Epichlorohydrin (1-chloro-2,3-epoxypropane)

Health based calculated occupational cancer risk values

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp	: Aanbieding advies
Uw kenmerk	: DGV/BMO-U-932542
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Bij brief van 3 december 1993, nr DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

Per 1 januari 1994 heeft mijn voorganger daartoe een commissie ingesteld die de werkzaamheden voortzet van de Werkgroep van Deskundigen (WGD). De WGD was een door genoemde minister ingestelde adviescommissie.

Hierbij bied ik u - gehoord de Beraadsgroep Gezondheid en Omgeving - een publicatie van de commissie aan over epichloorhydrine (1-chloor-2,3-epoxypropaan). Deze publicatie heb ik heden ter kennisname aan de Minister van Volksgezondheid Welzijn en Sport en aan de Minister van Volkshuisvesting Ruimtelijke Ordening en Milieubeheer gestuurd.

w.g.
prof. dr JJ Sixma

Epichlorohydrin (1-chloro-2,3-epoxypropane)

Health based calculated occupational cancer risk values

Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands

to

the Minister and State Secretary of Social Affairs and Employment

No. 2000/10OSH, The Hague, 6 September 2000

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Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid schat de Commissie WGD van de Gezondheidsraad het extra kankerrisico bij beroepsmatige blootstelling aan stoffen die door de Europese Unie of door de Commissie WGD als genotoxisch kankerverwekkend zijn aangemerkt. In dit rapport maakt zij zo'n schatting voor epichloorhydrine. Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (Dec95).

Naar schatting van de commissie is de extra kans op kanker voor epichloorhydrine:

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0.19 mg/m^3
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 19 mg/m^3

Executive summary

On request of the Minister of Social Affairs and Employment the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, estimates the additional lifetime cancer risk associated with occupational exposure to substances that have been classified by the European Union or the DECOS as genotoxic carcinogen. In this report the committee presents such estimates for epichlorohydrin. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (Dec95).

The committee estimated that the additional lifetime cancer risk for epichlorohydrin amounts to:

- 4×10^{-5} for 40 years of occupational exposure to 0.19 mg/m^3
- 4×10^{-3} for 40 years of occupational exposure to 19 mg/m^3

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, on request of the Minister of Social Affairs and Employment (annex A). This evaluation should lead to a health-based recommended exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if the toxic action cannot be evaluated using a threshold model, as is the case for substances with genotoxic carcinogenic properties.

In this case an exposure-response relationship is recommended for use in regulatory standard setting, ie. the calculation of so-called health-based calculated occupational cancer risk values (HBC-OCRVs). The committee calculates HBC-OCRVs for compounds which are classified as genotoxic carcinogens by the European Union or by the present committee.

For the establishment of the HBC-OCRV's the committee generally uses a linear extrapolation method, as described in the committee's report 'Calculating cancer risk due to occupational exposure to genotoxic carcinogens' (1995/06WGD). The linear model to calculate occupational cancer risk is used as a default method, unless scientific data would indicate that using this model is not appropriate.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister of Social Affairs and Employment on the feasibility of using the

HBC-OCRVs as regulatory occupational exposure limits. In the final step of the procedure the Minister sets the official occupational exposure limits.

1.2 Committee and procedure

The present document contains the derivation of HBC-OCRVs for epichlorohydrin by the committee. The members of the committee are listed in Annex B. The first draft of this report was prepared by MI Willems, from the TNO Nutrition and Food Research Institute in Zeist, by contract with the Ministry of Social Affairs and Employment.

In 1998, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in annex C. The committee has taken these comments into account in deciding on the final version of the report.

Chapter 2

Epichlorohydrin (1-chloro-2,3-epoxypropane)

2.1 Introduction

The carcinogenicity of epichlorohydrin has been evaluated by VROM (Bes84), IARC (IARC76; IARC87) and the ACGIH (ACG91). These organisations have concluded that there is sufficient evidence for carcinogenicity to animals, but inadequate evidence for carcinogenicity to humans. Previously, the Dutch Expert Committee on Occupational Standards has concluded that epichlorohydrin is a genotoxic carcinogen (WGD86).

The present evaluation of the carcinogenicity was based on a review by IARC (IARC76, IARC87). In addition, literature was retrieved from online databases Medline, Toxline and Cancerlit covering the period 1975 to 1996*.

2.2 Carcinogenicity studies and selection of study suitable for risk estimation in the occupational situation

The available epidemiological data do not allow quantitative risk assessment for epichlorohydrin.

Table 1 (Annex D) summarizes the main carcinogenicity studies with experimental animals with test conditions and results. Epichlorohydrin has been tested in rats by oral administration (via gavage or drinking water), inducing papillomas and carcinomas of the

* After completion of the report, IARC concluded in 1999 that epichlorohydrin is a IARC group 2A compound (IARC99).

forestomach and by inhalation, inducing papillomas and squamous cell carcinomas of the nasal cavity. Epichlorohydrin gave negative results after continuous skin painting, but was weakly active as an initiator on mouse skin using phorbolmyristate as promotor (Duu74, Bes84). Subcutaneous injection of epichlorohydrin in mice resulted in sarcomas on the injection site. Epichlorohydrin was negative in the mouse-lung tumour bioassay upon intraperitoneal injection (Duu74, Bes84). Rat inhalation experiments published by Laskin *et al*. (Las80) are used to calculate the potential risk of cancer at the workplace. Laskin *et al* (Las80) exposed male rats either to (I) atmospheres containing 0 and 100* ppm in air for a period of 30 days or to (II) atmospheres containing 0, 10 and 30 ppm for lifetime. The short-term 30 day-exposure regimen with 100 ppm epichlorohydrin produced malignant squamous cell carcinomas of the nasal cavity in 15 of 140 rats and respiratory tract papillomas in 3 rats. Among 100 rats, lifetime exposure to 30 ppm yielded 1 malignant squamous carcinoma of the nasal cavity plus 1 nasal papilloma. No nasal or respiratory tract tumours were produced by lifetime exposure of 100 rats to 10 ppm or in 100 air-treated and 50 untreated controls.

2.3 Carcinogenic activity in experimental animals, lifetime low-dose exposure

To calculate the carcinogenic activity expressed as the incidence per mg epichlorohydrin/m^3, the number of animals bearing tumours of interest i.e. squamous cell carcinomas in the nasal cavity, and nasal and bronchial papilloma in the 30 ppm group in the study of Laskin *et al*. was used as starting point (Las80). The committee is of the opinion that the available data do not indicate that the use of the linear model is not appropriate.

The committee is aware of the fact that after lifetime exposure to 30 ppm, only 2 out of 100 animals developed a treatment-related tumour, ie one squamus cell carcinoma and one pappiloma. However, these results were confirmed in another study of Laskin *et al* in which after exposure to 100 ppm epichlorohydrin for only 30 days, squamous cell carcinomas in the nasal cavity were found in 15/140 animals, nasal papilloma in 2/140 animals and bronchial papilloma in 1/140 animals. Because of the short exposure period (30 day), the committee did not found this latter study useful for the linear extrapolation to lifetime risk.

The incidence of tumour bearing animals per mg/m^3 (lifespan conditions assuming a linear dose-response relationship), $I_{concentration}$, is calculated as follows:

* 1 ppm = 3.78 mg/m^3

$$I_{concentration}{}^{*} = \frac{I_e - I_c}{C \times (X_{po}/L) \times (X_{pe}/L) \times \text{exposure hours per day}/24 \times \text{exposure days per week}/7} =$$

$$= \frac{\frac{2}{100} - \frac{0}{100}}{115 \times (\frac{952}{1000}) \times (\frac{952}{1000}) \times \frac{6}{24} \times \frac{5}{7}} = 1.1 \times 10^{-3} \ [mg/m^3]^{-1}$$

2.4 Health risk to humans

To estimate the additional lifetime risk of cancer in humans under lifespan conditions on the basis of results in animal experiments, it is assumed that no difference exists between experimental animals and man with respect to toxicokinetics, mechanism of tumour induction, target, susceptibility etc, unless specific information is available which justifies a different approach. Furthermore, it is assumed that the average man lives 75 years, weights 70 kg and is exposed 24 hours per day 7 days/week, 52 weeks per year for lifetime.

2.5 Calculation of the HBC-OCRV

To estimate the additional lifetime risk of cancer in humans under workplace exposure conditions, it is assumed that the average man lives 75 years, is exposed 8 hours per day, five days a week, 48 weeks a year, for 40 years, and inhales 10 m^3 per 8 hour-working day. Using as starting point the estimated incidence of 1.1 x 10^{-3} per mg/m^3, the additional lifetime cancer risk per mg/m^3 under occupational exposure conditions, HBC-OCRV, amounts to:

$$\text{HBC-OCRV} = 1.1x10^{-3} \ x\frac{40y}{75y}x\frac{48w}{52w}x\frac{5d}{7d}x\frac{10m^3}{18m^3} = 2.1x10^{-4}[mg/m^3]^{-1}$$

Based on the HBC-OCRV of 2.1 x 10^{-4} per mg/m^3 the reference additional lifetime cancer risk amounts to:

- 4 x 10^{-5} for 40 years of exposure to 0.19 mg/m^3
- 4 x 10^{-3} for 40 years of exposure to 19 mg/m^3

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* I =the carcinogenic activity attributable to the exposure to the substance per unit daily dose under lifespan conditions assuming a linear dose response relationship
Ie and Ic = incidence of tumour bearing animals or tumours in exposed and control amnimals, respectively,
Xpo = exposure period, Xpe = experimental period
and L = standard lifespan for the animals in question (L rat is assumed to be 1000 days)

2.6 Existing occupational exposure limits

Table 2 summarizes the occupational exposure limits established by the regulatory authorities of Germany, Sweden and United Kingdom and by USA-ACGIH. No occupational exposure limit has been established in The Netherlands and Germany.

The lowest occupational exposure limit settled by these countries amounts to 1.9 mg/m^3. In the United Kingdom, it was concluded that considering the carcinogenicity data, a threshold could not be identified and that consequently a maximum exposure limit (MEL)* (1.9 mg/m^3) was appropriate. This concentration is about a factor 10 lower than the concentration leading to an additional cancer risk of 4 x 10^{-3} (i.e., 19 mg/m^3) and about a factor 10 higher than the concentration leading to an additional cancer risk of 4 x 10^{-5} (i.e., 0.19 mg/m^3).

Table 2 Occupational exposure limits for epichlorohydrin.

country	level		time relation	annotations	ref.
	ppm	mg/m^3			
The Netherlands[a]	-	-	-	-	ISZW95
Germany[b]	(3)	(12)	-	skin	DFG96
UK[c]	0.5 1.5	2 6	8-h TWA, MEL STEL	new (this indicates a new addition to the list)	HSE95
Sweden[d]	0.5	1.9	8-h TWA	skin, sensitizing	NBO93
USA-ACGIH[e]	0.5	1.9	8-h TWA	skin	ACG99

[a] the substance is classified as a carcinogen

[b] The DFG classifies epichlorohydrin as a category A2 carcinogen; DFG category A carcinogens are not assigned a health-based occupational exposure limit, but a so called TRK-value (TRK = Technische Richtkonzentrationen), a concentration feasible with currently available technical means. TRK-values are given in brackets.

[c] In the UK, epichlorohydrin has been included in the list of substances defined as carcinogens for the purpose of the COSHH regulations 1994. Epichlorohydrin has been assigned the risk phrase “R45” (may cause cancer).

[d] The substance is classified as carcinogenic.

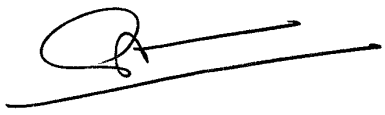
[e] Limits intended to be changed to 0.5 ppm (1.9 mg/m^3). Classified as A3 carcinogen; animal car-

* In setting a Maximum Exposure Limit (MEL), not only the protection of the health of the employee is considered, also socio-economic factors are taken into account. A cost benefit assessment is prepared to assist the considerations of these. In practice, MELs have been most often allocated to carcinogens, respiratory sensitizers and to other substances for which no threshold level of exposure for the effects can be identified and for which there is no doubt about the seriousness of the hazard(s) posed by the substance.

For the committee,
The Hague, 6 September 2000

dr ASAM van der Burght,
scientific secretary

Prof. dr GJ Mulder,
chairman



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ACG91 American Conference of Governmental Industrial Hygienists (ACGIH). Epichlorohydrin. In: Documentation of the Treshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati OH, USA: ACGIH, 1991: 550-5.

ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). 1999 TLVs(R) and BEIs(R). Guide to occupational exposure limits. Cincinnati OH, USA; ACGIH, 1996: 21, 39.

Bes84 Besemer AC, Eggels PG, van Esch GJ, *et al*. Criteriadocument over epichloorhydrine. The Hague, The Netherlands: Distributiecentrum Overheidspublikaties (DOP), 1984; Publikatiereeks Lucht 31.

DEC95 Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards (DECOS). Calculating cancer risk. The Hague: Health Council of the Netherlands, 1995 publication no 1995/06WGD.

DFG96 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 1996. Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte. Weinheim, FRG: VCH Verlagsgesellschaft mbH, 1996: 35, 107, 126 (Mitteilung 32).

Duu74 Duuren BL van, Goldschmidt BM, Katz C, *et al*. Carcinogenic activity of alkylating agents. J Natl Cancer Inst 1974; 53: 695-700.

HSE95 Health and Safety Executive (HSE). Occupational exposure limits 1995. Sudbury (Suffolk), UK: HSE Books, 1995: 15, 27, 49 (Guidance note 40/95).

IARC76 International Agency for Research on Cancer (IARC). Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anesthetics Lyon, France: IARC, 1976: 131-7.IARC monographs on the evaluation of carcinogenic risks of chemicals to man, Vol 11.

IARC87 International Agency for Research on Cancer. Overall evaluations of carcinogenicity: an updating of IARC monographs Lyon, France: IARC, 1987: 202-3 IARC monographs on the evaluation of carcinogenic risks to humans, Volumes 1 to 42; Suppl 7.

IARC99 International Agency for Research on Cancer (IARC). Re-evalualtion of some organic chemicals, hydrazine and hydrogen peroxide (part two). Lyon, France: IARC, 1999: 337-344. In: IARC monographs on the evaluation of carcinogenic risk of chemicals to man, Vol 71.

ISZW95 Inspectiedienst van het Ministerie van Sociale Zaken en Werkgelegenheid (I-SZW). De Nationale MAC-lijst 1995. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1995: 25, 63, 65 (pub no P145).

Las80 Laskin S, Sellakumar AR, Kuschner M, *et al*. Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J Natl Cancer Inst 1980; 65: 751-7.

NBO93 National Board of Occupational Safety and Health (NBOSH). Occupational exposure limits. Solna, Sweden: NBOSH, 1993: 32, 76, 77 (Ordinance AFS 1993/9).

Wes85 Wester PW, van der Heijden CA, Bisschop A , *et al*. Carcinogenicity study with epichlorohydrin (CEP) by gavage in rats. Toxicology 1985; 36: 325-39.

WGD86 Werkgroep van Deskundigen (WGD). Rapport inzake grenswaarde epichloorhydrine. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1986; rep no RA 1/86.

A	Request for advice
B	The committee
C	Comments on the public draft
D	Animal studies

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in

the case of genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The Committee

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- VJ Feron,
  professor of toxicology; TNO Nutrition and Food Research Institute, Zeist
- DJJ Heederik
  epidemiologist; Wageningen University, Wageningen
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- G de Jong
  occupational physician; Shell International Petroleum Maatschappij, The Hague
- J Molier-Bloot
  occupational physician; BMD Akers bv, Amsterdam
- IM Rietjens
  professor in Biochemical toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, Den Haag
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- HG Verschuuren
  toxicologist; DOW Europe, Horgen (Switzerland)
- F de Wit
  occupational physician; Labour Inspectorate, Arnhem
- CA Bouwman, *scientific secretary*
  Health Council of the Netherlands, Den Haag
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, Den Haag

The first draft of the present advisory report was prepared by M Willems, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research Institute, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: J Toet.
Lay-out: J van Kan.

Annex **C**

Comments on the public draft

A draft of the present report was relased in 1998 for public review. The following organisations and persons have commented on the draft document:

- WF ten Berge, DSM, Heerlen

Annex **D**

Animal studies

See table on the next page.

Table 1 Carcinogenicity studies with epichlorohydrin.

authors	species	exposure characteristics, dose, experimental period	findings	remark
Konishi[a] (1980, in Bes84)	rat[b], males, N=16	drinking water at doses of 0, 375, 750 and 1500 mg/L. Average total intakes were 0, 8.8, 15.7, and 26.6 mg/rat/day. Exposure-/experimental period 81 weeks	*forestomach* hyperplasia : 0%, 78%, 90%, 100% papillomas : 0%, 0%, 10%, 58% carcinomas: 0%, 0%, 10%, 17%	the absolute numbers of the "tumours" are not given. Publication not available
van Esch and Wester[c] (1982 in Bes84) Wes85	rat[b], 50/sex/ group	gavage, 5 times/week, 104 weeks, 0, 2 and 10 mg/kg bw/day	*forestomach lesions at 0, 2, 10 mg/*kg hyperplasia: male, 5/50, 24/40, 6/49 female, 3/47, 12/44, 7/39 papilloma: male, 1/50, 6/49, 4/49 female, 2/47, 3/44, 0/39 squamous cell carcinoma: male, 0/50, 6/49, 35/49 female, 0/47, 2/44, 24/39	the actual numbers of tumour bearing animals are given in Wester *et al*. 1985
Las80 exp. 1	rat[d], males (N=140)	inhalation, 6 hrs/day, 5 days/ week, exposure period 30 days, 0, 100 ppm (385 mg/m^3) Xpe = lifetime	nasal cavity 0, 100 ppm squamous cell carcinoma: 0/100 (150?), and 15/140 papillomas: 0/100 (150?), 3/140	duration of exposure was less than one-fourth the standard lifespan
exp. 2	rat[d] males (N=100)	inhalation, 6 hrs/day, 5 days/week, lifetime exposure (136 weeks), 0, 10, 30 ppm (0, 38.5, 115.5 mg/m^3)	nasal cavity 0, 10, 30 ppm squamous cell carcinomas: 0/100 (150?), 0/100, 1/100 papilloma: 0/100 (150?), 0/100, 1/100	
Duu74	mouse[e], females, (N=50)	skin application, 2 mg 3 times/week, Xpo = Xpe = 580 days	no tumours were found	
	mouse, females, (N=50)	s.c. injections dose: 1 mg, once a week Xpo = Xpe = 580 days	malignant tumours, local sarcomas: 1/50, 6/50 adenocarcinomas: 0/50, 1/50	epichlorohydrin induced sarcomas, but the P value was borderline (0.05)
	mouse, females, (N=30)	ip injections dose: 1 mg, once a week Xpo = Xpe = 580 days	lung papillomas 10/50, 11/30 local sarcomas 1/50, 0/30	

[a] Konishi Y, Kawabata A, Denda A, Ikedam T, Katada H, Maruyama H. Gann 1980; 71: 922-923

[b] strain not give

[c] Esch GJ van, and Wester PW. Unpublished report. National Institute of Public Health and the Environment, Bilthoven, the Netherlands 1982

[d] Sprague-Dawley rat

[e] ICR/HA Swiss mice