through 9, the second group on gestational day 10-15 and the third group on day 16-21.

Twelve rats fed tellurium during gestational day 10-15 gave birth to hydrocephalic rats. The average litter numbered nine, five of which were hydrocephalic. No hydrocephalic pups were noted in the other two dose groups. Also, single doses on one gestational day were given to five rats per group per gestational day. Seventy-two animals gave birth to an average of eight offspring. No hydrocephalic pups were noted.[5]

The Committee notes that the exact day of postnatal examination, the absence or presence of maternal toxicity and statistics were not reported.

Johnson and co-workers (1988) performed a standard developmental toxicity study in rats and rabbits generally performed according to OECD Test Guideline 414 (1981). Preliminary studies in the rat showed that gavage studies gave only developmental toxicity at doses ≥10,000 mg/kg bw/day while dietary intake resulted in effects at ≥559 mg/kg bw/day*. For the main studies, dietary administration was chosen.

Pregnant Sprague-Dawley rats (n=32-33) were given 0, 30, 300, 3,000 or 15,000 ppm of tellurium in the diet on gestational day 6-15 (equal to approximately 0, 2, 20, 166 and 633 mg/kg bw/day for gestational day 6-10 and 0, 2, 18, 173 and 580 mg/kg bw/day for gestational day 11-15**). On day 20 of presumed gestation, approximately two-thirds of the females in each group were killed and foetuses were investigated. The remaining dams in each group were allowed to deliver and pups were observed until postnatal day 7. Heads of pups which were stillborn, found dead or killed on postnatal day 7 were examined.

No effect was observed on the incidences of pregnancy, on the mean numbers of corpora lutea, implantations and resorptions, on the mean litter size, on the numbers of live and dead foetuses and on the percentages of male foetuses.

At 15,000 ppm, mean weights of female and male foetuses were decreased ($p \leq 0.05$). Increased incidences of litters with variations (100%, controls: 18%; $p \leq 0.01$) and of foetuses with variations (41%, controls: 2.1%; p-value not reported), of malformed foetuses (no details presented), and of foetuses with delayed ossification (no details presented) were reported. The most common

* Corresponds to 7,500 ppm Te in the diet as reported in Johnson et al.
** Calculated by Johnson et al. based on quantities of feed consumed.

malformation was internal hydrocephalus with dilatation of the lateral ventricles observed in 17 litters (85%; controls: 1 (4.6%); $p \leq 0.05$) and in 67 foetuses (55%; controls: 1 (0.7%); $p \leq 0.05$). More severely affected foetuses had also slight to marked dilatation of the third and/or fourth ventricles. Externally, hydrocephalus was noted only for two foetuses (litters not specified), one of which had an enlarged fontanel bordered by a haemorrhagic area. Moderate dilatation of the renal pelvis was also found (no details). Other malformations included kinked and/or stubbed tails, rotation of a hindlimb or hind foot, a malformed retina, malpositioned manubrium and clavicles, short radius, ulna and/or femur, wavy ribs and a thickened or split rib. Many of these foetuses from severely affected dams also showed delayed ossification of the parietals, interparietals, supraoccipitals, vertebral and sternal centra, pubes, ischia and/or ribs. At 3000 ppm, incidences of litters with variations (57%, $p \leq 0.01$) and of foetuses with variations (11%, p-value not reported), of malformed foetuses (no details presented) and of foetuses with delayed ossification (no details presented) were increased as well. Also in this group, the most common malformation was internal hydrocephalus with dilatation of the lateral ventricles observed in three litters (14%; not statistically significant from controls) and in 11 foetuses (55%; not statistically significant). Moderate dilatation of the renal pelvis was also found (no details). No other malformations were observed.

Regarding the groups that were allowed to litter, there were no effects on duration of gestation, on the number (percentage) of dams with stillborn, on litter size, on the number of live pups delivered and on mean pup weights on postnatal day 7. In the highest dose group, the number (percentage) of pups surviving seven days was decreased ($p \leq 0.01$). No gross, external or visceral anomalies were seen, but there was a significant increase in the incidence of slight to extreme dilatation of the lateral ventricles in pups at the highest dose at postnatal day 7 ($p \leq 0.01$).

No maternal mortality occurred. Maternal body weight gain and food consumption were decreased at 300 and 3,000 ppm ($p \leq 0.01$), while weight loss and halved food consumption were seen at 15,000 ppm ($p \leq 0.01$) during exposure.[11]

In the same study, New Zealand white rabbits (n=17) were artificially inseminated and fed diets containing 0, 17.5, 175, 1750 or 5,250 ppm of tellurium (equal to approximately 0, 0.8, 8, 52, 97 mg/kg bw/day using average feed intake on gestational days 6-18 and average maternal body weight on gestational day 6) on gestational days 6-18. Dams were killed on gestational day 29 and foetuses were examined.

The number of pregnancies varied between dose levels: 10, 15, 9, 15 and 13 at 0, 17.5, 175, 1,750 and 5,250 ppm, respectively. No effect was observed on the incidence of abortion, mean numbers of corpora lutea, implantations, resorptions, litter size or sex ratio (% of male foetuses/litter). At 5,250 ppm, decreased mean foetal weight (males 84%, females 95% of control; not statistically significant), increased incidences of litters with abnormalities (46%; controls: 2%) of foetuses with abnormalities (12%; controls: 6.7%), malformed foetuses (no details presented) and foetuses with delayed ossification (no details presented) were observed (no statistics reported). In the foetuses of this group, the following effects were reported: low incidences of hydrocephalus; enlarged and/or irregularly shaped anterior fontanel; incomplete ossification of, or small holes in, the frontals and parietals; frontals with thickened ossification; umbilical hernia; fused pulmonary artery and aorta; asymmetric and/or irregularly shaped and/or fused sternebrae; and thickened areas in the ribs. These foetuses also tended to be smaller than normal and had fewer caudal vertebral, xiphoid and forepaw phalangeal foetal ossification sites.

Maternal toxicity consisted of soft or liquid faeces, alopecia, thin appearance, and/or decreased motor activity and decreased body weight gain and food consumption at 1,750 and 5,250 ppm (body weight gain: $p \leq 0.01$ at both doses; food consumption: $p \leq 0.05$ at 1,750 and $p \leq 0.01$ at 5,250 ppm). [11]

Intramuscular injection

In a subsequent study (see diet studies above), Agnew and Curry (1972) investigated the precise period of teratogenic susceptibility of the rat embryo to tellurium. Pregnant rats (n=5-10/experiment) were injected intramuscularly with 13 mg/kg bw metallic tellurium suspended in olive oil on one day of gestational day 7 to 13; two or three pregnant controls were injected with single doses of olive oil from gestational days 9-13. Dams were allowed to deliver and offspring was observed for ten postnatal days, killed and examined for hydrocephalus and other visceral defects. Only those mothers failing to deliver were autopsied and examined for foetal resorptions the day following predicted delivery.

Apart from foetuses with hydrocephalus observed after injection on gestational day 7 (1/31, 3%), 9 (14/75, 19%) and 10 (10/32, 31%) (controls: 1/94, 1%), no biologically relevant effects were noted. Malformations other than hydrocephalus were not observed.

Data on maternal toxicity were not presented.[2]

Lactation

Two female rats were given a diet containing 0 or 1.25% of metallic tellurium (about 750 mg/kg bw/day*) from postnatal day 0 until sacrifice at postnatal days 7, 14, 21 or 28 (n=5 pups/group). Apart from a garlic odour and skin discoloration, no signs of toxicity were seen in the lactating dams. During the postnatal period, neonates from treated mothers showed effects such as garlic odour, skin discoloration, lethargy, hindlimb paralysis, incontinence, slow weight gain and smaller size. Microscopic examination of nerve tissues revealed hypomyelation, myelin degeneration, and Schwann cell degeneration.[10]

The Committee notes the limited study design.

2.4 Conclusions

Fertility

No human or animal studies on fertility effects of tellurium were available.

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

Developmental toxicity

No human studies on developmental toxicity effects of tellurium were available.

In one developmental toxicity study, maternally toxic levels of tellurium in the diet induced increased numbers of rat foetuses with dilated ventricles/ hydrocephalus, of rat foetuses with hydrocephalus and decreased weights and of rabbit foetuses with variations and malformations and delayed ossification.[11] In other less well performed and reported diet studies in rats, tellurium caused increased numbers of rat pups with hydrocephalus.[1,4-6] In one of the latter studies[6], levels affecting the offspring were stated to be not toxic to the dams while in the other studies[1,4,5], it was not reported whether effects were seen in the presence or absence of maternal toxicity.

The Committee is of the opinion that the developmental effects observed occurred independently from maternal toxicity. Therefore, based on the data from laboratory animal studies, the Committee recommends classification of tellurium in category 1B (*presumed human reproductive toxicant*).

* Based on the data of Duckett and Johnson et al. (see afore).

Lactation

No human data and only limited animal data were available regarding the excretion of tellurium in breast milk or the effects of exposure to tellurium on infants during the lactation period.

Therefore, the Committee concluded that a lack of appropriate data precludes assessment of tellurium for effects on or via lactation.

Proposed classification for fertility

Lack of appropriate data precludes the assessment of tellurium 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 tellurium 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
D	Regulation (EC) 1272/2008 of the European Community
E	Additional considerations to Regulation (EC) 1272/2008
F	Developmental toxicity studies

Annexes

Annex **A**

The Committee

- A.H. Piersma, *Chairman*
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The first draft of this report was prepared by Dr. H.M. Barentsen, 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 *Tellurium*
Your reference : DGV/MBO/U-932542
Our reference : U-8075/HS/cn/543-H14
Enclosed : 1
Date : April 3, 2014

Dear Minister,

I hereby submit the advisory report on the effects of tellurium 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. Lentz, K. Krajnak; National Institute for Occupational Safety and Health, Cincinnati OH, USA
- K. Heitmann; UMCO Umwelt Consult GmbH, Hamburg, 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 D. The classification of compounds is ultimately dependent on an integrated assessment of the nature of all parental and developmental effects observed, their specificity and adversity, and the dosages at which the various effects occur. The guideline necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the regulation, the Committee has agreed upon a number of additional considerations:

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

- the Committee 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**

Developmental toxicity studies

Table 1 Developmental toxicity studies with tellurium in animals.

authors	species	experimental period/design	dose/route	general toxicity	developmental toxicity
Garro/ Pentschew (1964)	Long-Evans rats(n>100)	low/mid dose: throughout gestation; high dose: throughout gestation until 3-5 d before expected delivery	0, 500, 1,250, 2,500 ppm (ca. 30, 75, 150 mg/kg bw/d[a]); diet	not toxic to dams: dams tolerated diets well; behaved normally	pups appeared normal although smaller than controls hydrocephalus developed immediately after birth; incidences: 500 ppm: unspecified increase 1,250 ppm: 60-90% 2,500 ppm: 99% mortality: 99% of all affected pups within 1 mo
Agnew et al. (1968)	Wistar rats (n=4 low/mid dose; n=10 high dose)	throughout gestation	0, 1,250, 2,500, 3,300 ppm (ca. 75, 150, 200 mg/ kg bw/d[a]); diet	not reported	1,250 ppm: no hydrocephalus 500 ppm; no hydrocephalus 3,300 ppm: hydrocephalus in 8/10 litters (allowed to live ≥19 d; appearing grossly after pnd 4 or 5) and in 36/77 pups
Duckett (1970)	Wistar rats (n=20)	daily throughout gestation; examination of foetal brains on gd 13, 15; only foetuses of tellurium-fed animals, eventually giving birth to hydrocephalic animals,and foetuses of similar age from the control rats	3,000 ppm (ca. 45 mg/rat or 180 mg/kg bw/d); diet	not reported	no effect on size and appearance of foetuses; no anomalies in sections of the brains of the tellurium foetuses, stained with haematoxylin-eosin; electron microscopic examination: morphological anomalies in cells of ependymal layer: ependymal layer of normal foetal rat resembled that of human, rabbit, and chick foetuses; on the ventricular surface of the ependymal cells from tellurium foetuses. normally

		examined and reported			present microvilli not present and number of mitochondria greatly diminished; mitochondria often abnormal, smaller and darker than normal and showed distortion of cristae; cells in the rest of the telencephalon appeared to be normal
Duckett et al. (1971)	rats (strain not specified) (n=20)	daily throughout gestation; on gd 1-9, 10-15, 16-21; (exact day of examination not reported)	2,500 ppm (ca. 150 mg/ kg bw/d); diet	not reported	12 rats fed during gd 10-15 gave birth to hydrocephalic rats (average litter 9 with 5 hydrocephalic); no hydrocephalic animals during other dosing periods
Duckett et al. (1971)	rats (strain not specified) (n=5)	one of gd 1-21; number of postnatal hydrocephalus (exact day of examination not reported)	2,500 ppm (ca. 150 mg/ kg bw/d); diet	3 animals died (not further specified)	72 animals gave birth to an average of 8 offspring; no hydrocephalic animals; no further information
Agnew/Curry (1972)	Long-Evans rats (n=5-10; controls 2-3)	one of gd 7-13; sacrifice: pnd 10 examined for hydrocephalus and other visceral effects; only mothers failing to deliver were autopsied and examined for foetal resorptions the day following predicted delivery	0, 13 mg/kg bw (suspended in olive oil); im	not reported	after injection on gd 8: delivery in 5/8 after injection on gd 7, 8, 10, 11: total number of offspring/group rather low, number of foetal resorptions increased; after injection on gd 7, 9, 10: number of foetuses with hydrocephalus: 1, 14, 10, resp. (vs. 1 in controls); no other malformations observed
Johnson et al. (1988)	Sprague-Dawley rats; (n=32-33)	gd 6-15; sacrifice: 2/3 on gd 20: foetuses examined; 1/3 allowed to deliver: pups observed until pnd 7; pup heads (stillborn, found dead or killed) examined	0, 30, 300, 3,000, 15,000 ppm (ca. 0, 2, 20, 166, 633 mg/kg bw/d for gd 6-10; 0, 2, 18, 173, 580 mg/kg bw/d for gd 11-15); diet	no mortality; 300, 3,000, 15,000 ppm: decreased maternal weight gain, food consumption (during exposure; $p \leq 0.01$ at gd 6-9, gd 6-15); 3,000, 15,000 ppm: thin appearance); not clear at which levels: preparturi-tional vaginal bleeding, decreased motor activity	foetuses: no effect on incidence of pregnancy, mean number of corpora lutea, implantations, live and dead foetuses, resorptions, litter size, % of males; 15,000 ppm: decreased weights of male, females ($p \leq 0.05$); % litters with variations: 100% (controls: 18%; $p \leq 0.01$); % foetuses with variations: 41% (controls: 2.1%; p-value not presented); increased incidence of malformed foetuses (no details), of foetuses with delayed ossification (no details); most common malformation: internal hydrocephalus with dilatation of the lateral ventricles: in 17 litters (85%) vs. 1 in controls (4.6%) ($p \leq 0.05$); in 67 foetuses (55%) vs. 1 in controls (0.7%) ($p \leq 0.05$); also slight to marked dilatation of the third and/or fourth ventricles in more severely affected foetuses; externally hydrocephalus in 2 foetuses (one had enlarged fontanelle bordered by

					a haemorrhagic area); dilatation of renal pelvis (no details); other malformations (no further details): kinked and/or stubbed tails, rotation of hind limb/foot, malformed retina, malpositioned manubrium and clavicles, short radius, ulna and/or femur, wavy ribs, thickened/ split rib; delayed ossification of the parietals, interparietals, supraoccipitals, vertebral and sternal centra, pubes, ischia, and/or ribs in many of these foetuses from severely affected dams 3000 ppm; % litters with variations: 57% (p≤0.05); % foetuses with variations: 11% (p-value not presented); increased incidence of malformed foetuses (no details), of foetuses with delayed ossification (no details); most common malformation: internal hydrocephalus with dilatation of the lateral ventricles: in 3 litters (14%) (n.s.); in 11 foetuses (8.3%) (n.s.); dilatation of renal pelvis (no details); no other malformations treatment had no effect on duration of gestation in groups allowed to litter; pups: no effect on number of dams with stillbirths, litter size, of live pups delivered, on mean pup weights at pnd 7 15,000 ppm; decreased number (%) of pups surviving 7 d (p≤0.01); % of litters with dilated lateral ventricles at pnd 7: 75% (controls:0) ((p≤0.01); % of pups with dilated lateral ventricles at pnd 7: 61% (controls:0) ((p≤0.01); no (other) gross, external or visceral anomalies
Johnson et al. (1988)	New Zealand white rabbits (n=17)	gd 6-18; sacrifice: gd 29	0, 17.5, 175, 1,750, 5,250 ppm (ca. 0, 0.8, 8, 52, 97 mg/kg bw/d using feed intake gd 6-18 and maternal bw on gd 6); diet	1,750, 5,250 ppm: decreased bw gain (p≤0.01), food consumption (p≤0.05, p≤0.01, resp.), soft or liquid faeces, alopecia, thin appearance, and/or decreased motor activity (p≤0.01) 5,250	number of pregnancies varied between dose levels: 10, 15, 9, 15 and 13 at 0, 17.5, 175, 1750 or 5250 ppm, respectively; no effect on incidences of abortion, mean numbers of corpora lutea, implantations, resorptions, litter size, on % male foetuses/litter; 5250 ppm: decreased foetal weight: males 84%, females 95% of controls; incidence of litters with abnormalities: 46% (controls: 2%); of foetuses with abnormalities: 12% (controls: 6.7%); increased in malformed foetuses (no details), foetuses with delayed ossification (no details); low incidences of hydrocephalus; enlarged and/or

	ppm: adverse clinical signs (not further specified) ($p \leq 0.01$)	irregularly shaped anterior fontanelle; incomplete ossification of, or small holes in, the frontals and parietals; frontals with thickened ossification; umbilical hernia; fused pulmonary artery, aorta; asymmetric and/or irregularly shaped and/or fused sternebrae; thickenedareas in ribs; foetuses also tended to be smaller than normal with fewer caudal vertebral, xiphoid, forepaw phalangeal ossification sites

[a] based on the data of Duckett (1970) and Johnson et al. (1988)

abbreviations: bw=body weight; d=day(s); gd=gestational day(s); im=intramuscular; mo=month(s); pnd=postnatal day(s).

Health Council of the Netherlands

Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory reports that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

Areas of activity

Optimum healthcare
What is the optimum result of cure and care in view of the risks and opportunities?

Prevention
Which forms of prevention can help realise significant health benefits?

Healthy nutrition
Which foods promote good health and which carry certain health risks?

Environmental health
Which environmental influences could have a positive or negative effect on health?

Healthy working conditions
How can employees be protected against working conditions that could harm their health?

Innovation and the knowledge infrastructure
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

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