Formic acid

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies 'Formic acid'
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Mijnheer de staatssecretaris,

Bij brief van 3 december 1993, nr DGV/MBO/U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid om naast het afleiden van gezondheidskundige advieswaarden ook te adviseren over andere onderwerpen ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen. In 1995 heeft de Staatssecretaris van Sociale Zaken en Werkgelegenheid besloten tot het opstellen van een zogenaamde niet-limitatieve lijst van voor de voortplanting vergiftige stoffen. Op deze lijst komen stoffen die volgens de richtlijnen van de Europese Unie ingedeeld moeten worden in categorie 1, 2 en 3 wat betreft effecten op de voortplanting en stoffen die schadelijk kunnen zijn voor het nageslacht via de borstvoeding. De Gezondheidsraad is verzocht om voor stoffen een classificatie volgens de EU-criteria voor te stellen.

In dit kader bied ik u hierbij een advies aan over mierenzuur. Dit advies is opgesteld door de Commissie Reproductietoxische stoffen van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik heb deze publicaties heden ter kennisname aan de minister van Volksgezondheid, Welzijn en Sport, de minister van Sociale Zaken en Werkgelegenheid en de staatssecretaris van Volkshuisvesting, Ruimtelijke Ordening en Milieu gestuurd.

Hoogachtend,

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Formic acid

Evaluation of the effects on reproduction, recommendation for classification

Committee for Compounds toxic to reproduction
A Committee of the Health Council of the Netherlands

to:

the Minister and State Secreatry of Social Affairs and Employment

No. 2006/02OSH, The Hague, June 13, 2006

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Samenvatting

In het voorliggende advies heeft de Gezondheidsraad mierenzuur onder de loep genomen. Mierenzuur is een kleurloze vloeistof met een sterke geur. Het wordt wereldwijd gebruikt als conserveringsmiddel in diervoeders voor de bereiding van kuilvoer. Daarnaast wordt het toegepast als chemisch intermediair in de leer industrie, textielindustrie en bij de rubber bereiding.

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 Commissie Reproductietoxische stoffen, een commissie van de raad, evalueert effecten op de vruchtbaarheid van mannen en vrouwen zowel als op de ontwikkeling van het nageslacht. Bovendien worden effecten van blootstelling van de zuigeling via de moedermelk beoordeeld.

Op basis van Richtlijn 93/21/EEC van de Europese Unie doet de commissie een voorstel voor classificatie. Voor mierenzuur komt de commissie tot de volgende aanbevelingen:

- voor effecten op de fertiliteit adviseert de commissie om mierenzuur niet te classificeren wegens onvoldoende geschikte gegevens.
- voor effecten op de ontwikkeling adviseert de commissie om mierenzuur niet te classificeren wegens onvoldoende geschikte gegevens.

- voor effecten tijdens de lactatie adviseert de commissie om mierenzuur niet te classificeren wegens onvoldoende geschikte gegevens.

Executive summary

In the present report the Health Council of the Netherlands reviewed formic acid. Formic acid is a colorless fuming liquid with a highly pungent, penetrating odor. The primary use of formic acid worldwide is as an anti-bacterial agent in animal feeds and as a silage additive. In addition, formic acid has been used as a chemical intermediate in leather processing, rubber manufacture and textile industry.

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 Committee for Compounds toxic to reproduction, a committee of the Health Council, 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 effects on the progeny via lactation.

Recommendations for classification by the committee are made in accordance with Directive 93/21/EEC of the European Union. The committee's recommendations for formic acid are:

- for effects on fertility, the committee recommends not classifying formic acid due to a lack of appropriate data.
- for developmental toxicity, the committee recommends not classifying formic acid due to a lack of appropriate data.
- the committee is of the opinion that a lack of appropriate data precludes the labelling of formic acid for effects during lactation.

Hoofdstuk 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. The classification is performed by the Health Council's Committee for Compounds Toxic to Reproduction according to the guidelines of the European Union (Directive 93/21/EEC). The committee'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 toxic to reproduction (class 1, 2 or 3) or labelled as 'may cause harm to breastfed babies' (R64).

1.2 Committee and procedure

The present document contains the classification of formic acid by the Health Council's Committee for Compounds Toxic to Reproduction. The members of the committee are listed in Annex A. The first draft of this report was prepared by dr ir APM Wolterbeek of TNO Quality of Life, Zeist, The Netherlands, by contract with the Dutch Health Council. The classification is based on the evaluation of published human, animal and *in vitro* studies concerning adverse effects

with respect to fertility and development and lactation of the above mentioned compound.

Classification and labelling was performed according to the guidelines of the European Union listed in Annex C.

Classification for fertility and development:	
Category 1	Substances known to impair fertility in humans (R60)
	Substances known to cause developmental toxicity in humans (R61)
Category 2	Substances which should be regarded as if they impair fertility in humans (R60)
	Substances which should be regarded as if they cause developmental toxicity in humans (R61)
Category 3	Substances which cause concern for human fertility (R62)
	Substances which cause concern for humans owing to possible developmental toxic effects (R63)
No classification for effects on fertility or development	
Labelling for lactation:	
	May cause harm to breastfed babies (R64)
	No labelling for lactation

In 2005, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft report are listed in Annex B. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Additional considerations

The classification of compounds toxic to reproduction on the basis of the Directive 93/21/EEC 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 directive necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the directive, 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 progeny, the compound will be classified in category 1, irrespective the general toxic effects (see Annex C, 4.2.3.1 category 1).

- Adverse effects in a reproductive or developmental study, in the absence of data on parental toxicity, occurring at dose levels which cause severe toxicity in other studies, need not necessarily lead to a category 2 classification.
- If, after prenatal exposure, small reversible changes in foetal growth and in skeletal development (e.g. wavy ribs, short rib XIII, incomplete ossification) in offspring occur at a higher incidence than in the control group in the absence of maternal effects, the substance will be classified in category 3 for developmental toxicity. If these effects occur in the presence of maternal toxicity, they will be considered as a consequence of this and therefore the substance will not be classified for developmental toxicity (see Annex C, 4.2.3.3 developmental toxicity final paragraph).
- Clear adverse reproductive effects will not be disregarded on the basis of reversibility per se.
- Effects on sex organs in a general toxicity study (e.g. in a subchronic or chronic toxicity study) may warrant classification for fertility.
- The committee not only uses guideline studies (studies performed according to OECD standard protocols*) for the classification of compounds, but non-guideline studies are taken into consideration as well.

1.4 Labelling for lactation

The recommendation for labelling substances for effects during lactation is also based on Directive 93/21/EEC. The Directive defines that substances which are absorbed by women and may 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, should be labelled with R64. Unlike the classification of substances for fertility and developmental effects, which is based on a hazard identification only (largely independent of the dosage), the labelling for effects during lactation is based on a risk characterisation and therefore also includes consideration of the level of exposure of the breastfed child.

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

* Organisation for Economic Cooperation and Development

1.5 Data

Literature searches were conducted in the on-line databases Current Contents and Medline, starting from 1966 up to 2005 and by searches on internet. 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.

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

1.6 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.

1.7 Final remark

The classification of compounds is based on hazard evaluation (Niesink *et al.*[1]) only, which is one of a series of elements guiding the risk evaluation process. The committee emphasises 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 characterisation, human exposure assessment and recommendations of other organisations.

Hoofdstuk **2**

Formic acid

2.1 Introduction[2]

Name	:	Formic acid
CAS-no	:	64-18-6
Synonyms	:	Hydrogen carboxylic acid, methanoic acid, aminic acid, formylic acid, Bilorin, Collo-didax, Formira, Formisotin
Use	:	Formic acid is a colorless, fuming liquid with a highly pungent, penetrating odor. The primary use of formic acid worldwide is as a silage additive and it is also used as an additive in animal feeds where it has anti-bacterial activity. Formic acid is also used in textile dying and finishing, as a chemical intermediate, in leather processing, in rubber manufacture, as a catalyst in hydrocarbon-formaldehyde resins and phenolic resins and as a plasticizer for vinyl resins. Besides, it is used in the electroplating industry, as an antiseptic in wine and beer brewing, as a preservative in animal feed additives, as a component of cleaning solutions, as a wire stripping compound, in the preparation of bare wires for soldering, as a laundry sour and as an oil well acidifying agent. Furthermore, it is used in the synthesis of aspartame.
Mol weight	:	46.03
Chem formula	:	CH_2O_2 (HCOOH)
Conversion factor	:	1 ppm = 1,88 mg/m^3; 1 mg/m^3 = 0,53 ppm
General toxicity	:	Formic acid is severely irritating and corrosive to the eyes, skin and mucous membranes and may cause permanent damage. Exposure to vapour or mist can cause tearing of the eyes, runny nose, coughing, sore throat, bronchitis and shortness of breath. Exposure to high concentrations of formic acid may cause pulmonary edema. The US EPA has affirmed the “generally regarded as safe” status for formic acid as a direct and indirect human food ingredient.

Exposure limit	:	The current administrative occupational exposure limit for formic acid in the Netherlands is 9 mg/m^3 (for 8 hours). The American Conference of Governmental Industrial Hygienists (ACHIH) has assigned a Threshold Limit Value for formic acid of 5 ppm (9.4 mg/m^3) for an 8-hour time-weighted average concentration. A short-term exposure limit of 10 ppm (19 mg/m^3) was established for periods not exceeding 15 minutes. These limits are based on the risk of severe irritation to eyes, skin and respiratory tract.
Kinetics	:	Formic acid is absorbed from the gastrointestinal tract, via the lungs and the intact skin. The absorbed substance is degraded to CO_2 and H_2O and is partially excreted unchanged in the urine. The major part of the absorbed formic acid is metabolized in the liver, but partially also in the intestinal mucosa, lungs and spleen. Formic acid is oxidized in relation to folate and according to a catalase-peroxidative mechanism. Humans and primates have reduced capacity for formate oxidation compared with rodents and dogs and are thus more sensitive to formate intoxication.

On dissolution in water, formic acid partially ionizes depending on the pH of the solution to formate ions (formic acid => formate + H^+). The pKa for formic acid is 3.7. For this reason, the effects of the calcium and sodium formate salts of formic acid are generally included in the evaluation of the toxic effects of formic acid (IUCLID[3]; American Chemistry Council[4]). Therefore, in the present evaluation of the effects of formic acid on development and reproduction, the effects of calcium and sodium formate are included.

Formic acid is one of the main metabolites of methanol and there is substantial evidence that formic acid is the metabolite responsible for some of the toxic effects (visual and metabolic acidosis) of methanol in humans and primates (Shelby[15]). It has to be noted that in the evaluation of the developmental toxic effects of formic acid by international agencies (*e.g*. U.S. Environmental Protection Agency), the available data regarding the developmental effects of methanol is included (American Chemistry Council)[4]. Although it is generally accepted that general toxic effects of methanol (*e.g.* visual effects and metabolic acidosis) are the result of its conversion to formic acid[15], the contribution of formic acid to methanol-induced developmental toxic effects is not yet clear.

2.2 Human studies

Fertility

No studies were found regarding the effects of exposure to formic acid on human fertility.

Developmental studies

Hantson *et al.*[5] reported a case of a 26-year-old woman who ingested 250-500 ml methanol in the 38th week of pregnancy. Five hours after methanol ingestion, the woman was slightly acidotic and had a serum methanol level of 2300 mg/l and a formic acid concentration of 336 mg/l. Treatment consisted of ethanol and bicarbonate administration together with hemodialysis. Six days later, the woman gave birth to an infant with no signs of distress. A 10-year follow-up of the child revealed no visual disturbances.

Lactation

No studies were found regarding the effects of exposure to formic acid on human lactation.

2.3 Animal studies

Tables 1 and 2 (Annex D) summarise the fertility and developmental studies with formic acid and formate salts in experimental animals.

Fertility studies

In a 2 week inhalatory toxicity study, F344/N rats (5/sex/group) and B6C3F1 mice (5/sex/group) were exposed to formic acid (0, 31, 62.5, 125, 250 and 500 ppm [0, 58.3, 117.5, 235, 470 and 940 mg/m^3]) for 6 h/day, 5 days/week (Thompson[6]). At sacrifice, among other organs, the right testis was weighed. Deaths occurred in the 500 ppm group (rats and all mice) and 250 ppm group (mice). Final body weights were statistically significantly decreased in the 250 and 500 ppm groups (rats and mice). No effects on testicular weights were observed.

In a 13 week inhalatory toxicity study, F344/N rats (10/sex/group) and B6C3F1 mice (10/sex/group) were exposed to formic acid (0, 8, 16, 32, 64 and 128 ppm [0, 15, 30.1, 120.3 and 240.6 mg/m^3]) for 6 h/day, 5 days/week (Thompson[6]). Sperm motility and concentration and oestrus cyclicity were analysed in rats and mice of the 0, 8, 32 and 128 ppm groups. At sacrifice, among other organs, the right testis was weighed. In the 128 ppm group two mice died. In rats, body weight gains of the male rats of the 8, 16, 32 and 64 ppm groups were slightly increased as compared to the control rats. In mice, body weight gains were significantly decreased in mice exposed to 64 and 128 ppm formic

acid. In both species, no effects were observed on oestrus cyclicity, testicular weight, epididymal weight, sperm motility and epididymal and testicular sperm concentration.

The oral toxicity of two formates in Wistar rats was investigated in a series of three poorly reported multi-generation and chronic toxicity studies by Malorny.[7] In the first study, 8 males and 24 females were given 0.2% calcium formate in drinking water (150-200 mg calcium formate/kg body weight/day) and a control group of 8 animals, sex not specified, was used. The exposure was continued with the offspring of the original rats, throughout 5 generations over a 3-year period.

In a second study, rats were given 0.4% calcium formate (300-400 mg/kg body weight/day) for up to 2 years (2 generations) at the date of publication. No treatment-related effects were observed on body weight (gain) and macroscopic- and histopathological examination of lung, spleen, stomach, liver and kidneys and other, not specified, organs. No effects were observed on reproduction (as presented by numbers of offspring).

Malorny[7] described another multi-generation and chronic study with Wistar rats (n=6/group) given 1% sodium formate in drinking water for, at the time of the publication, 1.5 years but no details of this study were described concerning toxicity of the compound.

Developmental studies

In a study of Dorman *et al.*[8] CD-1 mice (n=10-14) were given a single dose of sodium formate (0 and 750 mg/kg body weight) on day 8 of gestation by gavage (this dose resulted in a formate concentration of 1.05 mM in the plasma and 2 mmol/kg in the decidual swellings). Dams were sacrificed on day 10 or 18 of gestation and foetuses were examined for neural tube defects. Maternal toxic effects were not described. The incidence of neural tube defects was not affected by sodium formate whereas, in the same study, methanol (1.5 g/kg body weight by gavage, resulting in comparable levels of formate in plasma and decidual swellings) induced a statistically significant increase in the incidence of neural tube defects. These results suggest that the effects were directly induced by methanol rather than due to the accumulation of formate.

The oral toxicity of calcium formate was investigated in Wistar rats in a poorly reported study by Malorny.[7] In the first study, 8 males and 24 females were given

0.2% calcium formate in drinking water (150-200 mg calcium formate/kg body weight/day) and a control group of 8 animals, sex not specified, was used. The exposure was continued with the offspring of the original rats, throughout 5 generations over a 3-year period.

In a second study, rats were given 0.4% calcium formate (300-400 mg/kg body weight/day) for up to 2 years (2 generations) at the moment of the date of publication. No treatment-related effects were observed on body weight (gain) and macroscopic- and histopathological examination of lung, spleen, stomach, liver and kidneys and other, not specified, organs. No effects were observed on the development of the offspring (as presented by weight and length) in each generation.

Malorny[7] also performed a study with chicken eggs (n=1051 in control group. The number in the treatment groups was not specified). A single dose of sodium formate (0, 5, 10 and 20 mg/egg) was injected into the air space of incubated chicken eggs 48-96 h after the start of brooding and further incubated up to day 16. No effects were observed on mortality, weight of the embryos and on the incidence and type of malformations.

In vitro developmental toxicity studies

In a series of *in vitro* studies, the effects of formic acid[10,12] and sodium formate [8-10,13,14] were determined on rat and mouse embryos.

Mouse embryos (GD8) were cultured for 24 hours in the presence of formic acid (0-44 mM) and rat embryos (GD 9) were cultured for 24 or 48 hours in the presence of formic acid (0-24 mM). In general, after 24 h, dose related effects were observed on growth, development and the incidence of abnormalities (primarily open anterior and posterior neuropore, rotational defects, tail anomalies, enlarged pericardium and delayed heart development) in rat and mouse embryos[10]. In rats, the incidence of effects was increased after 48 h exposure, as compared to 24 h, but no qualitative differences in effects were observed. Cultured rat embryos (GD 10) exposed to formic acid (0-28 mM) for 40 hours, showed growth and development retardations at concentrations 19 mM formic acid[12].

Several studies were performed with embryos of rats and mice cultured with formate salts[8-11, 13,14] (0-30 mM and 0-44 mM, respectively). Dose related effects were observed on growth, development, the incidence of abnormalities and survival. The effects of formate increased when the pH of the culture medium was lowered (by adding HCl)[9, 12].

Lactation

No studies were found regarding the effects of exposure to formic acid during the lactation period.

2.4 Conclusion

No studies on the effects of formic acid on human fertility are available. In an NTP Technical Report on Toxicity Studies concerning formic acid, no effect on testicular weight, sperm parameters and oestrus cyclicity was observed in rats and mice after inhalatory exposure (Thompson) [6], although general toxicity was observed. The committee emphasizes, however, that no functional fertility parameters were studied by Thompson *et al.*. In a series of poorly reported multi-generation studies described by Malorny[7], no effects on fertility (as presented by the numbers of offspring) of Wistar rats were observed after exposure to calcium formate (but not formic acid), given in drinking water.

Considering the studies of Thompson en Malorny, the committee is of the opinion that a lack of appropriate human and animal data precludes the classification for effects on fertility. However, because of the high reactivity of formic acid (corrosive to the eyes, skin and mucous membrane), the committee is of the opinion that specific effects on fertility are not likely.

In a study of Hantson *et al.*[5], a woman intoxicated with methanol and a serum level of 336 mg/l formic acid gave birth to an infant with no signs of distress six days after intoxication.

In a single dose study of Dorman *et al.*[8], no effect of sodium formate on the incidence of neural tube defects was observed in mice. In the same study, methanol statistically significantly increased the incidence of neural tube effects. Because the formate levels in the plasma of rats given sodium formate or methanol were similar, the developmental effects induced by methanol are problably a direct effect of methanol rather than effects due to formates[8].

In a series of poorly reported multi-generation studies described by Malorny[7], no effect of calcium formate give in the drinking water to Wistar rats was observed on development (as presented by weight and length of the offspring). Furthermore, no effect of sodium formate on the development of chicken embryos (Malorny[7]) was observed.

In several *in vitro* studies, the effects of formic acid[10,12] and sodium formate [8-10,13,14] on rat [9-13] and mice embryos[8,10,14] was determined. In general, both formic acid and sodium formate inhibited the growth and development of the embryos and increased the incidence of abnormalities and lethality. Both the

acidity of the culture medium viewed apart and the concentration of formate in the culture medium appeared to contribute to the embryotoxicity of formic acid. However, the committee is of the opinion that a lack of data concerning the kinetics of formic acid *in vivo* precludes the assessment of the relevance of the concentrations used in *in vitro* studies.

Considering the studies of Dorman *et al.* and Malorny, the committee is of the opinion that a lack of appropriate data precludes the assessment of formic acid for effects on development. However, because of the high reactivity of formic acid, the committee does not expect that a well performed developmental study will show specific developmental effects of formic acid.

Proposed classification for fertility

Lack of appropriate data precludes the assessment of formic acid for effects on fertility

Proposed classification for developmental toxicity

Lack of appropriate data precludes the assessment of formic acid for effects on development

Proposed labelling for effects during lactation

Lack of appropriate data precludes the assessment of formic acid for labelling for effects during lactation.

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A The committee

B Comments on the public draft

C Directive (93/21/EEGC) of the European Community

D Fertility and developmental toxicity studies

E Abbreviations

Annexes

Annex **A**

The committee

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- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, Den Haag

The first draft of the present document was prepared by APM Wolterbeek 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 President 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 establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **B**

Comments on the public draft

A draft of the present report was released in 2005. The following persons and organisations have commented on the draft document:

- RD Zumwalde,
  National Institute of Occupational Safety and Health (NIOSH), USA
- E González-Fernández
  Ministerio de Trabajo y Asuntos Sociales, Spain.

Annex **C**

Directive (93/21/EEC) of the European Community

4.2.3 Substances toxic to reproduction

4.2.3.1 For the purposes of classification and labelling and having regard to the present state of knowledge, such substances are divided into 3 categories:

Category 1:

Substances known to impair fertility in humans

There is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility.

Substances known to cause developmental toxicity in humans

There is sufficient evidence to establish a causal relationship between human exposure to the substance and subsequent developmental toxic effects in the progeny.

Category 2:

Substances which should be regarded as if they impair fertility in humans:

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in impaired fertility on the basis of:

- Clear evidence in animal studies of impaired fertility in the absence of toxic effects, or, evidence of impaired fertility occurring at around the same dose levels as other toxic effects but which is not a secondary non-specific consequence of the other toxic effects.
- Other relevant information.

Substances which should be regarded as if they cause developmental toxicity to humans:

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in developmental toxicity, generally on the basis of:

- Clear results in appropriate animal studies where effects have been observed in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects.
- Other relevant information.

Category 3:

Substances which cause concern for human fertility:

Generally on the basis of:

- Results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which is not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2.
- Other relevant information.

Substances which cause concern for humans owing to possible developmental toxic effects:

Generally on the basis of:

- Results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2.
- Other relevant information.

4.2.3.2 The following symbols and specific risk phrases apply:

Category 1:

For substances that impair fertility in humans:

T; R60: May impair fertility

For substances that cause developmental toxicity:

T; R61: May cause harm to the unborn child

Category 2:

For substances that should be regarded as if they impair fertility in humans:

T; R60: May impair fertility

For substances that should be regarded as if they cause developmental toxicity in humans:

T; R61: May cause harm to the unborn child.

Category 3:

For substances which cause concern for human fertility:

Xn; R62: Possible risk of impaired fertility

For substances which cause concern for humans owing to possible developmental toxic effects:

Xn; R63: Possible risk of harm to the unborn child.

4.2.3.3 Comments regarding the categorisation of substances toxic to reproduction

Reproductive toxicity includes impairment of male and female reproductive functions or capacity and the induction of non-inheritable harmful effects on the progeny. This may be classified under two main headings of 1) Effects on male or female fertility, 2) Developmental toxicity.

1 *Effects on male or female fertility*, includes adverse effects on libido, sexual behaviour, any aspect of spermatogenesis or oogenesis, or on hormonal activity or physiological response which would interfere with the capacity to fertilise, fertilisation itself or the development of the fertilised ovum up to and including implantation.

2 *Developmental toxicity*, is taken in its widest sense to include any effect interfering with normal development, both before and after birth. It includes effects induced or manifested prenatally as well as those manifested postnatally. This includes embrytoxic/fetotoxic effects such as reduced body weight, growth and developmental retardation, organ toxicity, death, abortion, structural defects (teratogenic effects), functional defects, peripostnatal defects, and impaired postnatal-mental or physical development up to and including normal pubertal development.

Classification of chemicals as toxic to reproduction is intended to be used for chemicals which have an intrinsic or specific property to produce such toxic effects. Chemicals should not be classified as toxic to reproduction where such effects are solely produced as a non-specific secondary consequence of other toxic effects. Chemicals of most concern are those which are toxic to reproduction at exposure levels which do not produce other signs of toxicity.

The placing of a compound in Category 1 for effects on Fertility and/or Developmental Toxicity is done on the basis of epidemiological data. Placing into Categories 2 or 3 is done primarily on the basis of animal data. Data from *in vitro* studies, or studies on avian eggs, are regarded as 'supportive evidence' and would only exceptionally lead to classification in the absence of *in vivo* data.

In common with most other types of toxic effect, substances demonstrating reproductive toxicity will be expected to have a threshold below which adverse effects would not be demonstrated. Even when clear effects have been demonstrated in animal studies the relevance for humans may be doubtful because of the doses administrated, for example, where effects have been demonstrated only at high doses, or where marked toxicokinetic differences exist, or the route of administration is inappropriate. For these or similar reasons it may be that classification in Category 3, or even no classification, will be warranted.

Annex V of the Directive specifies a limit test in the case of substances of low toxicity. If a dose level of at least 1000 mg/kg orally produces no evidence of effects toxic to reproduction, studies at other dose levels may not be considered necessary. If data are available from studies carried out with doses higher than the above limit dose, this data must be evaluated together with other relevant data. Under normal circumstances it is considered that effects seen only at doses in excess of the limit dose would not necessarily lead to classification as Toxic to Reproduction.

Effects on fertility

For the classification of a substance into Category 2 for impaired fertility, there should normally be clear evidence in one animal species, with supporting evidence on mechanism of action or site of action, or chemical relationship to other known antifertility agents or other information from humans which would lead to the conclusion that effects would be likely to be seen in humans. Where there are studies in only one species without other relevant supporting evidence then classification in Category 3 may be appropriate.

Since impaired fertility may occur as a non-specific accompaniment to severe generalised toxicity or where there is severe inanition, classification into Category 2 should only be made where there is evidence that there is some degree of specificity of toxicity for the reproductive system. If it was demonstrated that impaired fertility in animal studies was due to failure to mate, then for classification into Category 2, it would normally be necessary to have evidence on the mechanism of action in order to interpret whether any adverse effect such as alteration in pattern of hormonal release would be likely to occur in humans.

Developmental toxicity

For classification into Category 2 there should be clear evidence of adverse effects in well conducted studies in one or more species. Since adverse effects in pregnancy or postnatally may result as a secondary consequence of maternal toxicity, reduced food or water intake, maternal stress, lack of maternal care, specific dietary deficiencies, poor animal husbandry, intercurrent infections, and so on, it is important that the effects observed should occur in well conducted studies and at dose levels which are not associated with marked maternal toxicity. The route of exposue is also important. In particular, the injection of irritant material intraperitoneally may result in local damage to the uterus and its contents, and the results of such studies must be interpreted with caution and on their own would not normally lead to classification.

Classification into Category 3 is based on similar criteria as for Category 2 but may be used where the experimental design has deficiencies which make the conclusions less convincing, or where the

possibility that the effects may have been due to non-specific influences such as generalised toxicity cannot be excluded.

In general, classification in category 3 or no category would be assigned on an ad hoc basis where the only effects recorded are small changes in the incidences of spontaneous defects, small changes in the proportions of common variants such as are observed in skeletal examinations, or small differences in postnatal developmental assessments.

Effects during Lactation

Substances which are classified as toxic to reproduction and which also cause concern due to their effects on lactation should in addition be labelled with R64 (see criteria in section 3.2.8).

For the purpose of classification, toxic effects on offspring resulting *only* from exposure via the breast milk, or toxic effects resulting from *direct* exposure of children will not be regarded as 'Toxic to Reproduction', unless such effects result in impaired development of the offspring.

Substances which are not classified as toxic to reproduction but which cause concern due to toxicity when transferred to the baby during the period of lactation should be labelled with R64 (see criteria in section 3.2.8). This R-phrase may also be appropriate for substances which affect the quantity or quality of the milk.

R64 would normally be assigned on the basis of:

c toxicokinetic studies that would indicate the likelihood that the substance would be present in potentially toxic levels in breast milk, and/or

d on the basis of results of one or two generation studies in animals which in- dicate the presence of adverse effects on the offspring due to transfer in the milk, and/or

e on the basis of evidence in humans indicating a risk to babies during the lactational period. Substances which are known to accumulate in the body and which subsequently may be released into milk during lactation may be labelled with R33 and R64.

Annex **D**

Fertility and developmental toxicity studies

Table 1 Fertility toxicity studies in animals with formic acid or formate salts.

Authors	Species	Experimental period/design	Dose and route	General toxicity	Effects on reproductive organs/ effects on reproduction	Remarks
Thompson (1992)	F344/N rats (n=5/sex/group) B6C3F1 mice (n=5/sex/group)	Treatment 6 h/d, 5 d/w for 2 weeks. At sacrifice, among other organs, the right testis was weighed.	0, 31, 62.5, 125, 250 and 500 ppm (0, 58.3, 117.5, 235, 470 and 940 mg/m^3) *formic acid* by inhalation	Deaths occurred in 500 ppm (rats and all mice) and 250 ppm group (mice). Final body weights decreased in 250 and 500 ppm groups (rats and mice)	No effect on testicular weight.	NTP study.
Thompson (1992)	F344/N rats (n=10/sex/group) B6C3F1 mice (n=10/sex/group)	Treatment 6 h/d, 5 d/w for 13 weeks. At sacrifice, among other organs, the right testis was weighed. Sperm and oestrus cyclicity was analysed in 0, 8, 32 and 128 ppm groups.	0, 8, 16, 32, 64 and 128 ppm (0, 15, 30.1, 120.3 and 240.6 mg/m^3) *formic acid* by inhalation.	Deaths occurred in 128 ppm group (mice). In rats body weight was slightly increased in 8, 16, 32 and 64 ppm groups. In mice body weight gan was slightly decreased in 64 and 128 ppm groups.	No effect on testicular weight, sperm parameters and oestrus cyclicity.	NTP study.

Malorny (1969)	Wistar rats (n=8 in control group, sex not specified and n=8 males and 24 females in treatment group)	0.2%: Treatment throughout 5 generations over a 3-year period. 0.4%: Up to moment of publication treatment throughout 2 generations over a 2-year period.	0.2% *calcium formate* in drinking water (150-200 mg/kg bw/d) 0.4% *calcium formate* in drinking water (300-400 mg/kg bw/d)	No effects on body weight (gain) and macroscopic and histopathology of lung, spleen, stomach, liver, kidneys and other not specified organs.	No effects on reproduction (as presented by the numbers of offspring).	Poorly reported studies.

Table 2 Developmental inhalation toxicity studies in animals with formate salts.

Authors	Species	Experimental period/design	Dose and route	General toxicity	Developmental toxicity	Remarks
Dorman (1995)	CD-1 mice (n=14/group)	Treatment: single dose on GD 8. At sacrifice on GD 10 or 18 foetuses were examined for neural tube defects.	0 and 750 mg/kg bw *sodium formate* by gavage	Not described	No effect of sodium formate on incidence of neural tube defects.	In the same study, methanol increased the incidence of neural tube defects.
Malorny (1969)	Wistar rats (n=8 in control group, sex not specified and n=8 males and 24 females in treatment group)	0.2%: Treatment throughout 5 generations over a 3-year period. 0.4%: Up to moment of publication treatment throughout 2 generations over a 2-year period.	0.2% *calcium formate* in drinking water (150-200 mg/kg bw/d) 0.4% *calcium formate* in drinking water (300-400 mg/kg bw/d)	No effects on body weight (gain) and macroscopic and histopathology of lung, spleen, stomach, liver, kidneys and other not specified organs.	No effects on development (as presented by weight and length of the foetuses).	Poorly reported studies.
Malorny (1969)	Chicken eggs (n=1051 in control group, not specified in treatment groups)	Treatment: single dose 48-96 h after the start of brooding	0, 5, 10 and 20 mg *sodium formate* / egg was incubated into the air space of incubated eggs.	Not described.	No effect on mortality, weight of the embryos and the incidence and type of malformations.	Poorly reported study.

Annex **E**

Abbreviations

Abbreviations used:

bw	body weight
d	day
GD	gestation day
h	hours
n	number
OECD	Organisation for Economic Cooperation and Development
ppm	part per million