SCOEL/REC/164
Hydrazine

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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EUROPEAN COMMISSION

Directorate-General for Employment, Social Affairs and Inclusion
Directorate B —Employment
Unit B.3 — Health and safety

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8-hour TWA:	not assigned (see executive summary)
STEL:	not assigned
BLV:	not assigned
Additional categorisation:	SCOEL carcinogen group B (genotoxic carcinogen, for which a mode of action-based threshold is not sufficiently supported)
Notation:	skin

The present Recommendation was adopted by SCOEL on 12 September 2016.

RECOMMENDATION EXECUTIVE SUMMARY

Outcome Considerations

The relevant toxicological endpoint for hydrazine is carcinogenicity. In addition, it is a potent contact sensitizer; allergic contact eczema caused by hydrazine has been described in numerous publications from different branches of industry. Evidence on respiratory sensitization is lacking.

When tested by oral administration, it has produced mainly lung and liver tumours in rats, mice and hamsters. The most useful information comes from the long-term inhalation studies in rodents, and is related to the upper respiratory tract. In mice, exposed in a preliminary study for 6 months at 0.2, 1, or 5 ppm, there was an increased incidence of pulmonary tumours in all groups (Haun & Kinkead, 1972; MacEwen, 1974). A subsequent inhalation study in rats, mice, dogs and hamsters (6h/d; 5d/wk at 0.05 ppm [rats, mice], 0.25, 1.0 ppm and 5 ppm [rats, mice, hamsters, dogs] for 1 year with a follow-up for life span or 38 months revealed an increased incidence of benign and malignant nasal tumours at 1 and 5 ppm in rats. At 0.05 ppm, the incidence of nasal tumours in rats was slightly, but not significantly, higher than in the controls. An increased incidence of benign nasal polyps was observed in hamsters at 5 ppm. In addition, hamsters exposed at 0.25 ppm showed pathological degenerative changes, including amyloidosis. An increased incidence of pulmonary adenomas was observed at 1 ppm in mice (MacEwen et al., 1979; Vernot et al., 1985).

While there is sufficient evidence of carcinogenicity in animals, the evidence of hydrazine carcinogenicity in humans has been recently evaluated by IARC (Grosse et al., 2016) as being limited. There are some data available on the carcinogenic effect in exposed aerospace workers, in particular to an increased risk of lung cancer (see 2.8.1). This would be compatible with the aforementioned experimental data from experimental animals.

Hydrazine has been characterised as genotoxic (2.6.1). Studies into the mode of action have revealed an indirect mechanism of genotoxicity, involving reaction with endogenous formaldehyde and ultimate formation of a DNA-methylating agent (for details, see 2.6.4).

In principle, the systemic genotoxicity of hydrazine, based on such an indirect mechanism, may be characterised by a threshold at low exposure levels (when hydrazine-induced DNA methylation becomes insignificant vs. the normal methylation background). However, the critical target upon occupational inhalation exposure is the respiratory tract, and specific studies into the local mode of carcinogenic action, as well as appropriate toxicokinetic modellings, are lacking. Hydrazine is categorised into the SCOEL carcinogen group B, as a genotoxic carcinogen, for which the existence of a threshold cannot be sufficiently supported at present (Bolt & Huici-Montagud, 2007). In this situation, the derivation of a health-based OEL is not possible at the present time. Therefore, SCOEL has decided to perform a dose-response analysis of the data on upper respiratory tract tumours from a long-term inhalation study of hydrazine in rats, mice, hamsters and dogs (Vernot et al., 1985) and derive risk numbers.

Derived Limit Values/dose-response analysis

The long term inhalation study of hydrazine in rats, mice, hamsters and dogs (Vernot et al., 1985) demonstrated that the nasal epithelium of rats and hamsters was most sensitive to the tumorigenic activity of hydrazine following inhalation exposure. Especially the data on neoplastic lesions in male and female rats were suitable for dose-response modelling. BMD modeling of the neoplastic lesions observed in male and female rats revealed BMD10 values that are summarised in Table 7. BMD10 values for malignant neoplasms varied between 5.67 and 22.33 ppm. Based on these data it was concluded that a BMD10 of 5.67 ppm (corresponding to 7.6 mg/m^3), based on malignant thyroid tumours, would provide an adequate point of departure for definition of risk numbers.

Using this value the following risk numbers were derived:

A tumor risk of 1 : 10 at 7.6 mg/m^3 (equal to 5.67 ppm)

A tumor risk of 1 : 1000 at 76 µg/m^3 (equal to 0.057 ppm)

A tumor risk of 1 : 10 000 at 7.6 µg/m^3 (equal to 0.0057 ppm)

A tumor risk of 1 : 10^6 at 0.08 µg/m^3 (equal to 0.000057 ppm)

Skin notation

The available data on skin absorption and systemic effects seen in animals following dermal contact warrant a "skin notation".

Biological Monitoring

As there are no adequate data, a recommendation for biological monitoring cannot be given.

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HYDRAZINE

RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Name:	Hydrazine
Synonyms:	Diamide
Molecular formula:	N_2H_4
Structural formula:	$H_2N\text{-}NH_2$
EC No.:	
CAS No.:	302-01-2
Molecular weight:	32.05
Boiling point:	113.5 °C
Melting point:	1.5-2 °C
Vapour pressure (20 °C):	21 hPa
Conversion factors: (20 °C, 101.3kPa)	1 ppm = 1.332 mg/m^3; 1 mg/m^3 = 0.751 ppm

Hydrazine is at room temperature a colourless liquid with a sharp ammoniacal odour. The odour threshold of hydrazine is about 3-4 ppm (DFG, 1991). Hydrazine is miscible with water and alcohols. It is highly flammable.

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonised classification and labelling for hydrazine is provided by ECHA (2016a) as summarized in Table 1.

Table 1: Classification according to Regulation (EC) No 1272/2008, Annex VI, Table 3.1 "List of harmonised classification and labelling of hazardous substances"

Index no.	CAS no.	EC / List no.	EC / List name	IUPAC Name
007-008-00-3	302-01-2	206-114-9	Hydrazine	Hydrazine

Classification		Labelling		Specific Concentration Limits, M-factors	Notes
Hazard Class & Category Codes	Hazard Statement Codes	Hazard Statement Codes	Pictograms, Signal Word Codes		
Flam. Liq. 3	H226	H226	GHS09 GHS06 GHS02 GHS08 GHS05 Dgr**	Skin Corr. 1B; H314: C ≥ 10% Eye Irrit. 2; H319: 3% ≤ C < 10% Skin Irrit. 2; H315: 3% ≤ C < 10%	
Acute Tox. 3	H301	H301			
Acute Tox. 3	H311	H311			
Skin Corr. 1B	H314	H314			
Skin Sens. 1	H317	H317			
Acute Tox. 3	H331	H331			
Carc. 1B	H350	H350			

*	*Flam. Liq. 3*	*H226*	*Flammable liquid and vapour*
	Acute Tox. 3	*H301*	*Toxic if swallowed*
	Skin Irrit. 2	*H311*	*Toxic in contact with skin*
	Skin Corr. 1B	*H314*	*Causes severe skin burns and eye damage*
	Skin Sens. 1	*H317*	*May cause an allergic skin reaction*
	Eye Irrit. 2	*H319*	*Causes serious eye irritation*
	Acute Tox. 3	*H331*	*Toxic if inhaled*
	STOT SE 3	*H335*	*May cause respiratory irritation*
	Carc. 1B	*H350*	*May cause cancer*
	Aquatic Acute 1	*H400*	*Very toxic to aquatic life*
	Aquatic Chronic 1	*H410*	*Very toxic to aquatic life with long lasting effects*
**	*Signal word code*	*'Dgr'*	*Danger*

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

Hydrazine is a hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

Hydrazine is also a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and falls within the scope of this Directive.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

At EU level, no OEL has been adopted yet for hydrazine. However, OEL's do exist in various EU Member States as well as outside the EU. These OEL's are presented in Table 2 as examples and the list should not be considered as exhaustive.

Table 2: Overview of existing OELs for hydrazine

EU	**TWA (8 hrs)**		**STEL (15 min)**		**Remarks**	**References**
	ppm	mg/m³	ppm	mg/m³		
Austria	0.1	0.13	0.4	0.52	TRK, i.e. TMW and KZW, skin not.	AU GKV (2011)
Belgium	0.01	0.013			8 hrs TGG (TWA), skin not.	BE KB (2014)
Denmark	0.01	0.013	0.02	0.026		DK DWEA (2011)
Germany (AGS)	0.017$	0.022$			4:1000 risk number (draft)	DE BAUA (2016a)
	0.0017 &	0.0022 &			4:10 000 risk number (draft)	
Finland	0.1	0.13	0.3	0.4	STEL = 15 min. average	FI MSAH 2012
France	0.1	0.1			VME = TWA 8 hrs	FR INRF (2012)
Hungary				0.13		HU MHSFA (2000)
Ireland	0.01	0.01				IE HSA (2016)
Latvia		0.1				DE IFA (2015)
Norway	0.01	0.01				NO NLIA (2011)
Spain	0.01	0.013			inhalable aerosol	ES INSHT (2011)
UK	0.02	0.03	0.1	0.13	TWA	UK HSE (2011)
Non-EU						
Australia	0.01	0.013			TWAEV	AU SWA (2011)
CA (Ontario)	0.01				TWA	CA OML (2013)
CA (Québec)	0.1	0.13				CA IRSST (2010)
China		0.06		0.13 (1)	STEL=15 min average	CH SUVA (2016)
New Zealand	0.01	0.013				NZ HS (2013)
Singapore	0.1	0.13				DE IFA (2015)
South Korea	0.05	0.06				DE IFA (2015)
Switzerland	0.1	0.13				CH SUVA (2015)
USA (OSHA)	1	1.3			PEL	US OSHA (2016)
USA (NIOSH)			0.03	0.04	REL (2 hrs); ceiling value	US NIOSH (2016)
USA (ACGIH)	0.01				TLV-TWA	US ACGIH 2015

- BAR [Biologische Arbeitsstoff Referenzwerte] = biological reference value.
- PEL = Permissible Exposure Level (OSHA).
- REL = Recommended Exposure Limit (NIOSH).
- STEL = Short Term Exposure Limit (usually 15 minutes average).
- TGG [TijdGewogen Gemiddelde] = TWA.
- TMW [Tagesmittelwer] = TWA; KZW [Kurzzeitwert] = STEL.
- TRK [Technische RichtKonzentration] = indicative concentration. Used when no 'safe' exposure level can be derived. Value based on technical feasibility.
- TWA = Time-Weighted Average (usually 8 hours average).
- TWAEV = Time-Weighted Average Exposure Value = TWA.
- VME [Valeur Moyenne d'Exposition] = TWA.
- $ Workplace exposure concentration corresponding to the proposed tolerable cancer risk.
- & Workplace exposure concentration corresponding to the proposed preliminary acceptable cancer risk.

No indications were found for any concrete Biological Limit Value (checked USA, EU SCOEL and Germany) or for any reference value in the general population (such as BAR - Biologischer Arbeitsstoff-Referenzwert). Yet, in Germany, exposure equivalents (as for carcinogenic substances) were established (EKA values = "Expositionsäquivalente für krebserzeugende Arbeitsstoffe"), see Chapter 6.2 (DE DFG 2015). In addition, also in Germany, provisionally, equivalent values in biological material are listed to an exposure that equals the (tolerated) risk number of 4:1000. For samples taken end of shift, the urine value is 62 µg/g creatinine and the value for blood plasma is 47 µg/L(DE BAUA 2016b).

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

5.1. Occurrence

Hydrazine is a highly volatile and explosive alkaline liquid. The agent occurs naturally as product of microbial nitrogen fixation and has been detected in cigarette smoke. Production of hydrazine, its use as a chemical intermediate, reducing agent, rocket fuel and boiler-water treatment agent and its waste disposal may result in its release to the environment through various waste streams. No data on environmental concentrations were found. In most environmental media, hydrazine is rapidly degraded by oxidation (IARC 1999, NTP 2014, HSDB 2016).

5.2. Production and use

Production

A century after its discovery, hydrazine is still difficult to synthesize, mainly for thermodynamic reasons. Most hydrazine is produced by oxidation of ammonia by hypochlorite or by the reaction of sodium hypochlorite, acetone, and a 20% aqueous solution of ammonia. However, the new plants built since 1980 are based on a process that uses hydrogen peroxide as oxidant (HSDB 2016).

In the EU the largest producers are Germany and France. Capacity estimates for hydrazine hydrate were 10,000 tpa in Germany and in France and 3,000 tpa in the UK (reference from 1989 in IOM, 2011). A more recent reference by UK HSE (1997) indicated that hydrazine is not manufactured in the UK (referenced in IOM, 2011) but only imported (1,000 tpa). The production capacity for hydrazine solutions in Europe in 1992 was 6,400 and 6,100 tpa in Germany and France, respectively (reference from 1995 in IOM, 2011).

According to REACH registration data, hydrazine is currently manufactured and/or imported in the European Economic Area in 1,000 – 10,000 tpa, the main producers being in Germany and France (ECHA 2016b).

Use

The principal applications of hydrazine solutions include chemical blowing agents (40%), pesticides (25%) and water treatment (20%). The remaining 15% is used in a variety of fields including pharmaceuticals, explosives, polymers and polymer additives, antioxidants, metal reductants, hydrogenation of organic groups, photography, xerography and dyes (reference from 1995 in IARC 1999). Hydrazine is used as an oxygen scavenger in boiler waters. Anhydrous hydrazine is used as a component of high-energy fuels and rocket propellants (reference from 1998 in IOM 2011).

5.3. Occupational exposure

Number of sites

According to an Eurostat overview of the 'manufacture of basic chemicals' sector, a sector having a high risk of exposure to hydrazine, this sector involves more than 30,000 enterprises in the EU (IOM 2011). This indicates the maximum number of sites linked to high risk of hydrazine exposure. In 2007 in USA, EPA's Toxics Release Inventory reported environmental releases of hydrazine from 23 facilities.

Number of workers exposed/levels of exposure

In general, there are limited data available on occupational exposure to hydrazine in Europe. A study by IOM (2011) classified industries by exposure level and the number of workers exposed to hydrazine in the EU. This estimate on hydrazine exposure is presented in Table 3.

Table 3: Classification of industries using and or producing hydrazine by exposure level and the number of workers exposed in the EU according to IOM (2011)

Industry	NACE (rev 1)	Historical Exposure Classification	Number of People Exposed 2006
Manufacture of Food Products and Beverages	15	L	56,613
Manufacture of pulp, paper and paper products	21	L	11,635
Manufacture of basic chemicals	24	**H**	833
Manufacture of rubber and plastic products	25	L	803,877
Manufacture of radio, television and communication equipment and apparatus	32	L	9,277
Electricity, gas, steam and hot water supply	40	L	977,427
Collection, purification and distribution of water	41	L	41,344
Research and development	73	L	68,513
Other business activities	74	L	164,374
Education	80	L	479
Agriculture, hunting and related service activities	1	M	14,674

L: low; M: medium; H: high

Overall, many of the current uses occur in closed systems with low potential for exposure, mainly e.g. in sampling activities. HSE (2006) published data from the National Exposure Data Base (NEDB) on workers' exposure to hydrazine during supply and distribution of hydrazine hydrate (the form in which it is produced and transported). The five (task-based) measurements lasting less than an hour) yielded exposure concentrations between 0.005 and 0.013 mg/m3. Older studies are predominantly from the USA and Japan and entail exposure during production and use of hydrazine as a rocket propellant and as fuel in fighter jets. The data that are available on relatively recent occupational exposures are listed in the Table 4.

Table 4: Overview of published occupational exposure data related to hydrazine

Industry	Exposure range individual measurements, nr. samples	AM, GM, GSD	Country Time period	References
Tire manufacturing, vulcanization unit	*In mg/m³:* Milling machine: 4.26 Vulcanization process: 8.00 Entrance: <0.01 Exit: <0.01	Single samples	Turkey, one site	Durmusoglu 2007
Distribution and use of hydrazine hydrate in chemical synthesis and/or power stations.	Open system: 0.0034 ppm Open system: 0.0073 ppm Open system: 0.01 ppm Closed system: 0.0015 ppm Closed system: 0.0023 ppm Time periods 15 – 60 min		Site 1 – visit 1 Site 1 – visit 2 Site 1 – visit 3 Site 1 – task 1 Site 2 – task 2 UK	HSE 2006
Paper industry	0.01 – 0.02 ppm 6 samples	*In ppm:* AM 0.02 GM 0.015	Country and time not indicated. One mill.	Korhonen et al 2004

5.4. Routes of exposure and uptake

Occupational exposure may be through inhalation and dermal contact with this compound at workplaces where hydrazine is produced or used (Keller 1988, IOM 2011, HSDB 2016).

Since hydrazine is evaporating easily at room temperature, the main exposure route in occupational settings is inhalation. There are also some data to suggest dermal penetration of hydrazine solutions.

The potential exposure for the general population is low and it may occur through inhalation of cigarette smoke (32 µg per cigarette) or ingestion of trace amounts in processed foods and by dermal contact with vapours and other products containing the compound (HSDB 2016). Furthermore hydrazine sulphate may be ingested intentionally, as it has been studied as a treatment for cancer (NTP 2014).

6. MONITORING EXPOSURE

6.1. External exposure

Hydrazine can be monitored in the workplace air using the following available methods:

- OSHA (1980). Method ORG-20 for hydrazine.
- OSHA (1997). Method ORG-108 for hydrazine.
- NIOSH (1994). Method 3503 for hydrazine.
- UK HSE (2014). Method MDHS 86/2 for hydrazine (two individual methods; one for active sampling and one for passive)
- INRS (2015a). MetroPol M-7 for hydrazine
- INRS (2015b). MetroPol M-12 for hydrazines (hydrazine, hydrazine monohydrate and N,N-Dimethylhydrazine.

In all six methods hydrazine is sampled from the air in the workplace by adsorption onto a solid sorbent, sulfuric acid-treated glass fibre filters or directly into modified impingers/bubblers, followed by extraction with an organic or inorganic solvent. The hydrazine-containing extract is subsequently chemically treated for derivatization and colorimetric screening before HPLC analysis (OSHA 20) or directly analysed by high-performance liquid chromatography (HPLC), with Ultra Violet (UV) detection or spectrophotometry as shown in Table 5.

Table 5: Overview of sampling and analytical methods for monitoring hydrazine in workplace air

Method	Filters/ adsorbent / sampler	Desorption solution	Analysis	EE (%)	LOD/LOQ	Target concentration	Flow rate/ sample volume/ time	Evaluation[$]	Refs
OSHA Method ORG-20 (active sampling)	Sulfuric acid coated Gas Chrom R	Water	Colorimetric screening followed by UV-HPLC	100 (both procedures)	LOD and LOQ (overall procedure): 1.2 ppb or 1.6 µg/m^3 (HPLC procedure) 5 ppb or 6.5 µg/m^3 (screening procedure)	Target concentration 0.03 ppm or 0.04 mg/m^3	0.1 to 1 L/min/ 20 L /maximum 120 min sampling	Fully	OSHA (1980)
OSHA Method ORG-108 (active sampling)	Sulfuric acid-treated glass fibre filters	Buffered EDTA disodium solution	LC/ UV detection	98.7 and 98.9 **	LOD (overall procedure): 0.017 ppb or 0.023 µg/m^3	10 ppb to 1 ppm or 13 µg/m^3 to 1.3 mg/m3	1.0 L/min/ 240 L / 15 min up to 4hrs	Fully	OSHA (1997)
NIOSH Method 3503	Bubbler	HCl 0.1M	Spectro-photometry	99.7*	LOD: 0.9 µg /sample	Working range: 9 to 400 µg/ sample	0.2 to 1.0 L/min/ 7 L -100 L at 1 ppm	Fully	NIOSH (1994)
Method MDHS 86/2 (active and passive sampling)	Acid-coated glass fibre filters	Sulfuric acid 0.1M	HPLC/ UV detection	n.s.	Sampled volume dependent, general formula indicated	0.002-2ppm	2 L/min^{-1}/ 240 L sampling volume/ a few minutes up to 2hrs (active sampling)	n.s.	UK HSE (2014)
	modified impingers	Sulfuric acid 0.1M	HPLC/ UV detection	n.s.	Sampled volume dependent, general formula indicated	0.002-2ppm	1 L/min^{-1} / 480 L sampling volume/ up to 8hrs (passive sampling)	n.s.	
MetroPol M-7 (active sampling)	Chromosorb impregnated with sulfuric acid	Water (derivatizating agent:benzaldehyde)	HPLC/ UV detection	n.s.	n.s.	n.s.	0.1-1 L/min/ 20 L sampling volume/ max 8hrs	n.s.	INRS (2015a)
MetroPol M-12 (active sampling)	Chromosorb impregnated with sulfuric acid	Water (derivatizating agent:salicylaldehyde)	LC/ UV detection	n.s.	n.s.	n.s.	0.5-1 L/min/ 30-120 L sampling volume/ max 8hrs	n.s.	INRS (2015b)

n.s. not specified; LOD:Limit of Detection; LOQ:Limit of Quantification; EE: Extraction efficiencies (average)

* The average extraction efficiencies over the range of 0.5-2 times the target concentrations based on 10 ppb and 1ppm respectively

** Average collection efficiency at 0.9 L/min for six bubblers at 3.4 mg/m^3

[$] Any evaluation statement is as given in the original method description. Wording may have different meanings in different methods.

6.2. Internal exposure/Biomonitoring of exposure

Biomonitoring of hydrazine exposures in the workplace can be carried out by the measurement in blood (plasma) or urine, and can be quantitated by gas chromatography (GC) with an electron capture detector (ECD) or by fluorimetry.

Table 6: Overview of the available methods for bio-monitoring of occupational exposures to hydrazine

Method	Application	Analysis	Standard deviation (rel)(*Sw*)	Prognostic range(*u*)	Recovery (%)	Detection limit	Refs
DFG 1998 (for hydrazine and N-acetylhydra-zine)	In urine and plasma	GC/ECD	7.5%* 7.2%**	16.7% (hydrazine in urine) 16.1% (hydrazine in plasma)	84-110 (hydrazine in urine) 86-115 (hydrazine in plasma)	2 µg hydrazine/ L of urine 5 µg hydrazine/ L of plasma	DFG (1998)
DFG 1984 (for hydrazine)	In blood (plasma)	Fluorimetry	8.7%***	19.6%	103	5 µg hydrazine/ L of blood	DFG (1984)

* Within series imprecision at a concentration of 50 µg hydrazine per litre of urine and where n= 20 determinations
** Within series imprecision at a concentration of 100 µg hydrazine per litre of plasma and where n= 20 determinations
*** Within series imprecision at a concentration of 60 µg hydrazine per litre of blood and where n= 10 determinations

In the MAK value documentations, external and internal exposure data are reported including their correlation, i.e the so-called EKA values "Expositionsäquivalente für krebserzeugende Arbeitsstoffe" (exposure equivalents for carcinogenic substances) (DE DFG, 1995):

Air Hydrazine		Urine[1] (µg hydrazine/g creatinine)	Plasma[1] Hydrazine
(ml/m^3)	(mg/m^3)		(µg/l)
0.01	0.013	35	27
0.02	0.026	70	55
0.05	0.065	200	160
0.08	0.104	300	270
0.10	0.130	380	340

[1)] Sampling: end of exposure or end of shift

7. HEALTH EFFECTS

7.1. Toxicokinetics (absorption, distribution, metabolism, excretion)

7.1.1. Human data

There are no human data available on the toxicokinetics of hydrazine.

7.1.2. Animal data

Kaneo et al. (1984) examined the tissue distribution of [^{15}N]hydrazine in rats after a subcutaneous dose of 10 mg/kg by gas chromatography/mass spectrometry, using stable isotope internal standards. Maximal tissue levels of hydrazine were seen 30 min after dosing, and hydrazine was eliminated from the liver, kidney, lung and plasma with half-lives of 3.3, 2.7, 3.0 and 2.3 h, respectively. At 8 h, levels in the kidney were higher than those in other tissues. The levels of acetylhydrazine in the kidney were much higher than those in other tissues and peaked at 1 h, while the highest concentrations in other tissues occurred between 1 and 4 h after dosing. Only trace amounts of diacetylhydrazine were detected in the tissues. Within 48 h, a total of 30% of the dose was recovered in the urine, 24% as hydrazine and 3% each as acetyl- and diacetylhydrazine. The partial reversibility of hydrazine acetylation was shown after the administration of equimolar doses of acetylhydrazine. Tissue levels of hydrazine were between one quarter and one half of those of acetylhydrazine, while 6% of the dose was recovered in the urine as hydrazine, compared with 19% as acetylhydrazine.

Preece et al. (1992) examined the influence of dose upon the disposition of hydrazine in rats using oral doses of 3, 9, 27 and 81 mg/kg. The plasma and liver areas under the concentration-time curves for hydrazine increased linearly with doses of up to 27 mg/kg bw but were lower than expected at 81 mg/kg. At 3 and 9 mg/kg bw, plasma and liver levels were equivalent but, at higher doses, there was relatively more compound in the plasma. At 24 h after dosing, the plasma:liver ratio was 4.4 at 60 mg/kg and 5.7 at 80 mg/kg. The urinary recovery of hydrazine and acetylhydrazine fell with increasing dose, from 38 to 17% of a dose for hydrazine and from 5 to 1% for acetylhydrazine. The extent of acetylation decreased with increasing dose, and the hydrazine:acetylhydrazine ratio declined from 0.125 to 0.061.

Bollard et al. (2005) administered oral single dose hydrazine hydrochloride to rats and mice at the doses of 90 and 250 mg/kg, respectively, and analysed urinary metabolites 8, 24 and 48 hours post-dosing. In both species the proportion of the dose recovered in the urine as hydrazine metabolites was <10%. 1,4,5,6-Tetrahydro-6-oxo-3-pyridase (THOPC) and diacetylhydrazine were detected in the urine of both species, whereas acetyl hydrazine was detected only at low levels (<1% of the dose excreted) in rats. After 24 h, no hydrazine metabolites were detected anymore in the urine of rats, whereas mice excreted still some diacetyl hydrazine and THOPC.

Llewellyn et al. (1986) exposed rats to 10-500 ppm hydrazine vapour for 1 hour and found that 8.4-29.5% of the inhaled dose was excreted in the urine within 48 hours. Highest excretion was found at the highest dose. More than half of the excreted dose was in the form of diacetylhydrazine. The amounts excreted to feces and through the lungs were estimated to be high.

I.p. administration studies by Dost et al. (1979) and Nelson and Gordon et al. (1982) have shown that a significant proportion (23 and 35% within 24 and 48 hours, respectively) of hydrazine is eliminated via the lungs as N_2 gas.

Dermal absorption of hydrazine has been studied in dogs and rabbits. Keller et al. (1984) applied hydrazine in anhydrous form as well as 2%, 15% and 70% water solutions to the skin of rabbits for up to 12 minutes and measured serum hydrazin concentrations. After

exposure to anhydrous hydrazine, serum peak levels were observed 50-90 minutes after the application, whereas after 70%, 15% and 2% hydrazine solutions peaks were observed after 30-50 min, 30 min and 10 min, respectively. After administration of anhydrous or 70% hydrazine, the total absorbed dose within 120 minutes was 87 and 55% of the applied dose, respectively. In the case of 15% and 2% solutions, the absorbed fraction was 31 and 13%, respectively. Severe chemical burns were observed in the skin of rabbits treated with anhydrous or 70% hydrazine solution, but not with 15 or 2% solution. A dose-dependent increase in the plasma hydrazine levels were observed in dogs when hydrazine at dermal doses of 96 or 480 mg/kg were applied to the shaved skin of the chest (approximately 300 cm^2, non-occlusive application)(Smith and Clark, 1972). Peak plasma levels were observed 60 minutes after the application and the absorption was complete within 70 minutes or sooner in the lower dose group. Also in this study chemical burns were observed at the site of application.

7.1.3. In vitro data

In vitro, it has been shown that nitrogen gas is formed from hydrazine via oxidation by oxyhemoglobin in erythrocytes and oxygenase in liver microsomes (Clark et al., 1968, Nelson and Gordon, 1982, Springler et al., 1981).

Jenner and Timbrell (1995) showed that hydrazine is rapidly metabolized by rat liver microsomal enzymes. This metabolism is dependent upon oxygen and NADPH, and increased by NADH in the presence of NADPH. Hydrazine metabolism was 20-70% lower in human microsomes prepared from three individuals compared with rats. Hydrazine was also metabolized by rat liver mitochondria, but the monoamine oxidase inhibitors clorgyline and pargyline did not significantly decrease this activity (Jenner & Timbrell, 1995).

7.1.4. Toxicokinetic modelling

No data available.

7.1.5. Biological monitoring

Although analytical methods for the detection of hydrazine or hydrazine metabolites are available (see Chapter 6.2), there are no industrial field studies on biological monitoring of hydrazine.

7.2. Acute toxicity

7.2.1. Human data

Ingested liquid hydrazine produces local irritation which leads to protracted vomiting. The main symptoms in humans are of central nervous system origin - somnolence, ataxia, restlessness, incoordination and paresthesia. With medical treatment these symptoms regress within a few days. Transient respiratory and cardiac rhythm disorders are also likely to be of central nervous system origin (Drews et al., 1960; Reid, 1965).

Acute exposure to high hydrazine vapour levels causes, sometimes after a latent period of several hours, nausea and vomiting as well as local eye irritation, especially of the conjunctiva, irritation of the mucous membranes of the upper respiratory tract - with respiratory distress - and of exposed skin areas (Byrkit, 1950; Sutton, 1963). One investigator found liver enzyme values in exposed persons to be increased (DFG, 1991).

One case of fatal poisoning was reported of a man who had handled hydrazine (hydrazine hydrate) once a week for an unknown number of hours over a period of six months. In simulated conditions, only 0.071 mg hydrazine/m^3 was measured, but probably skin exposure had also occurred. The man experienced conjunctivitis, tremor and lethargy after each exposure. Following the last exposure, he developed fever, diarrhoea and

vomited. In hospital, six days later, many disorders were noted: conjunctivitis, stomatitis, arrhythmia, upper abdominal pain, enlarged abdomen, icterus, a tender and palpable liver, black faeces, incoherence and oliguria. X-ray examinations showed pleural effusion and lung shadowing. Laboratory findings comprised elevated blood bilirubin and creatinine levels, and protein and red blood cells in urine. Treatments administered included haemodialysis and B vitamins, which brought only temporary relief. The man died 21 days after the last exposure. Autopsy revealed pneumonia, severe renal tubular necrosis and nephritis and mild hepatocellular damage (Sotaniemi et al., 1971).

Kao et al., (2007) describe a case of aircraft technician who was acutely exposed to hydrazine vapours and developed mild transaminitis. After the exposure, serum transaminases (ALT and AST) were increased from day 0 to day 6 but returned normal by day 28. Acute symptoms related to exposure included mild headache and slight dizziness.

A number of systemic CNS symptoms of acute hydrazine intoxication, e.g. seizures, have been attributed to a hyperammonemic state resulting from the metabolism of hydrazine (Zelnick et al., 2003).

7.2.2. Animal data

The results of studies on acute toxicity of hydrazine have been compiled in detail by DFG (1991) or CERI (2007). LC50 values calculated for 4 h inhalation in rats and mice were given as 570 and 252 ppm, respectively (Jacobsen et al., 1955). Smith and Clark (1972) report dermal lowest lethal dose (LDLo) of 96 mg/kg for hydrazine. In rabbits, a dermal LD50 of 91 mg/kg has been reported (Horton and Conn 1954 in CERI, 2007). Oral LD50's for hydrazine in rats and mice are around 60-90 mg/kg (CERI, 2007).

Main symptoms after acute administration include hypopnea followed by increased excitability and tonicoclonic convulsions, drop in blood pressure, nerve conduction disturbances and, after oral administration, vomiting (as a result of irritation of the mucous membranes of the stomach). Histopathological changes included fatty metamorphosis of the liver and kidney changes. Bando et al. (2011) studied the mechanisms of liver toxicity of hydrazine after single oral dose (120 or 240 mg/kg) in rats. Fatty degeneration and glycogen accumulation in the liver was associated with the increase in the markers of oxidative stress and GSH consumption.

7.2.3. In vitro data

No relevant data identified.

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. Human data

No relevant data identified.

7.3.2. Animal data

7.3.2.1. Inhalation

Experimental studies on the toxicity of inhaled hydrazine were mostly performed at high concentrations. Main symptoms, at concentrations above 5 ppm, included hyperexcitability, locomotor disturbances, anorexia, vomiting, weight loss and dyspnoea. A comprehensive compilation has been provided by DFG (1991) and by CERI (2007).

Several studies in animals have reported decreased body weight gain. Male and female hamsters experienced significantly decreased body weight gains compared with controls during a 10-week period of exposure to 750 ppm hydrazine (1 h per week; Latendresse et al., 1995). Weight gains returned to normal during the subsequent recovery period. Body weight gain was reduced in rats and dogs exposed continuously to 1 ppm hydrazine, or intermittently to 5 ppm (6 h/d; 5 d/week) for 6 months (Haun & Kinkead, 1973). No effects on body weight gain were observed in these species when exposed to 0.2 – 1.0 ppm hydrazine. In hamsters, however, exposure to 0.25 ppm hydrazine caused a 14% loss of body weight (Vernot et al., 1985).

Intermittent exposure to 5 ppm hydrazine for 1 year produced inflammation, hyperplasia, and metaplasia of the upper respiratory tract epithelium in rats and mice (Haun et al., 1984, Vernot et al., 1985). By contrast, no adverse effects were noted in the lungs of mice intermittently exposed to 1 ppm hydrazine. The tumour findings (nasal tumours) are summarised under 2.8.2.

No clinical or histopathological effects were noted on the cardiovascular system and the gastrointestinal tract of mice exposed intermittently to 1 ppm hydrazine for 1 year (Vernot et al., 1985).

In dogs exposed continuously to 1 ppm hydrazine for 6 months, haemoglobin, haematocrit, and red blood cell counts were all significantly reduced (by about 25-30%; Haun & Kinkead, 1973). These effects were not observed in dogs exposed to 0.2 ppm hydrazine in this study. No effects were reported on a large number of haematological parameters in rats and monkeys exposed to 1 ppm hydrazine continuously for 6 months (Haun & Kinkead, 1973).

Fatty changes were observed in the livers of mice, dogs and monkeys exposed continuously to 0.2-1 ppm hydrazine for 6 months (Haun & Kinkead, 1973). The hepatotoxic effects were notably more severe in mice than in dogs or monkeys and were responsible for the increased mortality observed in this species.

Mild renal effects including amyloidosis and mineralisation were observed in hamsters exposed intermittently to 0.25 ppm hydrazine for 1 year; however, no effects were noted in the kidneys of mice exposed intermittently to 1 ppm hydrazine for 1 year (Vernot et al., 1985).

Tonic convulsions were noted in one of 8 dogs exposed continuously to 1 ppm hydrazine for 6 months but were not seen in any dogs exposed to 0.2 ppm (Haun & Kinkead, 1973). As seizures were also produced by the chemically related 1,1-dimethylhydrazine, although at higher exposure concentrations, this was taken as a corroboration of observations in humans that the CNS system is a target of inhaled hydrazine (Choudhary & Hansen, 1998).

7.3.2.2. Oral exposure

In rats and mice, relatively mild effects on the liver such as megamitochondria formation, increased lipogenesis, and fatty changes occurred following daily dosings of 49-650 mg/kg bw (Marshall et al., 1983, Wakabayashi et al., 1983, Preece et al., 1992). Cirrhosis, reticuloendothelial cell proliferation, bile duct proliferation, and degenerative fibrous cells were observed in the livers of hamsters dosed with 4.9 mg/kg bw daily for 15-20 weeks (Biancifiori et al., 1966). No adverse effects were observed in the livers of mice receiving 9.5 mg/kg bw hydrazine daily for 2 years (Steinhoff et al., 1990).

Degeneration of the adrenals was noted in female mice given 1.1 mg/kg bw hydrazine daily for 25 weeks (Biancifiori et al. 1970). No effects were observed in the thyroid or adrenals of hamsters given 5.3 mg/kg bw hydrazine daily for 15-20 weeks (Biancifiori et al., 1970).

7.3.2.3. Dermal exposure

No data available.

7.3.2.4. Other routes of exposure

Anorexia, vomiting, weight loss, lethargy and increased levels of transaminases and bilirubin were observed in Rhesus monkeys who received up to 20 injections of 20 mg/kg hydrazine. Pathological-anatomical investigations revealed fatty deposits in the liver, myocardium, kidneys and skeletal muscles (Patrick & Back, 1965).

7.3.3. In vitro data

No relevant studies identified.

7.4. Irritancy and corrosivity

7.4.1. Human data

Skin lesions caused by direct contact with hydrazine have often been described. Particularly frequent are reports of inflammatory skin conditions in persons involved in the production of hydrazine or its derivatives. Even workers whose uncovered skin was splashed with soldering fluid containing hydrazine hydrobromide, or who handled metal components which had been soldered using this fluid, developed dermatitis on the exposed skin areas (for details, see DFG, 1991).

7.4.2. Animal data

7.4.2.1. Skin

In the skin penetration study by Keller et al. (1984, see section 7.1.2) up to 12 minutes application of anhydrous (95%) hydrazine or 70% hydrazine in aquous solution resulted in severe chemical burns with transdermal necrosis with varying degrees of dermal necrosis. No lesions were observed with 15 or 2% solutions. Similar findings were observed in dermal study in dogs by Smith and Clark (1972). REACH registration dossier (www.echa.europa.eu) describes additionally an industry study with 55% hydrazine showing corrosive effect in rabbits.

7.4.2.2. Eyes

Minimal irritation of the eyes was noted in monkeys during the first few weeks of inhalation exposure to 1 ppm hydrazine (Haun & Kinkead, 1973). This effect was not observed in monkeys exposed to 0.2 ppm hydrazine, or in mice exposed intermittently to 1 ppm hydrazine for 1 year (Haun & Kinkead, 1973, Vernot et al., 1985).

7.4.3. In vitro data

No data available.

7.5. Sensitisation

7.5.1. Human data

Allergic contact eczema has been described in numerous publications from different branches of industry (for details, see DFG 1999).

One publication reports about 150 notifications of allergic contact eczema from hydrazines between 1959 and 1983 (Pevny and Peter 1983). Noteworthy are the very low concentration of 0.08 mmol/l hydrazine sulfate in vaseline which was sufficient to cause sensitization in man in patch tests (Lepoittevin et al. 1995) and the extent of the eczema caused by the volatility of the substances. It is emphasized in some studies that, after sensitization has occurred, mere contamination of utensils with hydrazine and hydrazine in the ambient air (Brandt 1960, Wheeler et al. 1965, Wrangsjö and Martensson 1986) is sufficient to trigger eczema.

The sensitizing ability of hydrazine is further illustrated by the following observations.

In a factory producing hydrazine sulfate, 5 employees developed contact allergy to the substance although only 4 of them had contact with the sulfate either during production or in the laboratory. One worker apparently became sensitized because he regularly had to walk through the production plant. The eczema recurred when the hydrazine sulfate was transported in plastic (Igelit) sacks (Brandt 1960).

In a soldering shop with 34 female workers, eczema developed in 12 of the women after a new soldering fluid containing a mixture of hydrazine monohydrochloride and tin chloride was introduced. In 6 of these women tests with 1 % hydrazine sulfate in water yielded positive results, in 30 controls negative results. One of these patients also reacted to the hydrazine derivatives hydralazine, phenylhydrazine and isonicotinic acid hydrazide (Frost and Hjorth 1959). Also in a soldering plant for tin cans in Sweden, 8 of 22 employees became ill a few weeks after the introduction of a new soldering fluid on a 4.5 % to 60 % hydrazine monohydrobromide basis (Misfeldt and Thormann 1984). In 35 of 70 solderers in a factory which produced relays, skin alterations developed within a period of 3 weeks to a few months after the first contact with a new soldering agent containing hydrazine. As also reported in other studies, eczema developed on the face, in particular on the eyelids and on parts of the arms not covered by protective clothes (Wheeler et al. 1965). In an explosives factory, 25 cases of eczema were recorded in 3 years despite various protective measures, although on average only 12 workers worked at these workplaces (Querangal des Essarts 1955).

The high capacity of hydrazine to cause sensitization is illustrated by an unusual case of eczema in a partner of a hydrazine worker. A 30-year-old woman developed severe extensive contact eczema the first time she used a sun cream (active substance: dibenzalazine), which perhaps contained hydrazine or from which hydrazine was formed on the skin by rapid hydrolysis of the benzaldehyde hydrazone. The cause of the contact sensitization, which was confirmed by testing, finally proved to be the working clothes of her husband which also caused a reaction in epicutaneous tests and which she had frequently washed. As a boiler attendant the husband had regular contact with hydrazine (Ippen 1962).

Also to be mentioned is the treatment of nail mycosis with a 12.5 % aqueous hydrazine hydrate solution. Among 87 patients treated with the substance for 6 months, in 7 cases eczematous skin changes apparently occurred although application was supposed to be restricted to the body of the nail (Chen et al. 1991). Cross-reactions to hydrazine are apparently more frequent in cases in which the sensitization is caused by a hydrazide (e.g. isonicotinic acid hydrazide, hydralazine or dihydralazine) (Hövding 1967) than are reactions to hydrazides in those cases in which the primary sensitization is caused by hydrazine (Bandmann and Dohn 1967, Schultheiss 1959). In a re-exposure experiment, an auto-immune reaction which resembled systemic lupus erythematosus was observed in a laboratory technician after contact with hydrazine (Durant and Harris 1980). Such severe allergic reactions to hydrazine derivatives used as medicines, in particular the antihypertensives hydralazine (hydrazinophthalazine) and dihydralazine (dihydrazinophthalazine) have often been described (Malten 1962).

A maximization test was carried out in the U.S. with 23 healthy male prisoners (Kligman 1966). For induction, the test area on the forearm or lower leg was treated for 24 hours occlusively with a 5 % aqueous sodium dodecylsulfate solution and then for 48 hours

occlusively with a 5 % hydrazine solution (no further details). This procedure was repeated several times and, after a pause of 10 days, provocation was carried out with a 48-hour epicutaneous test with a 0.5 % hydrazine solution on the back. As all 23 test persons were found to be sensitized, hydrazine was regarded as an extremely strong sensitizer.

One case of reactive airway dysfunction syndrome ("irritant astma") has been described by Brooks et al (1985). This is, however, non-immunological reaction to high exposure to irritant substance. No cases of asthmas caused by allergic (IgE –mediated or delayed type) mechanisms are described.

7.5.2. Animal data

There are no published reports of animal experiments on sensitization from hydrazine, hydrazine hydrate or hydrazine salts available. Gould and Taylor (2011) report LLNA results of 28 sensitizing pharmaceutical agents or intermediates, which has been identified in Bristol-Myers Squibbs' screening program. Six of these were either hydrazine derivatives with hydrazine moiety in their molecular structure or hydrazine precursors, which are hydrolysed to hydrazine. These showed EC3 levels of 0.006-0.33% indicating moderate to extremely high potency for sensitization. Hydrazine itself was not tested.

7.5.3. In vitro data

No relevant data available.

7.6. Genotoxicity

7.6.1. Human data

There are no human data available on the genotoxicity of hydrazine.

7.6.2. Animal data

In an in vivo study in mice, hydrazine induced DNA strand breaks in liver and lungs (Parodi et al., 1981). lt induced a slight increase in bone marrow micronucleus frequency only in one of three studies in mice after i.p. administration (Kirkhard., 1981; Salamone et al., 1981; Tsuchimoro and Matter, 1981). Also a sister chromatid exchange study in bone marrow and liver of mice treated i.p. with hydrazine remained negative (Paika et al., 1981).

In germ cells, an UDS assay in mice spermatids remained negative (Sotomayor et al., 1982) and hydrazine did not induce dominant lethal mutations in a single study in mice or sperm abnormalities in two studies but a mouse spot test showed clear positive results (IARC, 1999).

Hydrazine has, however, induced the formation of N7-methylguanine and O6-methylguanine in the liver of mice, rats and hamsters treated in vivo (IARC, 1999). Syrian hamsters were given hydrazine sulphate in the drinking-water for two years, the levels of methylation of DNA guanine in liver, kidney and lung were measured. Both N7- and 06-methylguanine were readily detectable at six months of exposure, but only trace amounts of these bases were detected after 12 months of exposure; these bases were again detected in liver DNA at exposure times of 18 and 24 months (Bosan et al., 1987).

7.6.3. In vitro

In vitro genotoxicity studies on hydrazine have been summarized by IARC (1999). Hydrazine was mutagenic to yeast and bacteria and induced DNA damage in bacteria.

Hydrazine induced somatic mutations in Drosophila. It induced DNA strand breaks in rat hepatocytes and unscheduled DNA synthesis in mouse hepatocytes in vitro. Conflicting results were obtained for induction of gene mutations in mouse lymphoma L5178Y cells. Hydrazine did not induce chromosomal aberrations in a rat liver cell line in vitro but did induce sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells (for as detailed synopsis of all studies, see IARC, 1999).

7.7. Carcinogenicity

7.7.1. Human data

Single case reports in humans have proposed an association between occupational hydrazine exposure and skin cancers (basalioma or melanoma) or epithelioid sarcoma (Albert and Puliafito 1977; Aigner ey al., 2010; Helmers et al., 2004). A study of men engaged in hydrazine manufacture comprised 423 men, with 64% ascertainment of vital status. None of the cancers reported (three gastric, one prostatic and one neurogenic) occurred in the group with the highest exposure. A follow-up of this cohort extended the observations to 1982. Mortality from all causes was not elevated (49 observed, 61.5 expected) and the only excess was two lung cancer cases within the highest-exposure category, with a relative risk of 1.2 (95% confidence interval, 0.2-4.5) (Wald ym, 1984).

A cohort of 427 men who worked at a hydrazine plant in the United Kingdom for at least six months between 1945 and 1971 was followed up until 1992 (Morris et al., 1995). Follow-up was complete for 95%. Based an job history records, 78 of the workers were classified as having been exposed to high levels of hydrazine (estimated at about 1-10 ppm) and the remaining 375 to moderate or low exposure (< 1 ppm). There were 2145 person-years of follow-up in the latter group. Among the whole group, no increase was observed for all-cause mortality (86 deaths, standardized mortality ratio (SMR), 0.8), or for mortality from lung cancer (8 deaths; SMR, 0.7), cancer of the digestive tract (9 deaths; SMR, 1.0) or other cancers (8 deaths; SMR, 0.8), after comparison with the rates for England and Wales. Restricting attention to the high-risk group, the SMR for all-cause mortality was 0.7 (20 deaths) and that for lung cancer was 1.1 (3 deaths). No deaths from cancer of the digestive tract were observed. The SMR for other cancers was 0.8 (2 deaths). None of the SMRs was significantly different from 1.0. Of the three lung cancer cases in the high-exposure group, two occurred in workers with less than two years of occupational exposure to hydrazine. This study has been recently extended for 50-years of follow-up (Morris et al., 2015). No increased mortality due to lung or any other cancers were observed in this follow-up, either.

Ritz et al. (1999) conducted a retrospective cohort study of 6107 aerospace workers to examine whether exposure to chemicals (primarily hydrazine fuels) during rocket-engine fueling and testing affected cancer mortality. When conditional logistic regression analysis was applied and adjusted for confounding variables, the estimated rate ratio for lung cancer mortality, comparing exposed to unexposed workers from the same facility, ranged from 1.68 (95% confidence interval, 1.12 to 2.52) to 2.10 (95% confidence interval, 1.36 to 3.25), depending on job-duration threshold (6 or 24 months) and lag time (0 to 15 years). Results for hemato- and lymphopoietic cancer and for bladder and kidney cancer mortality were considered imprecise.

The same group (Ritz et al. 2006) further extended this mortality study in a follow-up from 1994 to 2001 and investigated the cancer incidence for the period 1988-2000 using population-registry data. Estimated hydrazine effects were adjusted for occupational exposures to other carcinogens and assessed through a job-exposure matrix. Rate-ratio estimates were derived from Cox proportional hazards and random-effects models using time-dependent exposure measures for hydrazine adjusting for trichloroethylene, polycyclic aromatic hydrocarbons, benzene, and mineral oil exposures. Exposures to hydrazine were positively associated with lung cancer incidence (estimated rate ratio for high vs. low exposure with 20-year lag = 2.5; 95% confidence interval = 1.3-4.9) and with colorectal cancer incidence (2.2; 1.0-4.6). Dose-response associations were observed for both outcomes; similar associations were found for lung cancer mortality

but not for colorectal cancer mortality. Effect estimates for cancers of the pancreas, blood and lymph system, and kidneys were based on only small numbers. The authors concluded that their findings were generally consistent with the previous results (Ritz et al. 1999) for lung cancer mortality, and that the total data suggested that exposure to hydrazine increased the risk of incident lung cancers. They also pointed to the possibility of induction of colon cancer by hydrazine.

In a further study on the mortality among this same cohort exposed during 1948-1999 and examined for their vital status at December 1999, only a non-significant increase in lung cancer mortality was seen among the workers exposed to hydrazine when compared to general population (Boyce et al., 2006). No increased trend with increasing exposure was seen but the classification of exposure was different to that in Ritz et al (2006) study and was based mainly on exposure duration and not on intensity of exposure.

No association between the incidence of prostate cancer and exposure to hydrazine was seen in a nested case-control study among aerospace and radiation workers (Krishnadasan et al., 2007).

7.7.2. Animal data

7.7.2.1. Oral

Groups of 50 male and 50 female NMRI mice, five to six weeks of age, were given hydrazine in the drinking-water at concentrations of 0, 2, 10 and 50 mg/L (ppm) for two years. The highest dose (50 ppm) was toxic, producing severely reduced weight gain and a lower survival; 10 ppm was the maximum tolerated dose (moderate body weight decrease). No increase in the incidence of tumours at any site or at any dose was observed (Steinhoff et al., 1990).

Groups of 50 male and 50 female specific pathogen-free bred Wistar rats, six weeks of age, were given hydrazine in the drinking-water at concentrations of 0, 2, 10 and 50 mg/L (ppm) for 24 months. The concentration of 2 ppm was tolerated with little toxicity; 10 ppm proved to be the maximum tolerated dose and 50 ppm was clearly toxic, producing severely decreased body weight gain. An increase in tumour incidence was observed in the liver: no tumour in the controls (0/100 both sexes combined); two tumours (2%) (1 hepatocellular adenoma, 1 haemangioma) in the 2-ppm group; three tumours (3%) (1 hepatocellular adenoma and 1 carcinoma, 1 cholangioma) in the 10-ppm group; and 14 tumours (14.6%) (8 hepatocellular adenomas, 3 carcinomas and 3 cholangiomas) in the 50-ppm group. In historical controls, the incidence of liver-cell tumours was 9/652 (1.4%) (Steinhoff & Mohr, 1988).

Syrian hamsters were given hydrazine sulphate in the drinking-water at concentrations of 170, 340 and 510 mg/L (ppm) for two years (average doses, 4.6, 8.3 and 10 mg/kg hydrazine (free base)). Hepatocellular carcinomas were observed in hamsters treated with the highest dose of hydrazine sulphate after 78 weeks of exposure; the incidence of hepatocellular carcinomas in the three treated groups was 0/31 at 170 ppm, 4/34 at 340 ppm and 11/34 at 510 ppm (Bosan et al., 1987).

7.7.2.2. Inhalation

Year-long, 5 days/week, exposures of rats, mice, hamsters, and dogs to hydrazine were conducted using concentrations of 0.05, 0.25, 1.0, and 5.0 ppm. Rats were held 18 months postexposure; hamsters, 1 year postexposure; mice, 15 months postexposure; and dogs, 38 months postexposure. Male and female rats exhibited dose-dependent increases of benign nasal adenomatous polyps and smaller numbers of malignant nasal epithelial tumours after 1 year of exposure to hydrazine and 18 months postexposure holding. Nasal tumours were often associated with chronic irritation and were most frequent in male rats, with an incidence of greater than 50% in the highest exposure

group. Hamsters exposed to 0.25-ppm and higher concentrations showed pathologic changes characteristic of degenerative disease, including amyloidosis. After exposure to 5 ppm hydrazine, hamsters developed a 10% incidence of benign nasal polyps compared to 0.5% in controls. Small numbers of colon neoplasms and thyroid parafollicular cell adenomas were found in hamsters, but only in the highest concentrations tested. Lung adenomas appeared to be marginally increased in mice exposed to 1.0 ppm hydrazine, the highest concentration tested in this species. No consistent clinical or pathological effects were seen in dogs during or after exposure to hydrazine at any concentration. In rats, there appeared to be a marginal production of nasal tumours at 0.05 ppm, while mice showed no effects at 0.25 ppm. This study demonstrated that the nasal respiratory epithelia of rats and hamsters are the most sensitive tissues to the tumorigenic action of hydrazine following inhalation exposures (Vernot et al., 1985).

In addition to this study, Latendresse et al. (1995) addressed the question of a carcinogenic potential of hydrazine in rats and male hamsters exposed to a high concentration of hydrazine for repeated short exposures, in order to investigate the relationships of acute and subchronic effects of hydrazine to nasal tumorigenesis. In Phase 1 (acute and subchronic) and Phase 2 (lifetime) experiments, groups of male and female Fischer 344 rats and male Syrian golden hamsters were exposed by inhalation to 0, 75 (Phase 2 only), or 750 ppm hydrazine for 1 (acute) or 10 (subchronic) 1-hr weekly exposures. Rodents were euthanized 24 hr after the exposures, 1, 10 or 24 to 30 months after the study initiation. Significant reductions in body weight were observed in hydrazine-treated rodents compared to controls during the exposure interval. No hydrazine-induced mortality was detected. Histopathologic examination after the acute and subchronic exposures revealed degeneration and necrosis of transitional, respiratory, and olfactory epithelia in the anterior nose and, in rats exposed subchronically, squamous metaplasia of the transitional epithelium. Minimal to mild rhinitis resulted from hydrazine exposures. Apoptosis was observed in olfactory and squamous metaplastic transitional epithelium. Lesions occurred at sites reportedly having high air-flow and generally appeared to be more severe in the anterior portion of the nose. By 24 months, the squamous metaplastic transitional epithelium reverted back to normal-appearing transitional epithelium. By 24+ months, low incidences (sexes combined) of hyperplasia (5/194, 2.6%) and neoplasia (11/194, 5.7%) were detected, principally in the transitional epithelium of the 750 ppm hydrazine-treated rats. A similar incidence of hyperplasia (2/94, 2%) and neoplasia (5/94, 5.3%) was detected in the high-exposure group of hamsters. The location and type of hydrazine-induced proliferative lesions were similar to those reported in a chronic N2H4-exposure study (5.0 ppm x 6 hr/day x 5 days/week for 1 year) conducted in the same laboratory, but the chronic study had much higher incidences of lesions (rats, sexes combined: hyperplasia 15.5% vs 2.6% and polypoid adenoma 44.6% vs 5.2%). The product of concentration x time was the same (7500 ppm hours) for the high-dose groups for both studies, but the duration of exposure was 150x longer and the concentration was 150x lower in the chronic study. According to the authors, these comparisons suggested that the duration of exposure is a more significant factor than concentration in hydrazine-induced nasal tumorigenesis. [The IARC Working Group, when assessing this study, noted that data were not presented for control tumour incidences, although the incidence of nasal adenomas in both sexes and that of nasal hyperplasia in males were significant (IARC, 1999)].

7.7.2.3. Dose-response analysis

The long term inhalation study of hydrazine in rats, mice, hamsters and dogs (Vernot et al., 1985) demonstrated that the nasal epithelium of rats and hamsters was the most sensitive to the tumorigenic activity of hydrazine following inhalation exposure. Especially the data on neoplastic lesions in male and female rats were suitable for dose-response modelling. Table 7 provides an overview of the BMD modeling results, of which details can be found in Appendix A.

In this study (Vernot et al. 1985) rats were exposed to hydrazine by long intermittent exposure (6hr/day 5 days/week) for 12 months followed by 18 month follow up without

exposure. Since this exposure was considered representative for the occupational settings dose levels were modelled as tested.

Table 7: Results from BMD analysis of the data reported by Vernot et al. (1985) for neoplastic lesions occuring at higher incidences in hydrazine exposed rats over controls. Details of the dose response modelling can be found in Appendix A.

Model	Tumor type	BMD10 ppm	BMDL10 ppm	Table in Annex with BMD data
Female rats	Nasal adenomatous polyp	2.77	2.02	Table A1
	Nasal villous polyp	16.16	7.30	Table A2
	Nasal adenocarcinoma	9.62	6.24	Table A3
	Nasal squamous cell papilloma	9.25	6.14	Table A4
	Nasal squamous cell carcinoma	11.36	6.98	Table A5
	Bronchial adenoma	5.55	5.00	Table A6
Male rats	Nasal adenomatous polyp	1.10	0.93	Table A7
	Nasal villous polyp	4.36	3.27	Table A8
	Nasal adenocarcinoma	*	*	-
	Nasal squamous cell papilloma	9.40	6.24	Table A9
	Nasal squamous cell carcinoma	22.33	7.54	Table A10
	Bronchial adenoma	9.40	6.24	Table A11
	Thyroid carcinoma	5.67	2.92	Table A12

* Data not suitable for dose-response modelling

BMD modeling of the neoplastic lesions observed in male and female rats revealed a lowest BMD10 of 1.10 ppm for benign nasal adenomatous polyps in male rats (Table A7). Also in female rats these nasal adenomatous polyps resulted in the lowest BMD10 value as compared to the other endpoints. BMD10 values for malignant neoplasms varied between 5.67 and 22.33 ppm. Based on these data it was concluded that a BMD10 of 5.67 would provide an adequate point of departure for definition of risk numbers.

7.8. Reproductive toxicity

7.8.1. Human data

There are no data available on the human reproductive effects of hydrazine.

7.8.2. Animal data

7.8.1.1. Fertility

Data on reproductive toxicity of hydrazine are scarce. No histopathological lesions in the ovaries were noted of mice and hamsters given orally 9.3 and 5.3 mg/kg hydrazine daily for 15-25 weeks (Biancifiori et al., 1970).

In female rats exposed by inhalation to 5 ppm hydrazine 5 d/week for one year, atrophy of the ovaries and inflammation of the endometrium and Fallopian tubes were noted (Vernot et al., 1985). "Senile" testicular atrophy was observed in male hamsters exposed by inhalation to 1 ppm hydrazine for one year, but not in hamsters exposed to 0.25 ppm (Vernot et al. 1985). An absence of sperm production was observed in hamsters exposed to 5 ppm hydrazine. The authors concluded that testicular changes normally associated with ageing were accelerated by hydrazine.

7.8.1.2. Developmental toxicity

After i.p. administration hydrazine has caused increased resorptions, decreased survival and body weight gain in pups in the presence of maternal toxicity (Lyng et al., 1980; Keller et al., 1980; Keller et al., 1982). At high doses also increases in exencephaly and hydrocephaly, hydronephrosis and extra ribs were described. Dermal application of hydrazine 50 mg/kg bw at gestation day 9 resulted in complete fetal resorptions. At 5 mg/kg bw no effects on foetuses were seen, but dams suffered from epidermal necrolysis at the site of application and body weight gain suppression (Keller et al., 1982).

7.8.3. In vitro data

No relevant data identified.

7.9. Mode of action and adverse outcome pathway considerations

Administration of hydrazine to rodents results in the formation of N7-methylguanine and O6-methylguanine in liver DNA. Co-administration of L-[methyl-^{14}C] methionine or [^{14}C]formate with the hydrazine led to labelling of the methylguanines, suggesting involvement of the one-carbon pool in the methylation process (Quintero-Ruiz et al., 1981). It has been proposed that the methylation mechanism involves reaction of hydrazine with endogenous formaldehyde to yield formaldehyde hydrazone, which could be metabolized to the potent methylating agent diazomethane (Bosan & Shank, 1983; Bosan et al., 1986; see Figure 1). According to data of Barrows et al. (1983), there was no increased direct incorporation of the tritium-labelled methyl group of methionine into 5-methyl-cytosine in hydrazine-treated rats. In experiments using free DNA incubated with postmitochondrial (S9), microsomal, cytosolic or mitochondrial cell fractions from rat liver *in vitro*, methylation of DNA guanine occurred, S9 being the most active fraction. Neither the P450 monooxygenase nor flavin monooxygenase systems appeared to be important in hydrazine/formaldehyde-induced methylation of DNA. However, sodium azide, cyanamide and carbon monoxide all inhibited S9-supported DNA methylation. Bovine liver catalase, a haem-containing cytochrome, readily transformed hydrazine/formaldehyde to a methylating agent. The data supported the proposal that formaldehyde-hydrazone, the condensation product of hydrazine and formaldehyde, is rapidly transformed in various (liver) cell fractions to a DNA-methylating agent (Lambert & Shank, 1988). This metabolic concept is summarised in Figure 1.

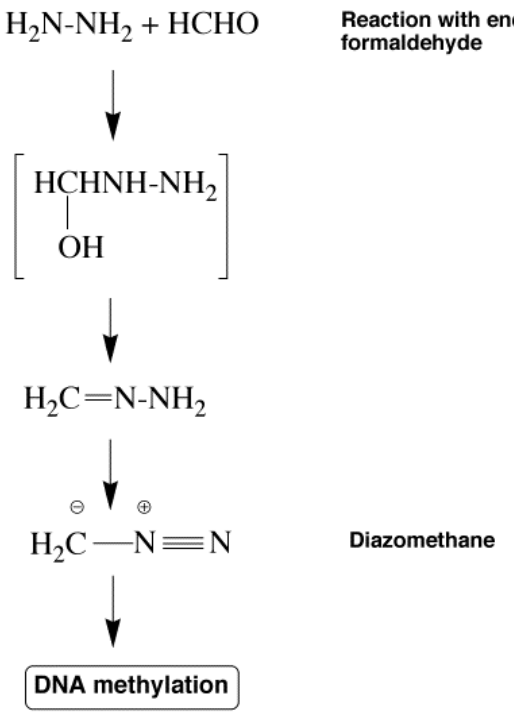

Figure 1: Metabolic concept of "indirect" methylation of DNA induced by hydrazine exposure: reaction of hydrazine with endodenous formaldehyde to the hydrazone, which is oxidised to the strong methylating agent diazomethane (Bosan & Shank, 1983)

Later, van Delft et al. (1997) further examined the pattern of DNA methylation. The induction of N7- and O6-methylguanine was studied in liver DNA of rats, 16 hr after treatment with various doses of hydrazine. After DNA isolation, the presence of N7-methylguanine in DNA was assessed with an immunochemical method and with a physicochemical technique (HPLC with electrochemical detection). Application of these two methods resulted in almost identical patterns of dose-dependent induction of guanine N7-methylation in rats dosed orally with 0.1 to 10 mg hydrazine per kilogram of body weight, increasing from 1.1-1.3 to 39-45 N7-methylguanine per 10^6 nucleotides. At lower dosages a constant adduct level was observed, equivalent to that in untreated rats (background level). The O6-methylguanine level was analyzed by a combination of HPLC separation and competitive radioimmunoassay. A background level was observed for untreated rats and no increase was visible up to the 0.2 mg/kg dose group. After hydrazine doses from 0.2 to 10 mg/kg, O6-methylguanine increased from 0.29 to 134 per 10^9 nucleotides. The data were interpreted to show that even at dosages below the maximum tolerated dose (0.6 mg/kg bw/day), for which carcinogenic effects have not been described experimentally, methyl DNA adducts are formed. The authors also concluded that their results were consistent with the aforementioned mechanistic concept of hydrazine-induced DNA methylation (Figure 1).

Zheng and Shank (1996) conducted a study to follow changes in DNA maintenance methylation in selected genes in liver DNA during the 21-month induction of liver adenomas and hepatocellular carcinomas by demonstrating changes in restriction fragment length polymorphism. Male Syrian golden hamsters were exposed to hydrazine sulphate in the drinking water at three concentrations (170, 340 and 510 mg/l) shown previously to result in a dose-dependent induction of liver tumours. Liver DNA from animals exposed to the high concentration for 6, 12, 16, 20 and 21 months and animals exposed to the low or mid concentration for 21 months was digested with the restriction

enzymes EcoRI, MspI, HindIII or BamHI, or a combination of one of these endonucleases and a methyl-sensitive restriction enzyme, HpaII or HhaI. The DNA digests were subjected to Southern analysis using a c-DNA probe for one of the following genes: DNA methyltransferase, c-Ha-ras, c-jun, c-fos, and c-myc proto-oncogenes, p53 tumor suppressor gene or gamma-glutamyltranspeptidase. Alteration in DNA restriction by methyl-sensitive endonucleases was detected in four (DNA methyltransferase, c-Ha-ras, p53 and c-jun) of the seven genes examined and as early as 6 months in animals exposed to the highest concentration of hydrazine sulphate; alteration of recognition sites in c-Ha-ras was also detected in DNA from animals exposed for 21 months to the intermediate concentration of hydrazine sulphate. Early changes in recognition sites, presumed to indicate altered methylation status of DNA cytosine and/or guanine moieties, were seen using c-DNA probes for DNA methyltransferase, c-Ha-ras and c-jun; in the p53 tumor suppressor gene alteration of such sites was a late event relevant to appearance of liver adenomas and hepatocellular carcinomas. Evidence for hypomethylation in the p53 and c-jun genes and hypermethylation of the c-Ha-ras and DNA methyltransferase genes was provided, and the study was interpreted to support the induction of both site-specific hypomethylation and hypermethylation reactions during the course of hydrazine carcinogenesis.

7.10. Lack of specific scientific information

There are no such major data gaps which would prevent the analysis of dose-responses of hydrazine.

8. GROUPS AT EXTRA RISK

No specific data on groups at extra risk were identified.

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APPENDIX A

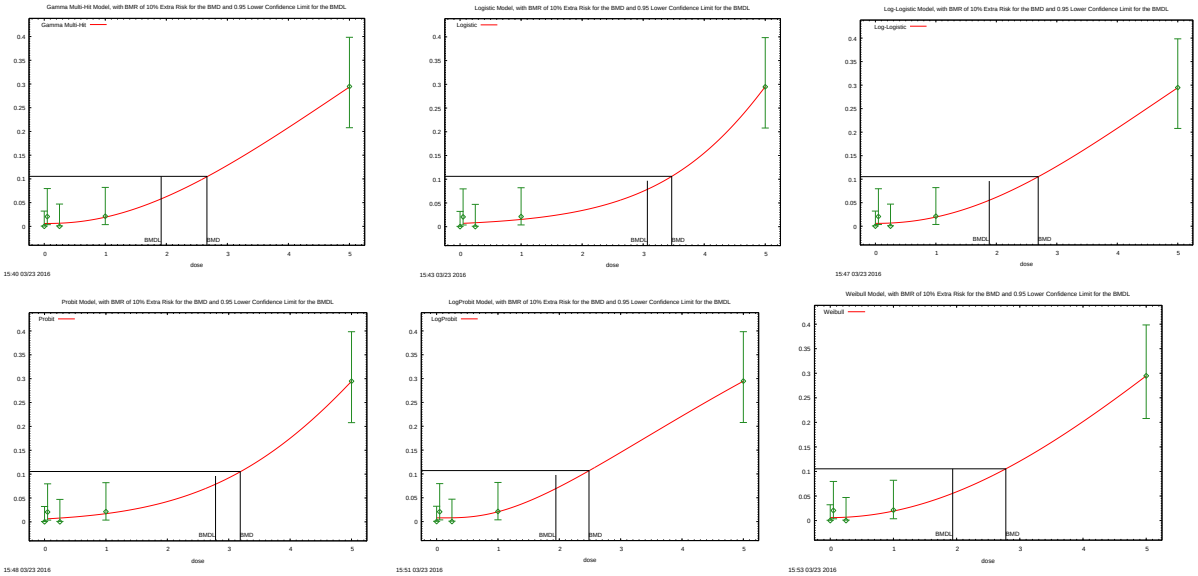
RESULTS FROM DOSE-RESPONSE MODELLING OF THE DATA ON TUMORS OCCURRING AT HIGHER INCIDENCES IN HYDRAZINE EXPOSED RATS OVER CONTROLS (VERNOT ET AL., 1985).

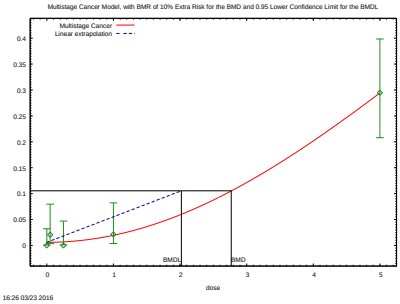
The data modelled can be found in Table 4 of Vernot et al., 1985.

Data from female rats

Table A1: Results from a BMD analysis of the data on incidences **of nasal adenomatous polyps** in **female rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD ppm	BMDL ppm	BMD/ BMDL
Gamma	Extra	0.1	yes	3	yes	0.08	165.22	2.67	1.92	1.39
Logistic	Extra	0.1	na	2	yes	0.14	163.53	3.47	3.07	1.13
LogLogistic	Extra	0.1	yes	3	yes	0.07	165.24	2.69	1.88	1.43
Probit	Extra	0.1	na	2	yes	0.15	163.46	3.19	2.79	1.14
LogProbit	Extra	0.1	yes	3	yes	0.07	165.30	2.48	1.94	1.28
Weibull	Extra	0.1	yes	3	yes	0.07	165.26	2.78	1.94	1.43
Multistage Cancer	**Extra**	**0.1**	**na**	**2**	**yes**	**0.16**	**163.26**	**2.77**	**2.02**	**1.37**
Multistage	**Extra**	**0.1**	**yes**	**2**	**yes**	**0.16**	**163.26**	**2.77**	**2.02**	**1.37**
Quantal Linear	Extra	0.1	na	2	no	0.02	168.47	-	-	-




Multistage Cancer Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Multistage Cancer
Linear extrapolation
BMDL
BMD
dose
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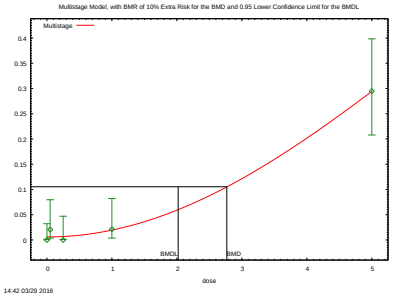
Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Multistage
BMDL
BMD
dose
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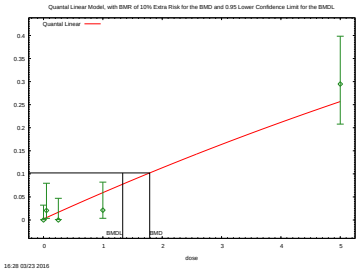
Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Quantal Linear
BMDL
BMD
dose
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Table A2: Results from a BMD analysis of the data on incidences **of nasal villous polyps** in **female rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD ppm	BMDL ppm	BMD/ BMDL
Gamma	Extra	0.1	yes	1	yes	0.59	43.54	15.60	7.24	2.15
Logistic	Extra	0.1	na	2	yes	0.16	47.93	8.97	5.94	1.51
LogLogistic	**Extra**	**0.1**	**yes**	**1**	**yes**	**0.60**	**43.51**	**16.16**	**7.30**	**2.21**
Probit	Extra	0.1	na	2	yes	0.17	47.83	9.71	6.12	1.59
LogProbit	Extra	0.1	yes	2	yes	0.11	48.85	11.47	5.48	2.09
Weibull	Extra	0.1	yes	1	yes	0.59	43.54	15.60	7.21	2.16
Multistage Cancer	Extra	0.1	na	1	yes	0.59	43.54	*	*	
Multistage	Extra	0.1	yes	1	yes	0.59	43.54	*	*	
Quantal Linear	Extra	0.1	na	1	yes	0.59	43.54	15.60	7.57	2.06

* BMD computation failed. BMD is larger than three times maximum input doses.

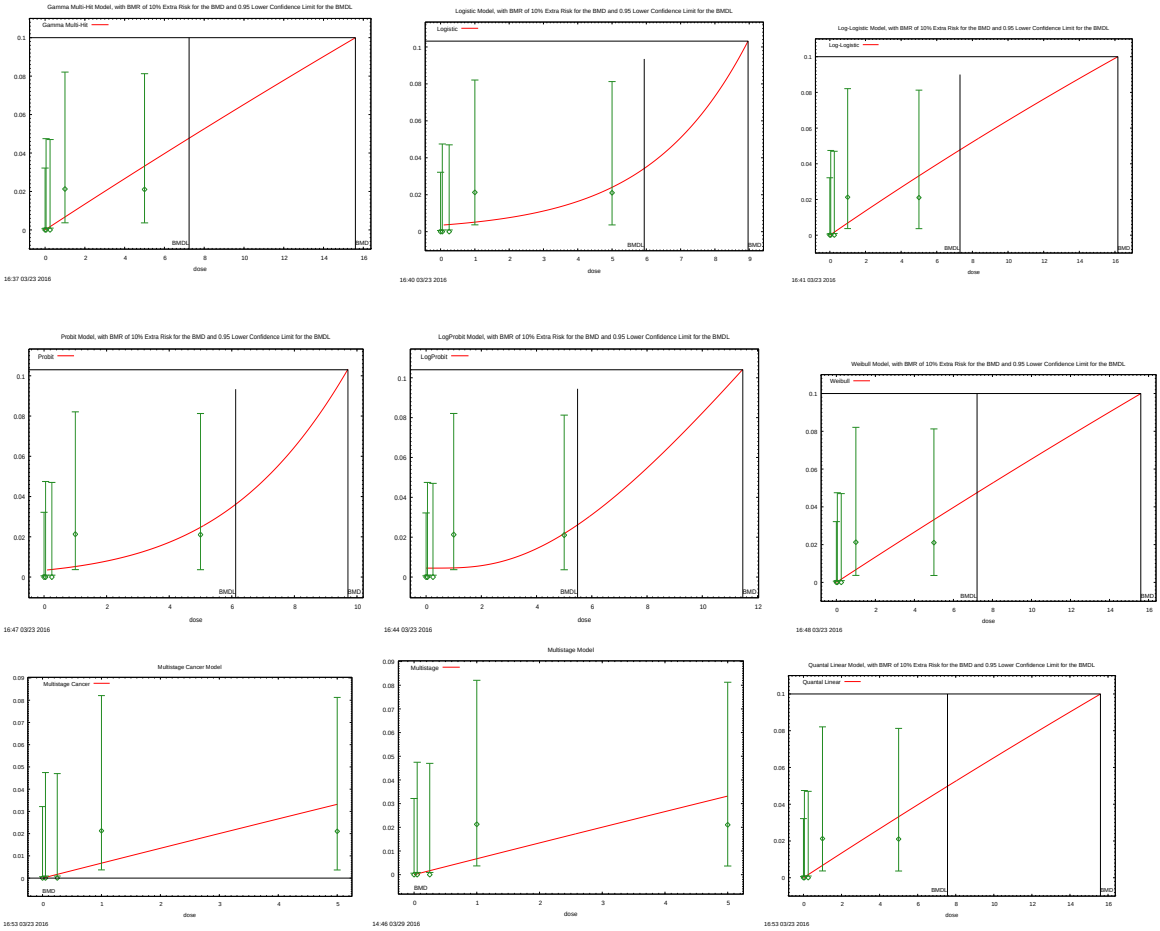


Table A3: Results from a BMD analysis of the data on incidences **of nasal adenocarcinomas** in **female rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD/BMDL
Gamma	Extra	0.1	yes	3	yes	0.22	46.78	6.21	5.28	1.18
Logistic	Extra	0.1	na	2	yes	0.35	45.09	7.32	5.54	1.32
LogLogistic	Extra	0.1	yes	3	yes	0.22	46.78	5.67	5.12	1.11
Probit	Extra	0.1	na	2	yes	0.34	45.14	8.01	5.72	1.40
LogProbit	Extra	0.1	yes	3	yes	0.22	46.78	6.38	5.06	1.26
Weibull	Extra	0.1	yes	3	yes	0.22	46.78	5.66	5.11	1.11
Multistage Cancer	**Extra**	**0.1**	**na**	**2**	**yes**	**0.34**	**45.01**	**9.62**	**6.24**	**1.54**
Multistage	**Extra**	**0.1**	**yes**	**2**	**yes**	**0.34**	**45.01**	**9.62**	**6.24**	**1.54**
Quantal Linear	Extra	0.1	na	2	yes	0.25	45.87	21.83	9.07	2.41

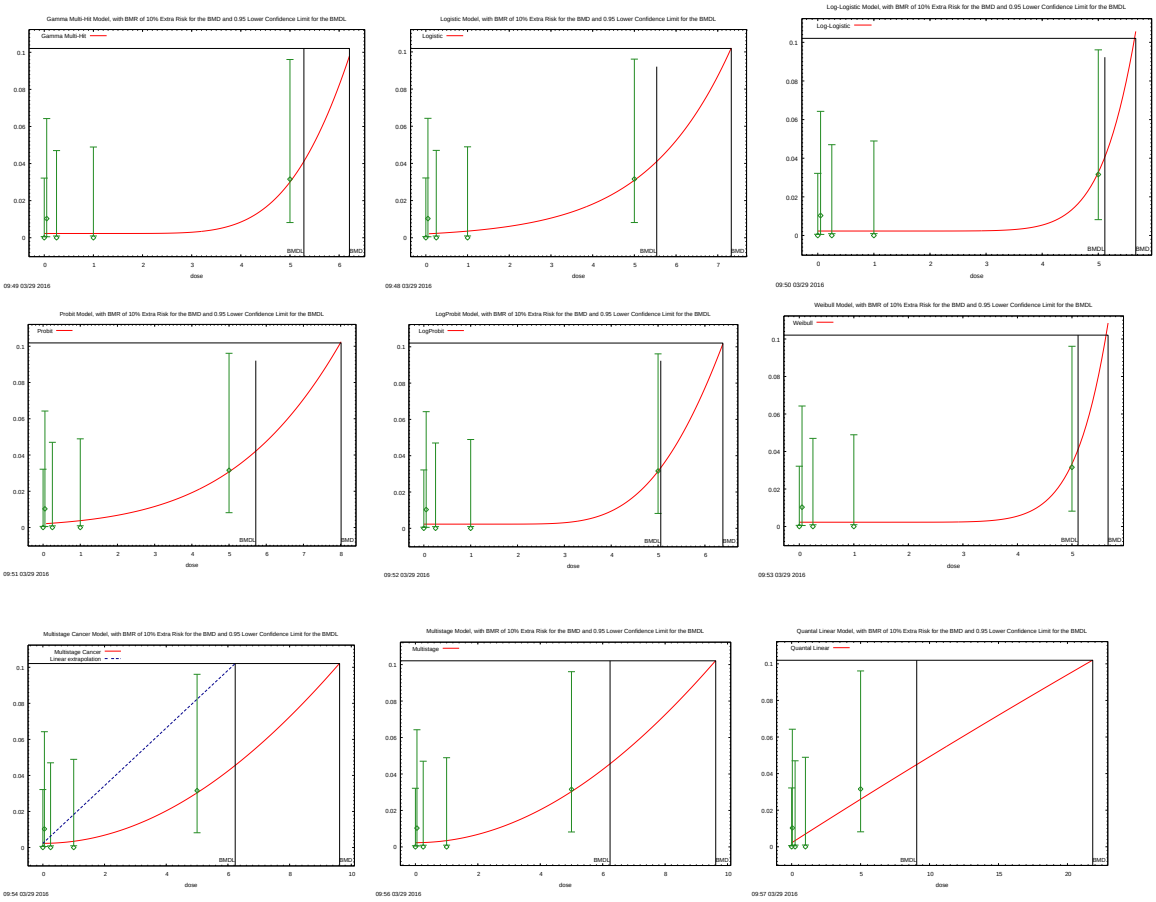


Table A4: Results from a BMD analysis of the data on incidences of **nasal squamous cell papilloma** in **female rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD/ BMDL
Gamma	Extra	0.1	yes	2	yes	1.00	30.64	6.10	5.26	1.16
Logistic	Extra	0.1	na	2	yes	1.00	30.64	5.29	4.99	1.06
LogLogistic	Extra	0.1	yes	2	yes	1.00	30.64	5.62	5.11	1.10
Probit	Extra	0.1	na	2	yes	1.00	30.64	5.56	5.00	1.11
LogProbit	Extra	0.1	yes	2	yes	1.00	30.64	6.25	5.05	1.24
Weibull	Extra	0.1	yes	2	yes	1.00	30.64	5.60	5.10	1.10
Multistage Cancer	**Extra**	**0.1**	**na**	**1**	**yes**	**0.99**	**28.99**	**9.25**	**6.14**	**1.51**
Multistage	**Extra**	**0.1**	**yes**	**1**	**yes**	**0.99**	**28.99**	**9.25**	**6.14**	**1.51**
Quantal Linear	Extra	0.1	na	1	yes	0.84	30.04	20.75	9.14	2.27

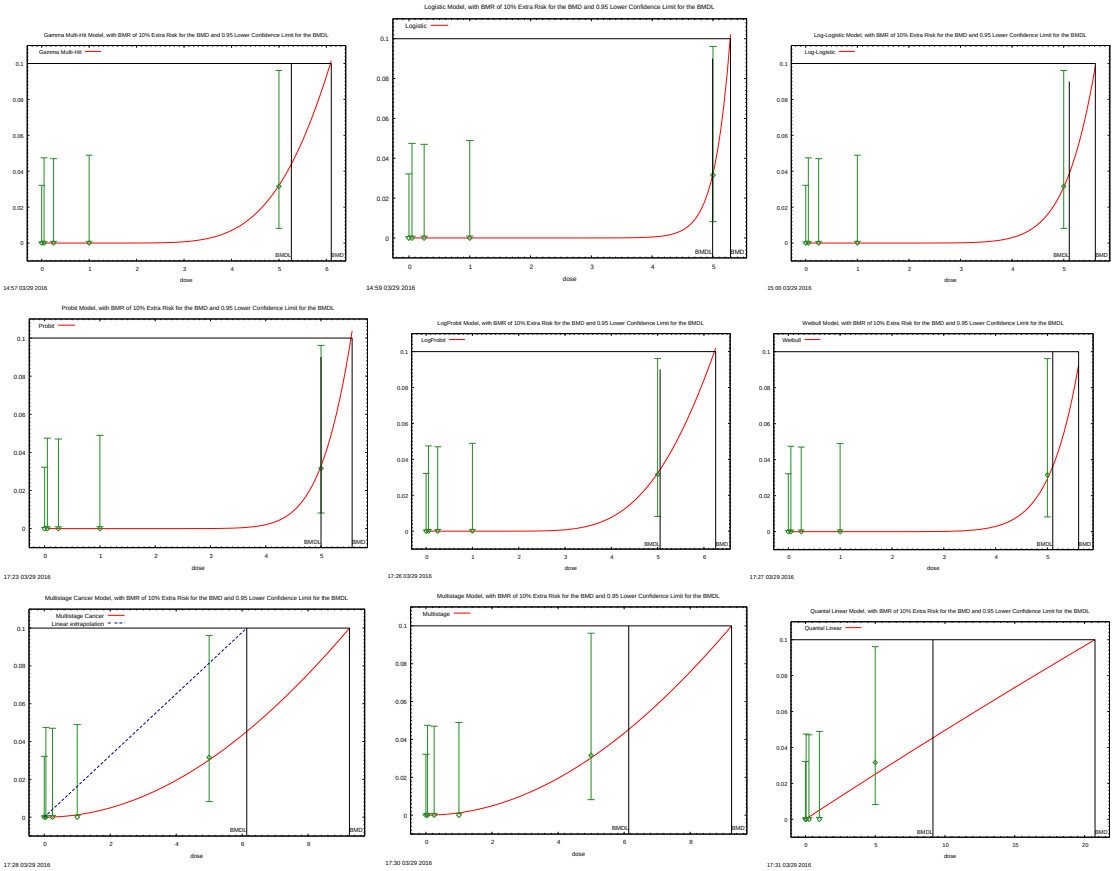


Table A5: Results from a BMD analysis of the data on incidences of **nasal squamous cell carcinoma** in fe**male rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD/ BMDL
Gamma	Extra	0.1	yes	2	yes	1.00	23.40	6.53	5.44	1.20
Logistic	Extra	0.1	na	2	yes	1.00	23.40	5.38	4.99	1.08
LogLogistic	Extra	0.1	yes	2	yes	1.00	23.40	5.84	5.18	1.13
Probit	Extra	0.1	na	2	yes	1.00	23.40	5.75	5.00	1.15
LogProbit	Extra	0.1	yes	2	yes	1.00	23.40	6.80	5.09	1.34
Weibull	Extra	0.1	yes	2	yes	1.00	23.40	5.81	5.18	1.12
Multistage Cancer	**Extra**	**0.1**	**na**	**1**	**yes**	**1.00**	**21.57**	**11.36**	**6.98**	**1.63**
Multistage	**Extra**	**0.1**	**yes**	**1**	**yes**	**1.00**	**21.57**	**11.36**	**6.98**	**1.63**
Quantal Linear	Extra	0.1	na	1	yes	0.92	22.33	31.26	11.79	2.65

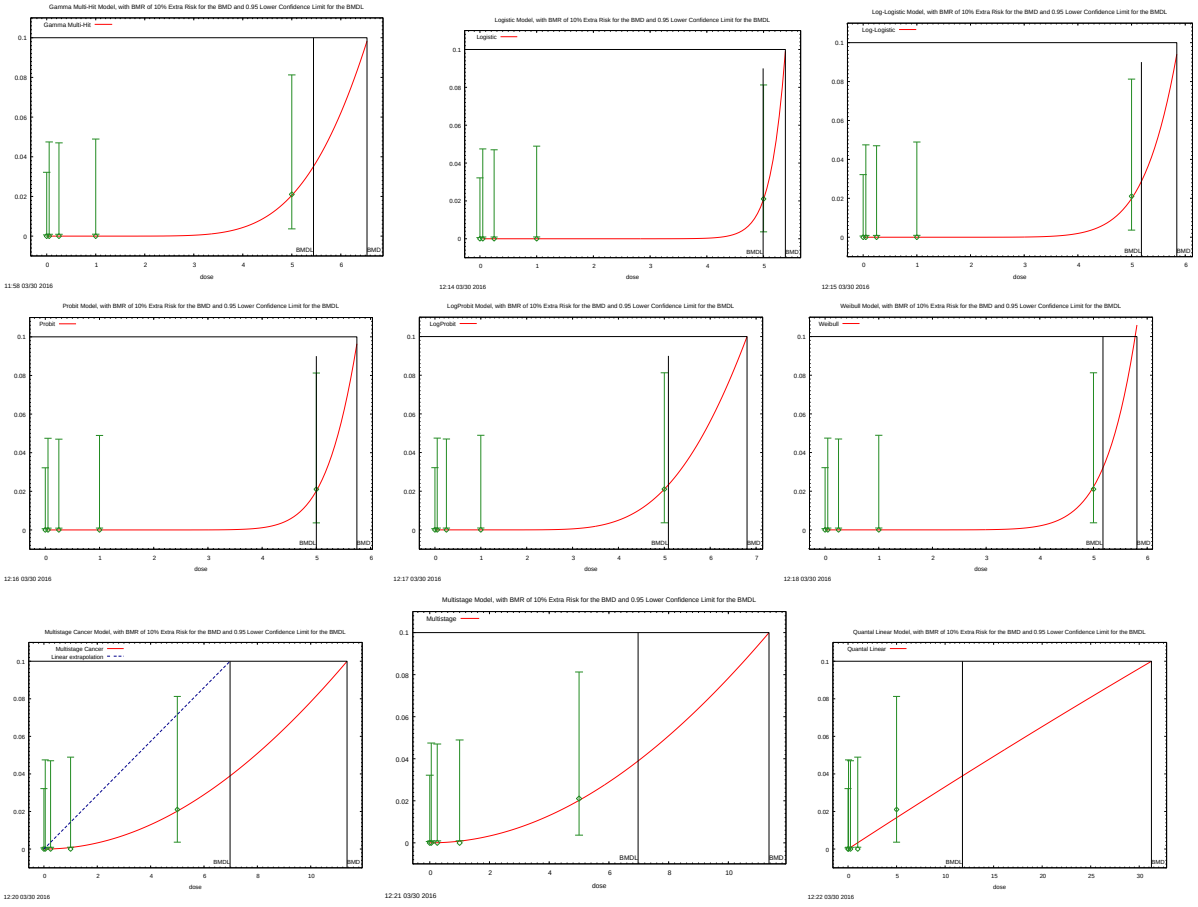
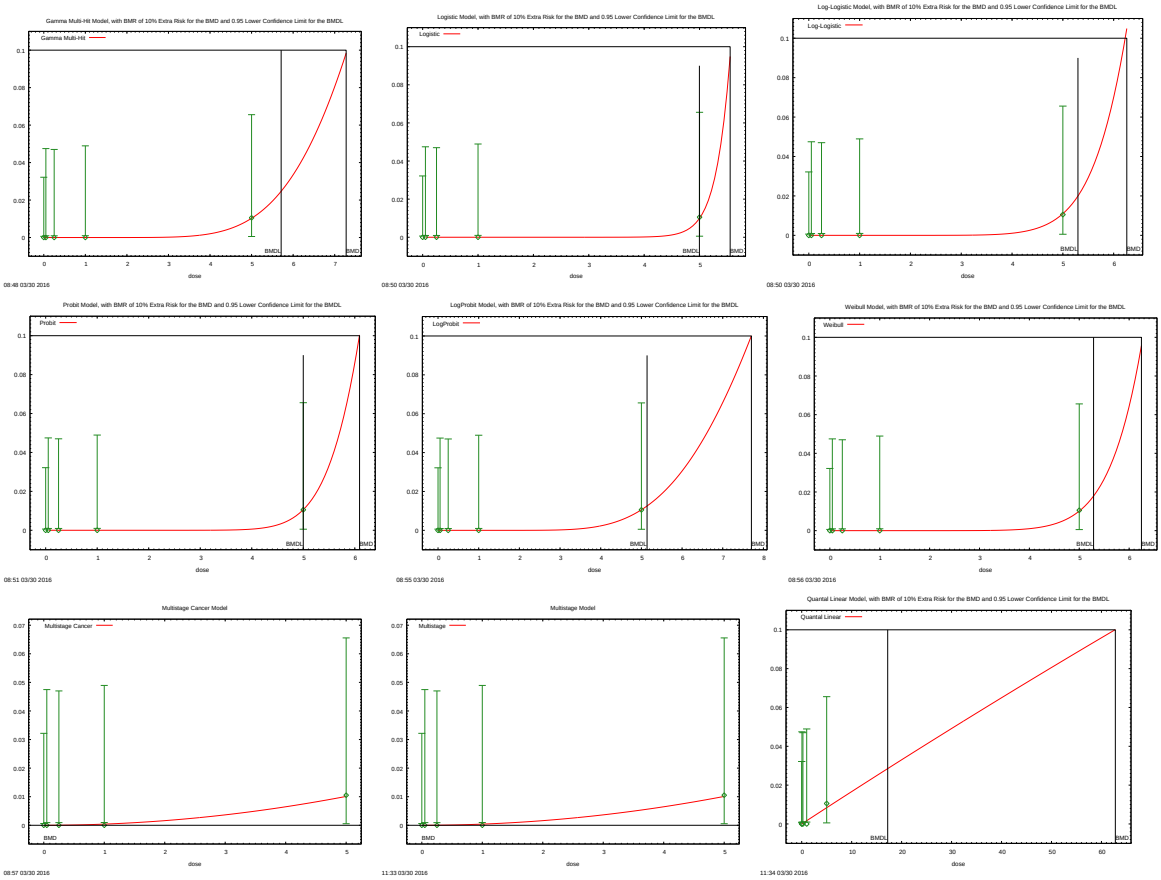


Table A6: Results from a BMD analysis of the data on incidences of **bronchial adenoma** in **female rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC, lowest BMD) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD/ BMDL
Gamma	Extra	0.1	yes	2	yes	1.00	15.10	7.28	5.71	1.27
Logistic	**Extra**	**0.1**	**na**	**2**	**yes**	**1.00**	**15.10**	**5.55**	**5.00**	**1.11**
LogLogistic	Extra	0.1	yes	2	yes	1.00	15.10	6.26	5.30	1.18
Probit	Extra	0.1	na	2	yes	1.00	15.10	6.09	5.00	1.22
LogProbit	Extra	0.1	yes	2	yes	1.00	15.10	7.70	5.14	1.50
Weibull	Extra	0.1	yes	2	yes	1.00	15.10	6.25	5.29	1.18
Multistage Cancer	Extra	0.1	na	1	**yes**	1.00	13.18	*	*	
Multistage	Extra	0.1	yes	1	**yes**	1.00	13.18	*	*	
Quantal Linear	Extra	0.1	na	1	yes	0.98	13.56	62.78	17.21	3.65

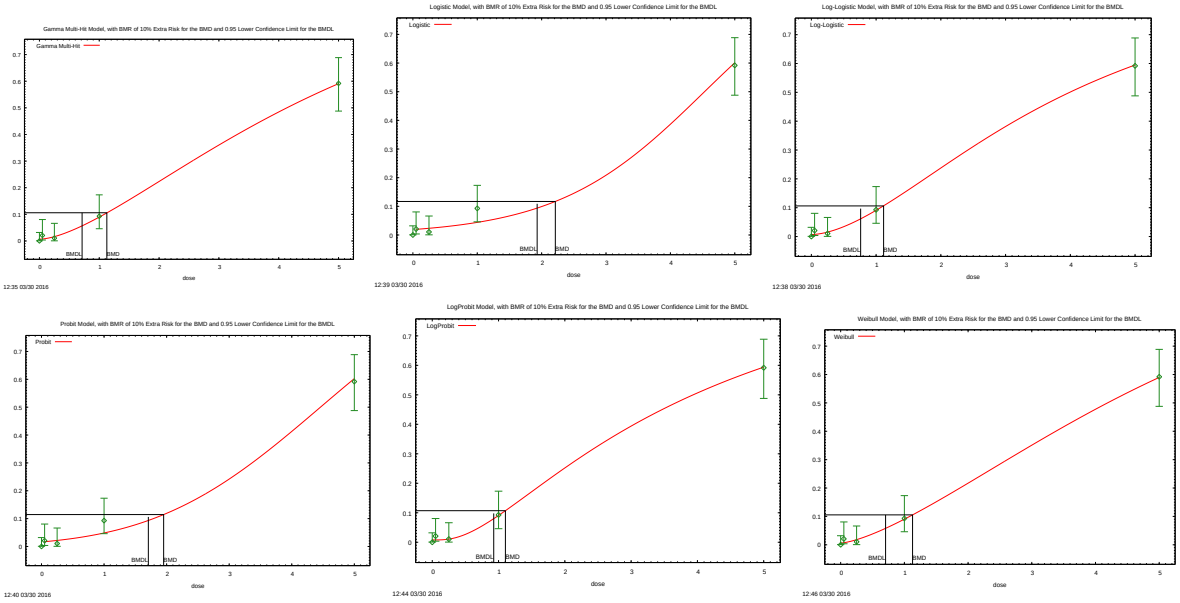
* BMD computation failed. BMD is larger than three times maximum input doses.

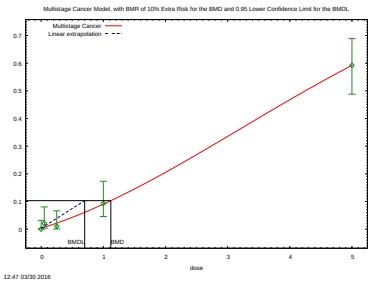


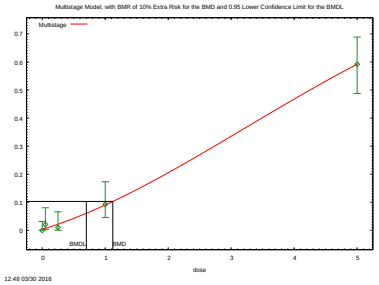
Data from male rats

Table A7: Results from a BMD analysis of the data on incidences of **nasal adenomatous polyps** in **male rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD/ BMDL
Gamma	Extra	0.1	yes	3	yes	0.15	232.75	1.13	0.71	1.59
Logistic	Extra	0.1	na	2	no	0.01	237.64	2.21	1.93	1.15
LogLogistic	Extra	0.1	yes	3	yes	0.15	232.73	1.12	0.76	1.47
Probit	Extra	0.1	na	2	no	0.03	235.83	1.95	1.71	1.14
LogProbit	**Extra**	**0.1**	**yes**	**2**	**yes**	**0.29**	**230.72**	**1.10**	**0.93**	**1.18**
Weibull	Extra	0.1	yes	3	yes	0.15	232.74	1.13	0.71	1.59
Multistage Cancer	Extra	0.1	na	3	yes	0.18	232.43	1.12	0.70	1.60
Multistage	Extra	0.1	yes	3	yes	0.18	232.43	1.12	0.70	1.60
Quantal Linear	Extra	0.1	na	1	yes	0.11	232.50	0.67	0.55	1.22




Multistage Cancer Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Multistage Cancer
Linear extrapolation
BMDL
BMD
dose
12:47 03/30 2016


Multistage Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Multistage
BMDL
BMD
dose
12:48 03/30 2016

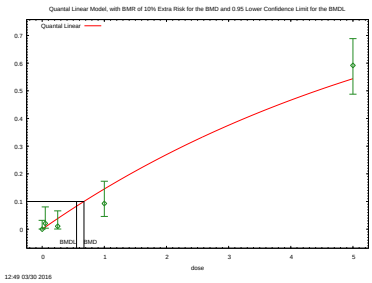

Quantal Linear Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Quantal Linear
BMDL
BMD
dose
12:49 03/30 2016

Table A8: Results from a BMD analysis of the data on incidences of **nasal villous polyps** in **male rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD/ BMDL
Gamma	**Extra**	**0.1**	**yes**	**2**	**yes**	**0.98**	**88.18**	**4.36**	**3.27**	**1.33**
Logistic	Extra	0.1	na	2	**yes**	0.60	89.87	4.75	4.26	1.12
LogLogistic	Extra	0.1	yes	2	yes	0.98	88.20	4.36	3.25	1.34
Probit	Extra	0.1	na	2	yes	0.66	89.61	4.68	4.07	1.44
LogProbit	Extra	0.1	yes	1	yes	0.90	87.05	4.21	3.29	1.30
Weibull	Extra	0.1	yes	2	yes	0.98	88.21	4.39	3.31	1.33
Multistage Cancer	Extra	0.1	na	2	**yes**	0.96	88.32	4.43	3.48	1.27
Multistage	Extra	0.1	yes	2	**yes**	0.96	88.32	4.43	3.48	1.27
Quantal Linear	Extra	0.1	na	1	yes	0.68	88.33	4.74	3.10	1.53

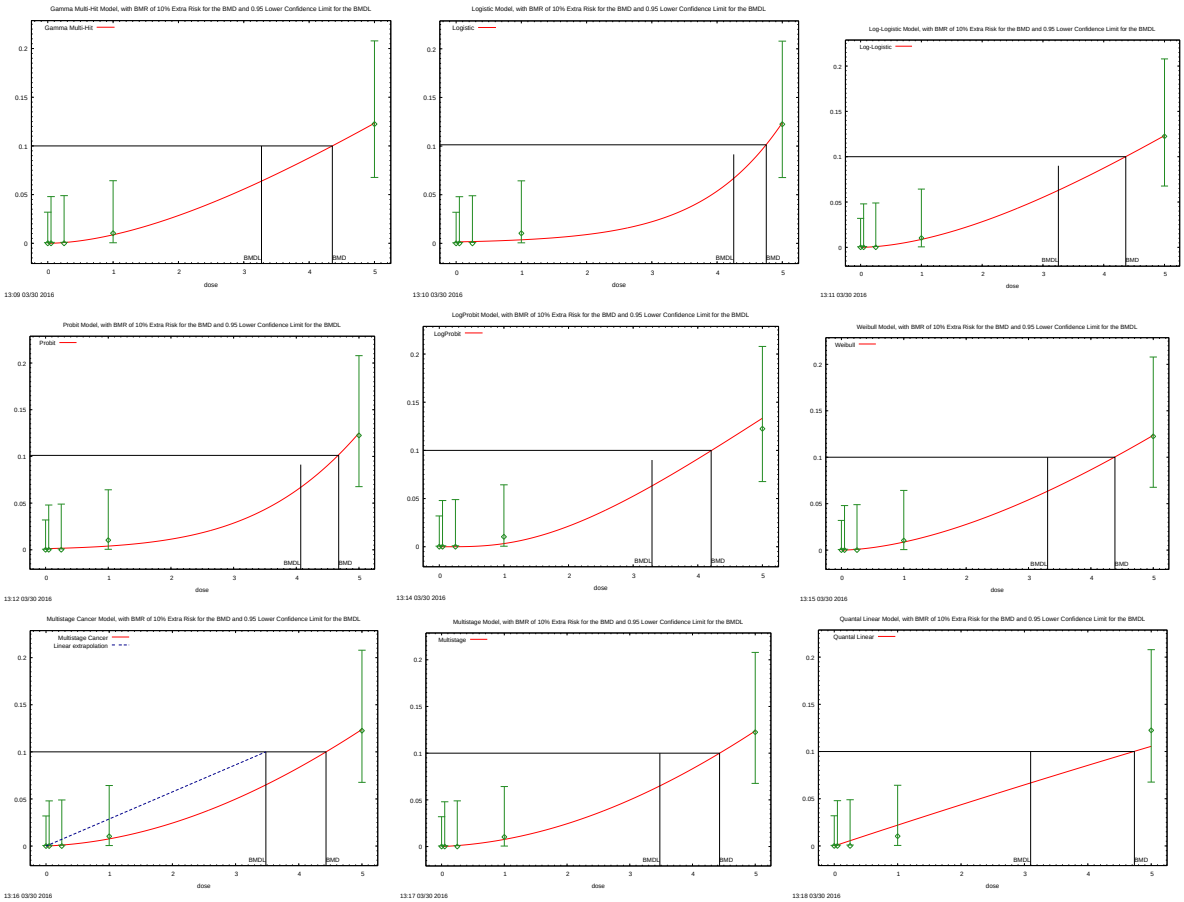


Table A9: Results from a BMD analysis of the data on incidences of **nasal squamous cell papilloma** in **male rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD/ BMDL
Gamma	Extra	0.1	yes	2	yes	1.00	30.83	6.12	5.28	1.16
Logistic	Extra	0.1	na	2	yes	1.00	30.83	5.30	5.01	1.06
LogLogistic	Extra	0.1	yes	2	yes	1.00	30.83	5.63	5.12	1.10
Probit	Extra	0.1	na	2	yes	1.00	30.83	5.58	5.00	1.12
LogProbit	Extra	0.1	yes	2	yes	1.00	30.83	6.30	5.09	1.24
Weibull	Extra	0.1	yes	2	yes	1.00	30.83	5.62	5.11	1.10
Multistage Cancer	**Extra**	**0.1**	**na**	**1**	**yes**	**0.99**	**29.08**	**9.40**	**6.24**	**1.51**
Multistage	**Extra**	**0.1**	**yes**	**1**	**yes**	**0.99**	**29.08**	**9.40**	**6.24**	**1.51**
Quantal Linear	Extra	0.1	na	1	yes	0.85	30.21	21.35	9.40	2.27

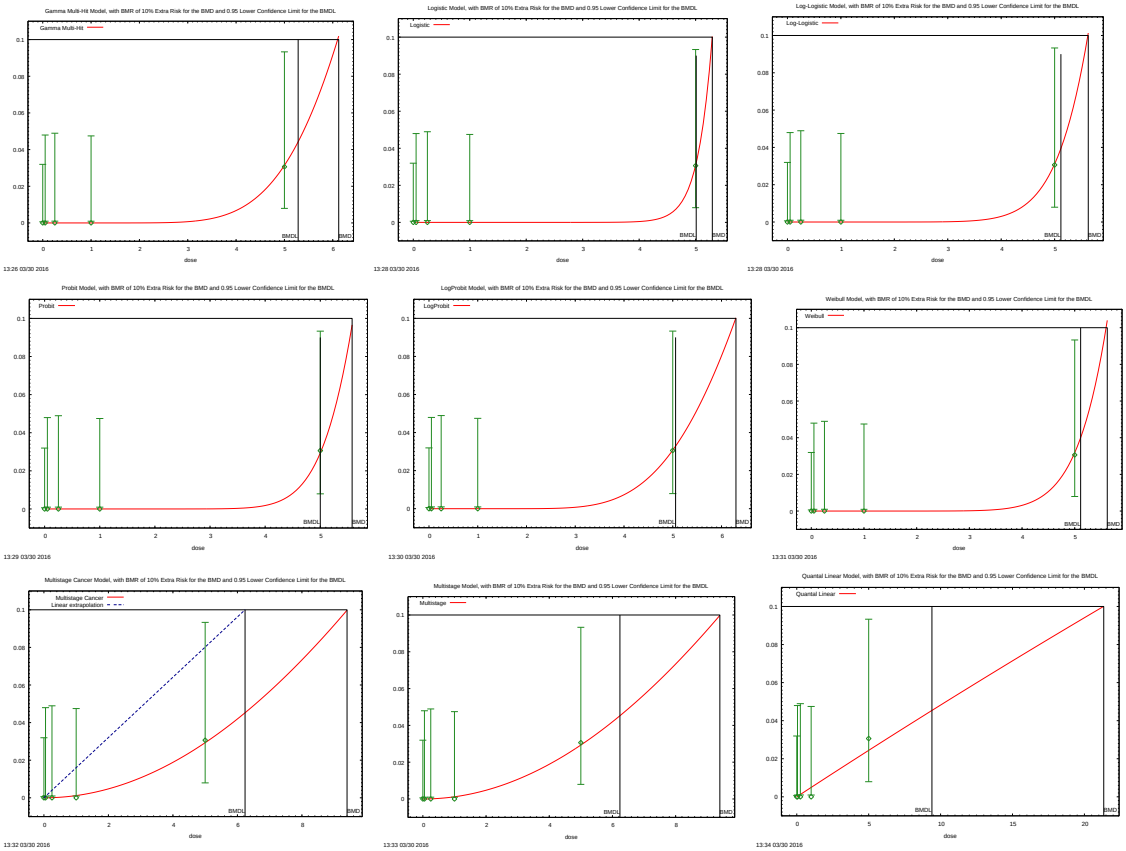


Table A10: Results from a BMD analysis of the data on incidences of **nasal squamous cell carcinomas** in **male rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD/ BMDL
Gamma	Extra	0.1	yes	1	yes	0.94	33.45	21.42	7.59	2.82
Logistic	Extra	0.1	na	2	yes	0.51	37.00	8.15	5.81	1.40
LogLogistic	**Extra**	**0.1**	**yes**	**1**	**yes**	**0.94**	**33.44**	**22.33**	**7.54**	**2.96**
Probit	Extra	0.1	na	2	yes	0.52	36.93	8.93	6.05	1.48
LogProbit	Extra	0.1	yes	2	yes	0.40	37.59	11.06	5.29	2.09
Weibull	Extra	0.1	yes	1	yes	0.94	33.45	21.42	7.45	2.88
Multistage Cancer	Extra	0.1	na	1	yes	0.94	33.45	*	*	
Multistage	Extra	0.1	yes	1	yes	0.94	33.45	*	*	
Quantal Linear	Extra	0.1	na	1	yes	0.94	33.35	21.42	9.43	2.27

* BMD computation failed. BMD is larger than three times maximum input doses.

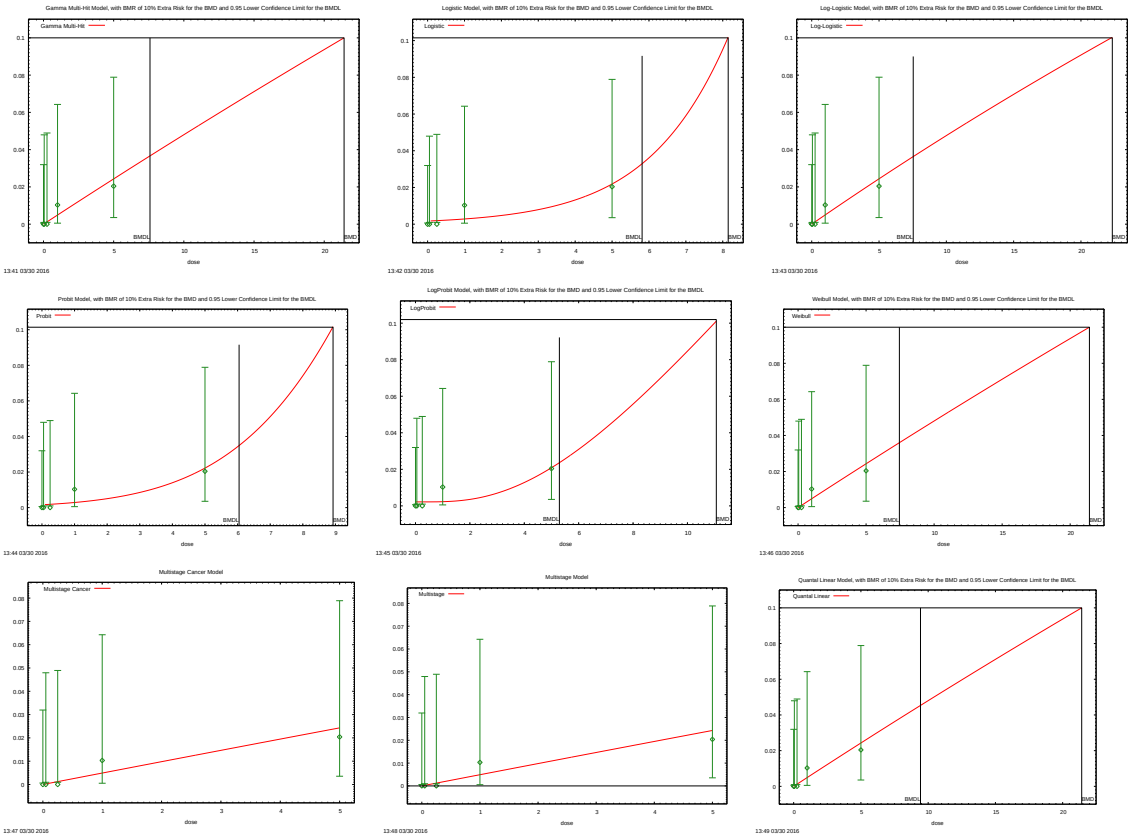


Table A11: Results from a BMD analysis of the data on incidences of **bronchial adenomas** (similar incidences) in **male rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD/ BMDL
Gamma	Extra	0.1	yes	2	**yes**	1.00	30.83	6.12	5.28	1.16
Logistic	Extra	0.1	na	2	**yes**	1.00	30.83	5.30	5.01	1.06
LogLogistic	Extra	0.1	yes	2	yes	1.00	30.83	5.63	5.12	1.10
Probit	Extra	0.1	na	2	yes	1.00	30.83	5.58	5.00	1.12
LogProbit	Extra	0.1	yes	2	yes	1.00	30.83	6.30	5.09	1.24
Weibull	Extra	0.1	yes	2	yes	1.00	30.83	5.62	5.11	1.10
Multistage Cancer	**Extra**	**0.1**	**na**	**1**	**yes**	**0.99**	**29.08**	**9.40**	**6.24**	**1.51**
Multistage	**Extra**	**0.1**	**yes**	**1**	**yes**	**0.99**	**29.08**	**9.40**	**6.24**	**1.51**
Quantal Linear	Extra	0.1	na	1	yes	0.85	30.21	21.35	9.40	2.27

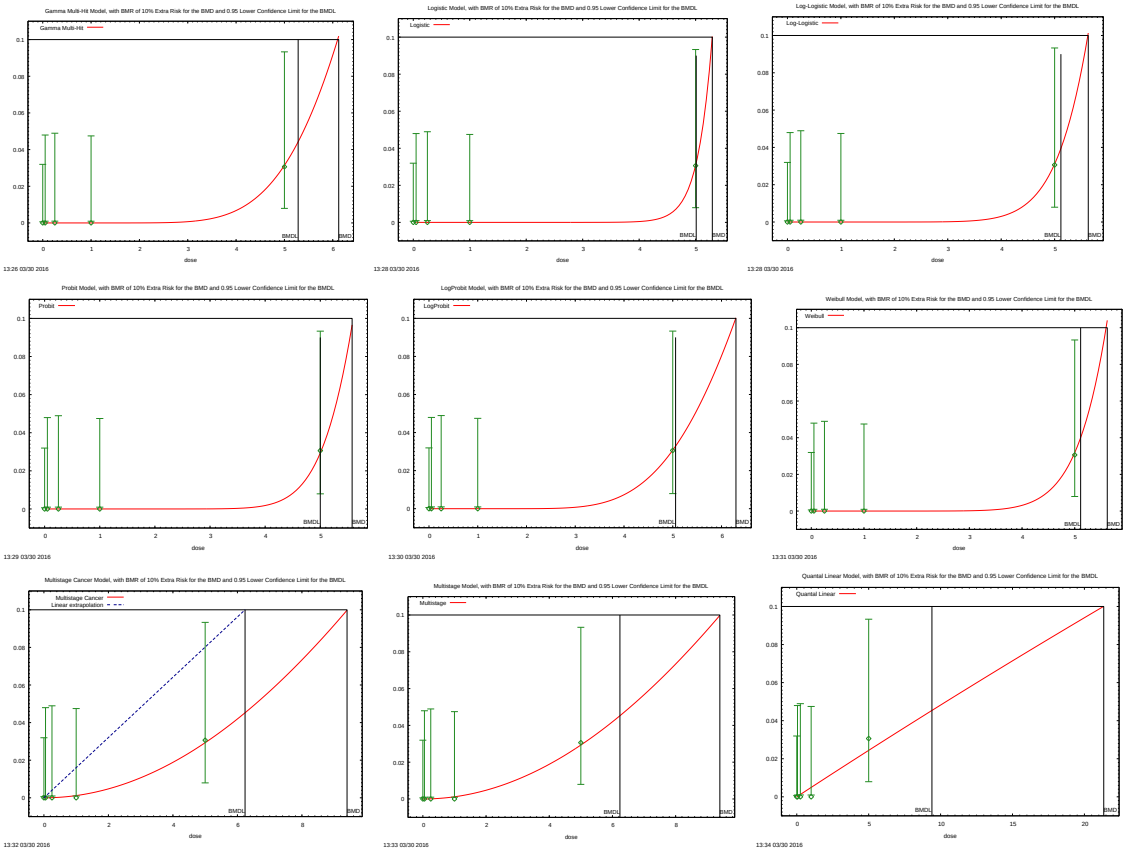
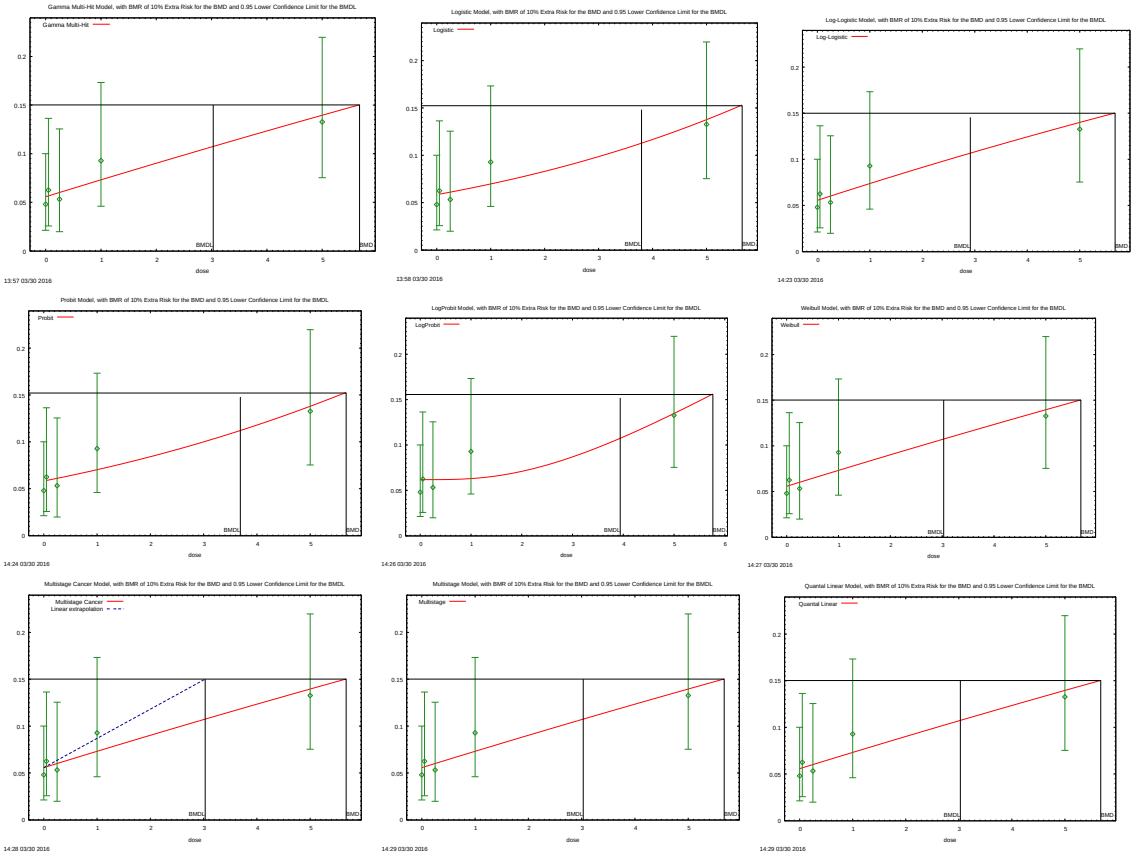


Table A12: Results from a BMD analysis of the data on incidences of **thyroid carcinomas** in **male rats** exposed to hydrazine by long intermittent exposure (6hr/day 5day/week) for 12 months followed by 18 month follow up without exposure (Vernot et al. 1985). The table presents the benchmark dose (BMD_{10}) and the 95 % benchmark dose lower confidence limit ($BMDL_{10}$) values for a BMR of 10% extra risk with characteristics of the model fit. The selected model (BMD/BMDL < 3, lowest AIC) is given in bold.

Model Type	Risk Type	BMFR	Restricted model	No of parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD/ BMDL
Gamma	Extra	0.1	yes	2	yes	0.83	281.66	5.68	3.03	1.87
Logistic	Extra	0.1	na	2	yes	0.76	281.97	5.66	3.80	1.49
LogLogistic	**Extra**	**0.1**	**yes**	**2**	**yes**	**0.84**	**281.63**	**5.67**	**2.92**	**1.94**
Probit	Extra	0.1	na	2	yes	0.77	281.93	5.67	3.69	1.54
LogProbit	Extra	0.1	yes	2	yes	0.58	282.73	5.77	3.94	1.46
Weibull	Extra	0.1	yes	2	yes	0.83	281.66	5.68	3.03	1.87
Multistage Cancer	Extra	0.1	na	2	yes	0.83	281.66	5.68	3.03	1.87
Multistage	Extra	0.1	yes	2	yes	0.83	281.66	5.68	3.03	1.87
Quantal Linear	Extra	0.1	na	2	yes	0.83	281.66	5.68	3.03	1.87



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