[Frontiers in Bioscience E4, 2071-2084, January 1, 2012]

Arylamine drugs: genotoxic-carcinogenic activity of NO-derivatives

Antonietta Martelli[1], Giovanni Brambilla[1]

[1]Department of Internal Medicine, Division of Clinical Pharmacology and Toxicology, University of Genoa, Viale Benedetto XV, 2, I-16132 Genoa, Italy

TABLE OF CONTENTS

1. ABSTRACT

This review provides information on arylamine drugs which have been tested for the formation of N-nitroso compounds (NOC) by reacting with nitrite, and on the genotoxic-carcinogenic effects of their nitrosation products. In an extensive search we have found that 109 arylamine drugs were examined for their ability to react with nitrite, and 105 of them (96.3%) were found to form NOC or in some cases other reactive species. Moreover, 78 arylamine drugs were examined in short-term genotoxicity tests and/or in long-term carcinogenicity assays, either in combination with nitrite or using their nitrosation product; 67 of them (85.9%) have been found to give at least one positive response. Only a small fraction, the 19.1% of theoretically nitrosatable arylamine drugs, has been examined for the possible formation of genotoxic-carcinogenic NOC, guidelines for genotoxicity testing of pharmaceuticals do not indicate the need of appropriate tests, and patients are not informed that the drug-nitrite interaction and the consequent risk can be reduced to a large extent by consuming the nitrosatable drug with ascorbic acid.

2. INTRODUCTION

N-nitroso compounds (NOC) are known for their capability of inducing the development of tumours in a large number of animal species (1). This suggests that they may also be carcinogenic to humans, even if a causal relationship between exposure to NOC and human cancer has not yet been rigorously established. In this respect it should be considered that to demonstrate in the human population such a relationship is difficult due to the exposure to low levels of NOC, to the limited sensitivity of epidemiological instruments, and to the lack of a truly unexposed population that can be used as control. Human exposure to NOC can be the consequence either to intake of preformed NOC or to endogenous formation of NOC *in vivo* from nitrosatable precursors and nitrosating agents. The chemistry of NOC formation has been previously extensively described (2,3). In brief, the formation of NOC requires the presence of a nitrosatable compound, acid and inorganic nitrite. The main site of the NOC endogenous synthesis is undoubtedly the stomach where after consumption of nitrite-rich meals the concentration of nitrite can reach 100-300 micromol/liter.

As reviewed by Mirvish (2), NOC can be also formed from aryl, diaryl and alkylaryl amines. As pharmacologists we are primarily concerned with the genotoxic-carcinogenic risk possibly linked to NOC generated *in vivo* by the nitrosation of pharmaceutical preparations. In the 2007 edition of Martindale –The Complete Drug Reference (4) are listed 570 aryl- , diaryl-, and alkylaryl-amine drugs. The aim of this review is to list which of these drugs have been found to form NOC by reacting with nitrite, and to indicate the genotoxic and carcinogenic effects of their nitrosation products.

3. DRUG-NITRITE INTERACTION PRODUCTS

Table 1 lists 109 arylamine drugs, representing a wide variety of chemical structures and therapeutic families, the large majority of which (96.3%) by reacting with nitrite have been found to form NOC or, in a few cases, other reactive species. For each drug is indicated the yield(s) of NOC as % of the theoretical one and, when it was identified, the NOC formed. Since the nitrosation of many drugs was investigated in various studies in different reaction conditions, for these drugs is indicated in the table the lowest and highest yield obtained in each of these studies. For each study the corresponding reference is indicated in parentheses. Because the yield of NOC depends not only on the chemical structure of the drug but also on the drug-nitrite molar ratio, pH, temperature and reaction time, the wide range of yields obtained for the same drug in different reaction conditions is not surprising. For most drugs the lowest yield was obtained in simulated *in vivo* conditions, and the highest yield when the reaction was carried out according to the nitrosation assay procedure of the WHO (5) or in even more favourable conditions. The WHO nitrosation assay procedure (NAP test) must conform to the following criteria: concentration of drug, 10 mM; concentration of nitrite, 40 mM; reaction temperature, 37°C; pH, 3-4; reaction times, 1 and 4 h. Obviously, the results so obtained do not allow a quantitative prediction of the nitrosation rate and yield in the stomach of a patient treated with a therapeutic dose of a nitrosatable drug that depend on substrates, catalysts and inhibitors, and are influenced by the stomach content, pH and several other factors.

4. GENOTOXIC AND CARCINOGENIC EFFECTS OF DRUG-NITRITE INTERACTION PRODUCTS

Table 2 lists the results of genotoxicity and/or carcinogenicity assays carried out with the arylamine drugs which have been found to form by reacting with nitrite a NOC or in some cases a different type of reactive species. *In vitro* assays were performed by treatment either with the nitrosation reaction mixture or directly with the NOC formed by the specific drug; in *in vivo* assays either the treatment with the drug and nitrite or the administration of the NOC formed by the drug were employed. Of the 78 drugs listed in Table 2, 66 formed a NOC that tested positive in at least one, and often in more than one, genotoxicity assay. Only 10 were tested for carcinogenicity, and 6 of them gave at least one positive response. However, it should be considered that the nitrosation of 28 drugs listed in Table 1 gave rise to one of the following well known carcinogenic NOC described in IARC Monographs (101) : N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosmorpholine, N-nitrosopiperidine, N-nitrosodipropylamine, or N-nitrosopyrrolidine.

5. DISCUSSION AND CONCLUSIONS

The large majority of NOC have been found to be genotoxic and carcinogenic; four NOC have been classified by the International Agency for Research on Cancer (IARC) as probably and other 15 as possibly carcinogenic to humans (102). In our extensive search we have found that 105 arylamine drugs have been found to form NOC or other reactive species (Table 1) and we cannot exclude that additional published and unpublished results exist. Certainly the number of theoretically nitrosatable arylamine drugs that have not been tested for their possible nitrosation to genotoxic-carcinogenic derivatives is very high.

Conditions suitable to nitrosation reactions are present in the human organism, mainly in the stomach where, after consumption of nitrite-rich meals, the concentration of nitrite can reach 100-300 micromol/liter. One of the major factors regulating the formation of NOC in the gastric environment is the concentration of nitrosating agents (N_2O_3, NO+, and ON-NCS) which are derived from nitrite ion (NO_2-) or nitrous acid (HNO_2). Gastric nitrite can be ingested directly with food or water, but most of it arises from enzymatic reduction of nitrate in saliva or gastric juice. Two distinct mechanisms of endogenous formation of NOC have been identified. The first, a direct chemical reaction between secondary amino compounds and nitrite, is strongly pH dependent and does not proceed rapidly at neutral pH. The second mechanism depends on direct bacterial catalysis of N-nitrosation and proceeds much more rapidly at neutral pH than the chemical reaction.

In spite of these possibilities, guidelines for genotoxicity testing of pharmaceuticals (103) do not indicate the need of performing adequate tests in order to assess whether a nitrosatable drug may undergo endogenous nitrosation to a genotoxic-carcinogenic NOC. The amounts of NOC formed in the human stomach are presumably very small, but it cannot be excluded that some arylamine drugs might yield a not negligible amount of genotoxic reaction product(s). According to Preussmann (104), the continuous exposure to a NOC leads to a linear dose-effect and dose-time relationship which do not indicate deviations from linearity at low doses; consequently there would be no indication of a no-effect level, and small single doses should be additive. In comparison to the dietary exposure to nitrosatable amines, that is normally below 100 mg/day, several nitrosatable arylamine drugs are used therapeutically at doses higher than 100 mg/day, and some non-prescription arylamine drugs at much higher doses, e.g. acetaminophen that can reach the daily dose of 4 g. Obviously the genotoxic-carcinogenic risk related to the endogenous drug nitrosation

Table 1. Arylamine drugs which have been tested for the formation of NOC by reaction with nitrite

Drug	Yield (% of the theoretical yield)[1]	NOC or other reactive species formed
Acetaminophen[2]	n.d[3]. (6)	4-acetylamino-6-diazo-2,4-cyclohexadienone
Acetohexamide[2]	5-6% (7)	
Alprenolol[2]	91% (8)	
Ambroxol[2]	< 0.001% (9)	
Aminopyrine[2]	< 0.001% (9), 55-65% (10), 13-55% (11), 87.5% (12), 31.4-71.4% (13), 48-73% (14), 9.4-10.8% (15), 1.6% (16), 76,5-87.5% (17), 0.01-47% (18), 43% (19), 0.0015-0.013% (20), 73% (21)	N-nitrosodimethylamine
Amitriptyline	0.003-0.006% (10), 0.06% (16), 0.05% (19)	N-nitrosodimethylamine
Ampicillin	0.06-5.5% (7), 5.5% (12), 3.7-5.5% (17), 0.06 (18), 0.007-0.057 (20)	
Antipyrin[2]	0-60.8% (13)	4-nitrosoantipyrine
Atenolol[2]	0.003-0.012% (20),7.45% (22)	N-nitrosoatenolol
Azapropazone	25-49% (7)	
Bamethan[2]	80% (8)	N-nitrosobamethan, 3-diazo- N-nitrosobamethan
Bephenium[2] hydroxynaftoate	0% (23)	
Bromazepam[2]	25% (24)	
Bromhexine[2]	0-0.02% (25), 0% (26), 0.1-47% (27), 0% (28)	N-nitroso-N-methyl-N-cyclohexylamine
Captodiame	0-0.7% (13)	N-nitrosodimethylamine
Carbamazepine	0.02-2% (29)	N-nitrosodibenzazepine
Carbidopa[2]	4-9% (7)	
Carpipramine[2]	2.9% (24)	
Cefadroxil[2]	18-19% (7)	
Chloramphenicol	5-6% (7)	
Chlordiazepoxide[2]	69-70% (7), 0.011-0.28% (18), 0.28% (19), 0.011% (20), 57.4% (24), 55% (30) 2.5-54.8% (31), 75% (32)	N-nitrosochlordiazepoxide
Chloroquine[2]	15% (7), 12-17% (23)	
Chlorphenoxamine	1-3% (7)	
Chlorpromazine[2]	0.5-1.2% (7), <0.001-0.002% (10), 0.05-0.88% (11), 0.4-1.7% (13), 0.005-0.23% (18), 0.23% (19), 0.0002-0.005% (20), 5.3% (24)	N-initrosodimethylamine, N-nitrosodesmethylchlorpromazine
Chlorpropamide	7% (7)	
Chlorprothixene[2]	14.21% (7), 43.4% (24)	
Chlortetracycline	0.007-3.7% (18), 3.7% (19), 0.007 (20), 0% (33)	N-nitrosodimethylamine
Chlorthalidone	0% (7), 0% (18)	
Cimetidine[2]	<0.001% (9), 90% (34)	N-nitrosocimetidine
Clomiphene	0% precipitate (7), 0% (16), 0.41% (19), 0.0004-0.008% (20)	N-nitrosodiethylamine
Clomipramine	<1% (12), 0.3-21.5% (15), 1-14.4% (17), 0.15% (19), 0.0035-0.017% (20)	N-nitroso-3-chlorodibenzazepine
Clonidine[2]	75% (8), 0.15% (20)	
Cloxacillin	0.2% (18), 0.018-0.21 (20)	
Cyclizine[2]	0.03-0.19% (18), 0.19% (19), 0.002-0.031% (20)	Dinitrosopiperazine
Demeclocycline	0% (33)	
Desipramine	10% (7), <1% (12), 2.8-10.9% (13), <0.4-35.5% (15), <1-27.5% (17)	N-nitrosodesipramine, N-nitrosodibenzazepine
Dextropropoxyphene[2]	0.003-0.16% (11)	N-nitrosodimethylamine
Diazepam[2]	7% (24)	
Diclofenac	1,21% (9)	
Diethazine	0-0.4% (13)	N-nitrosodiethylamine
Diltiazem[2]	15% (8), 0.2-2.4% (35)	
Dimenhydrinate	5-6% (7)	
Dimetofrine[2]	68-73% (7), 3-60% (36)	2,6-dimethoxy-1,4-benzoquinone
Diphenhydramine[2]	7-9% (7), <0.001% (10), 0.04% (19)	N-nitrosodimethylamine
Diphenylpyraline	0.21% (19)	
Dipyridamole[2]	19% (8), 0.024-0.11% (10)	N-nitrosopiperidine
Dipyrone[2]	0.61% (9), 100% (12), 16.8-22.5% (15), 75-100% (17)	N-nitrosodimethylamine and other NOC
Doxycycline	0% (16), 0.03-0.04% (33)	N-nitrosodimethylamine
Ephedrine[2]	62-68% (7), 30% (19), 0.016% (20)	N-nitrosoephedrine
Etilefrine[2]	23-30% + 5-35% (37)	N-nitrosoetilefrin + diazo-N-nitrosoetilefrin
Flufenamic acid	1.5% precipitate (7), 0.08% (19)	
Furosemide	50-52% (7)	
Gallopamil[2]	0.3-4.8% (35)	
Glyclopyramide	0.047-0.71 (10)	N-nitrosopyrrolidine

Hydralazine[2]	10-15% (7), 0% (8)	
Hydrochlorothiazide[2]	8% precipitate (7), < 0.001% (9) 64% (38)	4-nitrosohydrochlorothiazide
Hydroxyzine[2]	0.026% (20), 5.5% (24)	N,N'-dinitrosopiperazine and other NOC
Imipramine[2]	1-2% (7), 0.05-0.12% (10), <1% (12), 0.3-1.2% (13), <1-14.9% (17), 0.02-0.24% (18), 0.24% (19), 0.0003-0.02% (20), 0.1-2% (29)	N-nitrosodimethylamine, N-nitrosodesipramine, N-nitrosodihydrodibenzazepine
Indomethacin	0.01% (19)	
Iproniazid	0.51% (19), 0.0042-0.023% (20)	
Isoniazid[2]	28-30% (7)	
Isoxsuprine[2]	31% (8)	
Maprotiline[2]	2.2% (19), 0.003-0.02% (20)	
Mebendazole[2]	38-50% (23)	
Mefenamic acid	15% precipitate (7)	
Methadone[2]	0.04-0.18% (11)	N-nitrosodimethylamine
Methamphetamine[2]	94% (39)	N-nitrosomethamphetamine
Metoclopramide[2]	5-9% (7)	
Metoprolol[2]	34-57% (7), 3.8% (19), 0.01% (20), 5.85% (22)	N-nitrosometoprolol
Minocycline	11% (10), 34% (19), 0.021% (20), 0.021-34% (23), 0.05-2% (33)	N-nitrosodimethylamine
Nadolol[2]	12-19% (7), 5.95% (22)	N-nitrosonadolol
Nicardipine[2]	6.2-36.6% (35)	
Nifedipine[2]	38.8-40.0% (35)	
Niketamide	0.1% (21)	N-nitrosodiethylamine
Nimodipine[2]	9.9-44.6% (35)	
Nitrendipine[2]	28.7-44.0% (35)	
Nortriptilyne	0.012-9.8% (18), 9.8% (19), 0.0007-0.012% (20)	
Oxprenolol[2]	9.60% (22)	N-nitrosooxprenolol
Oxytetracycline[2]	0.35-1.3% (10), 0.3-15% (11), 0.6-63.2% (13), 0% (16), 0.005-2.7% (18), 2.7% (19), 0.005% (20), 0.08% (33), 44-63% (40)	N-nitrosodimethylamine
Phenacetin[2]	0.4-7% (41)	N-nitroso-2-nitro-4-ethoxyacetanilide
Phenelzine[2]	24-39% (7)	
Phenmetrazine[2]	0.13% (9)	N-nitrosophenmetrazine
Phenobarbital	3% precipitate (7)	
Phenoxymethyl-penicillin	54.9% (12), 2.6-5.2% (15), 39.0-54.9% (17), 0.5-6.8% (18), 6.8% (19), 0.039-0.51% (20)	
Phenylpropanolamine	0.0016-0.01% (20)	
Phenytoin	3-20% (7), 0-0.12% (18), 0.12% (19)	
Pindolol	0.14% (18), 14% (19)	
Pirenzepine	0% (7)	
Probenecid	<0.001% (10), 0% (18)	N-nitrosodiethylamine, N-nitrosodipropylamine
Procainamide[2]	75-100% (7), <0.001% (10)	N-nitrosodiethylamine
Proglumide	0.007-0.009% (10)	N-nitrosodipropylamine
Promethazine	5-6% (7), 0.055-0.27% (10), 0.011-2% (18), 2% (19), 0.0007-0.011% (20)	N-nitrosodimethylamine
Propranolol[2]	58-71% (7), <0.001 (9), 6-7% (22), 94% (8), 0.015-29% (18), 29% (19), 0.0066-0.015% (20), 0.003-45% (42,43), 0.03-10.78% (44), 0.04-12.44% (45)	N-nitrosopropranolol
Protriptyline	3.4-11.6% (13)	N-nitrosoprotriptyline
Ranitidine[2]	16-22% (7), 89.1% (46)	N-nitroso-nitrolic acid derivative of ranitidine
Rifampicin	n.d. (7)	
Sotalol[2]	9.25% (22)	N-nitrososotalol
Sulphadimidine[2]	22% (47)	1,3-di(4-[N-dimethyl-2-pyrimidinyl)-sulfamoylphenyl]triazene
Tetracycline[2]	n.d. (7), 2.6% (19), 0.007% (20), 0% (33)	N-nitrosodimethylamine
Thioproperazine	0.003-0.013% (10)	N-nitrosodimethylamine, N-nitroso-N'-methylpiperazine
Timolol	0.035-8.8% (18), 8.8% (19), 0.0011-0.030% (20)	N-nitrosomorpholine
Tolazamide[2]	0% precipitate (7), 1.9-7% (10), 0.6-3.4% (11)	N-nitrosohexamethyleneimine, N-nitrosopiperidine
Tolazoline[2]	1-2% (7), 0.01% (19)	
Tolbutamide[2]	0.59% (19), 0-43% (38)	3'-Nitrosotolbutamide
Triflupromazine	0.5-0.8% (7)	
Trimipramine	<0.001% (9), 0.1-4% (29)	N-nitrosodibenzazepine, N-nitrosodihydrodibenzazepine
Tripelennamine[2]	9-14% (7), 0.7-5.8% (13)	N-nitrosodesmethyltripelennamine
Triprolidine	<0.001-0.001% (10)	N-nitrosopyrrolidine
Verapamil[2]	0.1-1.8% (35)	

[1] Data are followed by the corresponding references in parentheses. When more than one yield is reported, the data indicate the different yields obtained in different experimental conditions. [2] The genotoxic and/or carcinogenic effects of the drug-nitrite reaction products are reported in Table 2. [3] n.d. : not determined

Table 2. Genotoxic and carcinogenic effects of arylamine drugs-nitrite reaction products

Drug and test system(s)	Dose (LED or HID)[1]	Result[2]	Reference
Acebutolol			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (12.6 mg/ml)	+	(48)
Acetaminophen[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (0.5 µmol/plate of parent drug)	+	(6)
Acetohexamide[3]			
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitrosoderivative(s) 18.1 µM	+	(7)
Alprenolol[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	-	(8)
Ambroxol[3]			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (0.48 mg/ml)	(+)	(48)
Aminopyrine[3]			
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, reverse mutation	Nitrosation reaction mixture (1 mg of parent drug)	-	(49)
S. typhimurium TA100, reverse mutation	Aminopyrine 0.25 µmol/plate + $NaNO_2$ 72,5 µmol/plate preincubated in human gastric juice	+	(50)
S. typhimurium G46, host-mediated assay	Aminopyrine 0.2 mmol/kg + $NaNO_2$ 0.2 mmol/kg p.o.	+	(51)
DNA strand breaks, rat liver *in vivo*	Aminopyrine 320 mg/kg +$NaNO_2$ 80 mg/kg p.o.	(+)	(52)
Long-term carcinogenesis assay, rats	Aminopyrine 250 ppm + $NaNO_2$ 250 ppm in drinking water	+ (liver tumours)	(53,54)
Long-term carcinogenesis assay, rats	Aminopyrine 1000 ppm + $NaNO_2$ 1000 ppm in drinking water	+ (liver tumours)	(55)
Long-term carcinogenesis assay, hamsters	Aminopyrine 1000 ppm + $NaNO_2$ 1000 ppm in drinking water	+	(56)
Transplacental carcinogenesis assay, induction of 8-AG resistant mutants in embryo cells	Aminopyrine 25 mg/kg + $NaNO_2$ 25 mg/kg p.o.	+	(57)
Hepatotoxicity in rats	Aminopyrine 0.4 mmol/kg + $NaNO_2$ 1.0 mmol/kg p.o.	+	(58)
Binding covalent to rat DNA *in vivo*	*d6*-Aminopyrine 100 mg/kg + $NaNO_2$ 100 mg/kg p.o.	+	(59)
Binding covalent to rat liver DNA *in vivo*	14C-Aminopyrine 140 mg/kg + $NaNO_2$ 80 mg/kg p.o.	+	(60)
Amlodipine			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (0.12 mg/ml)	(+)	(48)
Antipyrin[3]			
S. typhimurium TA97, TA98, TA100, TA102, TA104, reverse mutation	N-nitrosoantipyrine (62.5 nmol/plate)	+	(61)
Atenolol[3]			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (0.70 mg/ml)	(+)	(48)
DNA strand breaks, Chinese hamster lung V79 cells *in vitro*	N-nitrosatenolol 1.0 mM	-	(22)
DNA strand breaks, rat primary hepatocytes	N-nitrosoatenolol 0.1 mM	+	(22)
UDS, rat primary hepatocytes	N-nitrosoatenolol 0.3 mM	+	(22)
DNA strand breaks, human primary hepatocytes	N-nitrosoatenolol 1.0 mM	+	(22)
UDS, human primary hepatocytes	N-nitrosoatenolol 0.1 mM	+	(22)
Micronucleus test, rats *in vivo*	N-nitrosoatenolol 1.0 g/kg p.o	-	(62)
Micronucleus test, rat spleen cells *in vivo*	N-nitrosoatenolol 1.0 g/kg p.o	-	(62)
Micronucleus test, rat liver cells *in vivo*	N-nitrosoatenolol 1.0 g/kg p.o	+	(62)
Bamethan[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	+	(8)
Bephenium hydoxynaphthoate[3]			
S. typhimurium TA1535, reverse mutation	Nitrosation reaction mixture drug-nitrite molar ratio 1/1.3)	-	(23)
S. typhimurium TA1535, reverse mutation	Mutagenicity of urine from mice given 1000 mg/kg bephenium hydroxynaphthoate + 80 mg/kg NaNO2	-	(63)
Bromazepam[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	+	(24)
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (1.50 mg/ml)	+	(48)
Bromhexine[3]			
Binding covalent to DNA, rat cells *in vivo*	Bromhexine 30 mg/kg + NaNO2 30 mg/kg p.o.	+	(28)
Binding covalent to DNA, in humans	d3-Bromhexine 48 mg p.o.	-	(64)
Carbidopa[3]			
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitroso derivative(s) 214 µM	+	(7)
Carpipramine[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	+	(24)
Cefadroxil[3]			
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitrosoderivative(s) 610 µM	+	(7)
Cefalexin[1]			
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitrosoderivative(s) 330 µM	+	(7)
Chlordiazepoxide[3]			

S. typhimurium TA98, TA100, reverse mutation	Nitrosation product reaction mixture (1 µmol of parent drug)	(+)/+	(24)
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, reverse mutation	Nitrosation reaction mixture (1 mg of parent drug)	+	(49)
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (10 µg/ml)	+	(48)
DNA strand breaks, Chinese hamster lung V79 cells *in vitro*	N-nitrosochlordiazepoxide 33 µM	+	(30)
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitroso derivative(s) 229 µM	+	(7)
DNA strand breaks, rat primary hepatocytes	N-nitrosochlordiazepoxide 33 µM	+	(30)
UDS, rat primary hepatocytes	N-nitrosochlordiazepoxide 100 µM	+	(30)
Gene mutation, Chinese hamster lung V79 cells, *hprt* locus	N-nitrosochlordiazepoxide 100 µM	+	(30)
DNA strand breaks, human primary hepatocytes	N-nitrosochlordiazepoxide 100 µM	+	(30)
UDS, human primary hepatocytes	N-nitrosochlordiazepoxide 100 µM	+	(30)
*Saccharomyces cerevisia,*mitotic gene conversion, host-mediated assay	N- nitrosochlordiazepoxide 0.05 mmol/kh i.v.	+	(65)
DNA strand breaks, rat liver *in vivo*	Chlordiazepoxide 0.14 mmol/kg + $NaNO_2$ 1.16 mmol/kg p.o.	+	(66)
DNA strand breaks, rat liver *in vivo*	N.nitrosochlordiazepoxide 0.012 mmol/kg p.o.	+	(66)
DNA strand breaks, rat gastric mucosa *in vivo*	N.nitrosochlordiazepoxide 0.024 mmol/kg p.o.	+	(66)
DNA strand breaks, rat brain	N.nitrosochlordiazepoxide 0.024 mmol/kg p.o.	+	(66)
Long-term carcinogenesis assay, mice	N-nitrosochlordiazepoxide 6.2 mg/kg/day in drinking water	-	(67)
Long-term carcinogenesis assay, rats	Chlordiazepoxide 2000 ppm + $NaNO_2$ ppm in drinking water	(+) (tumors of nervous system and other organs)	(55,68)
Chloroquine[3]			
S. typhimurium TA1535, reverse mutation	Nitrosation reaction mixture (drug/nitrite molar ratio 1/2.6)	+	(23)
S. typhimurium TA1535, reverse mutation	Mutagenicity of urine from mice given 55 mg/kg chloroquine + 80 mg $NaNO_2$ p.o.	+	(63)
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitrosoderivative(s) 495 µM	+	(7)
Chlorpromazine[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	(+)/+	(24)
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, reverse mutation	Nitrosation reaction mixture (25 µg of parent drug)	(+)	(49)
Long-term carcinogenesis assay, rats	Chlorpromazine 1000 ppm + NaNO2 2000 ppm in drinking water	-	(55)
Chloprothixene[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	(+)/+	(24)
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitroso derivative(s) 28.9 µmol	+	(7)
Cimetidine[3]			
S. typhimurium TA100, reverse mutation	Cimetidine 0.62 mg + $NaNO_2$ 5 mg preincubated in human gastric juice	+	(69)
S. typhimurium TA98, TA1535, TA1537, TA1538, reverse mutation	Cimetidine 20 mg + NaNO2 5 mg preincubated in human gastric juice	+	(69)
S. typhimurium TA1535, reverse mutation	N-nitrosocimetidine 0.5 µM	+	(70)
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (12.80 mg/ml)	(+)	(48)
DNA strand breaks, mouse epithelial cell line *in vitro*	N-nitrosocimetidine 0.5 mM	+	(71)
Gene mutation, BHK-21/CL13 cells, ouabain resistance	N-nitrosocimetidine 10 µM	+	(72)
SCE, Chinese hamster ovary cells *in vitro*	N-nitrosocimetidine 0.12 µM	+	(73)
SCE, Chinese hamster ovary cells *in vitro*	Dinitrosocimetidine 0.1 µM	+	(74)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	N-nitrosocimetidine 0.12 µM	+	(74)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	Dinitrosocimetidine 0.01 µM	+	(74)
Cell transformation, BHK cells	N-nitrosocimetidine 20 µM	+	(72)
DNA strand breaks, human lymphoblastoid cell line *in vitro*	N-nitrosocimetidine 1.0 mM	+	(75)
UDS, human lymphocytes *in vitro*	N-nitrosocimetidine 0.18 mM	+	(75)
SCE, human lymphocytes *in vitro*	N-nitrosocimetidine 9.4 µM	+	(76)
DNA strand breaks, rat liver *in vivo*	Cimetidine 250 mg/kg + NaNO2 80 mg/kg/day p.o. x 20 days	-	(77)
DNA strand breaks, rat gastric mucosa	Cimetidine 250 mg/kg + NaNO2 80 mg/kg/day p.o. x 20 days	-	(78)
Long-term carcinogenesis assay, mice	N-nitriosocimetidine 1130 ppm in drinking water	+ (lung tumours)	(34)
Long-term carcinogenesis assay , mice	Cimetidine 1130 ppm + NaNO2 1840 ppm in drinking water	+ (lung tumours)	(34)
Long-term carcinogenesis assay, rats	N-nitrosocimetidine 0.5 mM in drinking water	-	(79)

Long-term carcinogenesis assay, rats	N-nitrosocimetidine 500 mg/kg p.o., twice weekly	-	(80)
Binding covalent to DNA *in vitro*	[14 C] N-nitrosocimetidine 80µM	+	(72)
Binding covalent to DNA *in vitro*	N-nitrosocimetidine 10 mM	+	(81)
Binding covalent to rat DNA *in vitro*	*d3*-N-nitrosocimetidine 5 mM	+	(59)
Binding covalent to rat DNA *in vivo*	*d3*-N-nitrosocimetidine 2.5 mg/kg p.o.	-	(59)
Binding covalent to rat DNA *in vivo*	Cimetidine 25 mg/kg + NaNO2 25 mg/kg p.o.	-	(59)
Binding covalent to rat DNA *in vivo*	Cimetidine 70 mg/kg + NaNO2 38 mg/kg p.o. twice weekly x 3 days	-	(82)
Binding covalent to rat DNA *in vivo*	14C-nitrosocimetidine 0.135 mmol/kg i.v.	(+)	(83)
Binding covalent to rat DNA *in vivo*	14C-nitrosocimetidine 0.20 mmol/kg p.o.	+	(84)
Clonidine[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	+	(8)
Cyclizine[3]			
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, reverse mutation	Nitrosation reaction mixture (0.1 mg of parent drug	+	(49)
Long-term carcinogenesis assay, rats	Cyclizine 1000 ppm + $NaNO_2$ 2 ppm in drinking water	-	(55)
Dextropropoxyphene[3]			
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, reverse mutation	Nitrosation reaction mixture (1 mg of parent drug)	(+)	(49)
Diazepam[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	(+)	(24)
Diltiazem[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	(+)/+	(8)
DNA strand breaks, rat liver *in vivo*	Diltiazem 280 mg/kg + $NaNO_2$ 80 mg/kg p.o.	(+)	(35)
Dimetofrine[3]			
DNA strand breaks, Chinese hamster lung V79 cells *in vitro*	2,6-Dimethoxy-1,4-benzoquinone 10 µM (nitrosation product of dimethofrine)	+	(85)
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitroso derivative 233 µM	+	(7)
DNA strand breaks, rat primary hepatocytes	2,6,Dimethoxy-1,4-benzoquinone 10 µM	+	(85)
UDS, rat primary hepatocytes	2,6-Dimethoxy-1,4-benzoquinone 20 µM	+	(85)
Gene mutation, Chinese hamster lung V79 cells, *hprt* locus	2,6-Dimethoxy-1,4-benzoquinone 10 µM	+	(85)
DNA strand breaks, rat liver *in vivo*	2,6-Dimethoxy-1,4-benzoquinone 300 mg/kg p.o.	-	(85)
DNA strand breaks, rat kidney *in vivo*	2,6-Dimethoxy-1,4-benzoquinone 33 mg/kg p.o.	+	(85)
DNA strand breaks, rat gastric mucosa *in vivo*	2,6-Dimethoxy-1,4-benzoquinone 33 mg/kg p.o.	+	(85)
DNA strand breaks, rat brain *in vivo*	2,6-Dimethoxy-1,4-benzoquinone 33 mg/kg p.o.	+	(85)
Diphenhydramine[3]			
S. typhimurium TA98, TA100, TA1535, TA1538, reverse mutation	Nitrosation reaction mixture (250 µg of parent drug)	(+)	(86)
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitrosoderivative(s) 264 µM	+	(7)
Dipyridamole[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	-	(8)
Dipyrone[3]			
S. typhimurium TA98, TA100, reverse mutation	4-(N-methyl-N-nitroso)amino- antipyrine (10 mg/plate)	(+)	(87)
S. typhimurium TA98, TA100, reverse mutation	1-diketobutirryl-1-phenyl-2-methyl-2-nitrosohydrazide (1 mg/plate)	(+)	(87)
S. typhimurium, G49, host mediated assay	Dipyrone 2 mmol/kg + NaNO2 2 mmol/kg p.o.	(+)	(51)
Enalapril			
S. typhimurium TA1535 *umu*-test	Drug-nitrite interaction product (1.12 mg/ml)	+	(48)
Ephedrine[3]			
S. typhimurium TA98, TA100, reverse mutation	N-nitrosoephedrine (50/500 µg/plate)	+	(39)
S. typhimurium TA1535 *umu*-test	Drug-nitrite interaction product (1.0 mg/ml)	(+)	(48)
Long-term carcinogenesis assay, mice	N-nitrosoephedrine 200 mg/kg 3x, i.p	+ (liver cells carcinomas)	(88)
Long-term carcinogenesis assay, rats	N-nitrosoephedrine 120 mg/kg twice weekly p.o.	+ (liver, lung and forestomach tumours)	(89)
Long-term carcinogenesis assay, rats	Ephedrine 80 mg/kg + NaNO2 50 mg/kg twice weekly p.o.	?	(90)
Long-term carcinogenesis assay, rats	Ephedrine 5000 ppm + NaNO2 2000 ppm in diet x 50 days	?	(90)
Etilefrine[3]			
S. typhimurium TA98, TA100, reverse mutation	Diazo-N-nitrosoetilefrine (0.1 µmol/plate)	+	(8)
Fluoxetine			
S. typhimurium TA1535 *umu*-test	Drug-nitrite interaction product (60 µg/ml)	+	(48)
Folic acid			
Long-term carcinogenesis assay, mice	Nitrosofolic acid 125 mg/kg 3x, i.p.	(+) (lung adenocarcinoma)	(88)
Gallopamil[3]			
DNA strand breaks, rat liver *in vivo*	Gallopamil 54 mg/kg + NaNO2 80 mg/kg p.o.	+	(35)

Hydralazine[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 mmol of parent drug)	+	(8)
Hydrochlorothiazide[3]			
S. typhimurium TA98, TA100, TA1535, TA1538, reverse mutation	Nitrosation reaction mixture (1 mg of parent drug)	(+)	(86)
Hydroxyzine[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	(+)	(24)
Imipramine[3]			
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitrosoderivative(s) 4.95 µM	+	(7)
Isoniazid[3]			
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitrosoderivative(s) 957 µM	+	(7)
Isoxsuprine[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	+	(8)
Maprotiline[3]			
S. typhimurium TA1535, *umu*-test	N-nitrosomaprotiline (76 µg/ml)	(+)	(48)
Mebendazole[3]			
S. typhimurium TA1535, reverse mutation	Nitrosation reaction mixture (drug nitrite molar ratio 1/4.6)	+	(23)
Methadone[3]			
S. typhimurium TA98, TA100, TA1535, TA1538, reverse mutation	Nitrosation reaction mixture (1 mg of parent drug)	-	(49)
Methamphetamine[3]			
S. typhimurium TA98, TA100 reverse mutation	N-nitrosomethamphetamine (50 µg/plate)	+	(39)
Metoclopramide[3]			
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N- nitrosoderivative(s) 231 µM	+	(7)
Metoprolol[3]			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (0.60 mg/ml)	(+)	(48)
DNA strand breaks, Chinese hamster lung V79 cells *in vitro*	N-nitrosometoprolol 1.0 mM	-	(22)
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitrosoderivative(s) 1.5 mM	+	(7)
DNA strand breaks, rat primary hepatocytes	N-nitrosometoprolol 0.1 mM	+	(22)
UDS, rat primary hepatocytes	N-nitrosometoprolol 1.0 mM	+	(22)
DNA strand breaks, human primary hepatocytes	N-nitrosometoprolol 0.1 mM	+	(22)
UDS, human primary hepatocytes	N-nitrosometoprolol 0.3 mM	+	(22)
Micronucleus test, rats *in vivo*	N-nitrosometoprolol 1.0 g/kg p.o.	-	(62)
Micronucleus test, rat spleen cells *in vivo*	N-nitrosometoprolol 1.0 g/kg p.o.	-	(62)
Micronucleus test, rat liver cells *in vivo*	N-nitrosometoprolol 1.0 g/kg p.o.	+	(62)
Nadolol[3]			
DNA strand breaks, Chinese hamster lung V79 cells *in vitro*	N-nitrosonadolol 10 mM	-	(22)
DNA strand breaks, rat primary hepatocytes	N-nitrosonadolol 1.0 mM	+	(22)
UDS, rat primary hepatocytes	N-nitrosonadolol 1.0 mM	+	(22)
DNA strand breaks, human primary hepatocytes	N-nitrosonadolol 3.0 mM	+	(22)
UDS, human primary hepatocytes	N-nitrosonadolol 3.0 mM	+	(22)
Micronucleus test, rats *in vivo*	N-nitrosonadolol 1.0 g/kg p.o.	-	(62)
Micronucleus test, rat spleen cells *in vivo*	N-nitrosonadolol 1.0 g/kg p.o.	-	(62)
Micronucleus test, rat liver cells *in vivo*	N-nitrosonadolol 1.0 g/kg p.o.	+	(62)
Nicardipine[3]			
DNA strand breaks, rat liver *in vivo*	Nicardipine 317 mg/kg + NaNO2 80 mg/kg p.o.	(+)	(35)
Nifedipine[3]			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (70 µg/ml)	(+)	(48)
DNA strand breaks, rat liver *in vivo*	Nifedipine 511 mg/kg + NaNO2 80 mg/kg p.o.	+	(35)
Nimodipine[3]			
DNA strand breaks, rat liver *in vivo*	Nimodipine 1369 mg/kg + NaNO2 80 mg/kg p.o.	+	(35)
Nitrendipine[3]			
DNA strand breaks, rat liver *in vivo*	Nitrendipine 1 g /kg + NaNO2 80 mg/kg p.o.	+	(35)
Oxprenolol[3]			
DNA strand breaks, Chinese hamster lung V79 cells *in vitro*	N-nitrosooxprenolol 3.0 mM	-	(22)
DNA strand breaks, rat primary hepatocytes	N-nitrosooxprenolol 0.1 mM	+	(22)
UDS, rat primary hepatocytes	N-nitrosooxprenolol 0.3 mM	+	(22)
DNA strand breaks, human primary hepatocytes	N-nitrosooxprenolol 0.3 mM	+	(22)
UDS, human primary hepatocytes	N-nitrosooxprenolol 0.3 mM	+	(22)
Gene mutation, Chinese hamster lung V79 cells, *hprt* locus	N-nitrosooxprenolol 0.03 mM	+	(91)

Gene mutation, Chinese hamster lung V79 cells, ouabain resistance	N-nitrosooxprenolol 0.1 mM	-	(91)
Micronucleus test, mice *in vivo*	N-nitrosooxprenolol 1.0 g/kg p.o.	+	(91)
Micronucleus test, mice spleen cells *in vivo*	N-nitrosooxprenolol 1.0 g/kg p.o.	+	(91)
Micronucleus test, mice liver cells *in vivo*	N-nitrosooxprenolol 1.0 g/kg p.o.	+	(91)
Oxytetracycline[3]			
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, reverse mutation	Nitrosation reaction mixture (0.2 µg of parent drug)	(+)	(49)
Long-term carcinogenesis assay, rats	Oxytetracycline 1000 pppm + NaNO2 1000 ppm in drinking water	+ (liver tumours)	(55)
Paroxetine			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (1.40 mg/ml)	+	(48)
Phenacetin[3]			
S. typhimurium TA98, TA100, TA1535, TA1538, reverse mutation	N-nitrosophenacetin (0,1 µg/plate)	+	(92)
Phenelzine[3]			
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitrosoderivative(s) 1.04 mM	+	(7)
Phenmetrazine[3]			
Long-term carcinogenesis assay, rats	N-nitrosophenmetrazine 180 ppm in drinking water	-	(93)
Primaquine			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (primaquine 5.5.mM + NaNO2 5 mM)	+	(94)
E.coli WP2*uvrA*/pKM101 reverse mutation	Nitrosation reaction misture (100 µg of parent drug/plate)	+	(94)
Procainamide[3]			
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitrosoderivative(s) 2.89 mM	+	(7)
Propranolol[3]			
S. typhimurium TA92, TA98, TA100, TA1535, TA1537, TA1538, reverse mutation	N-nitrosopropranolol (1.4 µmol/plate)	-	(43)
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (1 µmol of parent drug)	(+)	(43)
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (0.16 mg/ml)	+	(48)
DNA strand breaks, Chinese hamster lung V79 cells *in vitro*	N-nitrosopropranolol 1.0 mM	-	(22)
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitroso derivative(s) 213 µM	+	(7)
DNA strand breaks, rat primary hepatocytes	N-nitrosopropranolol 0.03 mM	+	(22)
UDS, rat primary hepatocytes	N-nitrosopropranolol 0.1 mM	+	(22)
DNA strand breaks, human primary hepatocytes	N-nitrosopropranolol 0.03 mM	+	(22)
UDS, human primary hepatocytes	N-nitrosopropranolol 0.03 mM	+	(22)
Micronucleus test, rats *in vivo*	N-nitrosopropranolol 1.0 g/kg p.o.	-	(62)
Micronucleus test, rat spleen cells *in vivo*	N-nitrosopropranolol 1.0 g/kg p.o.	-	(62)
Micronucleus test, rat liver cells *in vivo*	N-nitrosopropranolol 1.0 g/kg p.o.	+	(62)
Pseudoephedrine			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (1.68 mg/ml)	+	(86)
Pyrimethamine			
E.coli WP2*uvrA*/pKM101 reverse mutation	Nitrosation reaction mixture (250 µg of parent drug/plate)	-	(94)
Ranitidine[3]			
S. typhimurium TA97, TA98, TA100, TA1535, TA1537, TA1538, reverse mutation	Nitrosation reaction mixture (0.3 mg ranitidine + 5 mg NaNO2)	(+)	(95)
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (3 mM ranitidine + 13m mM NaNO2)	+	(96)
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (4.0 mg/ml)	+	(48)
*E.coli,*WP2, WP2 *uvrA,*reverse mutation	Nitrosation reaction mixture (0.3 mg ranitidine + 5 mg NaNO2)	+	(95)
Saccharomyces cerevisiae, gene	Nitrosation reaction mixture (ranitidine 3 mM + NaNO2 13 mM)	+	(96)
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitroso derivative(s) 627 µM	+	(7)
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitrosoranitidine 0.27 mM	+	(46)
UDS, rat primary hepatocytes	N-nitrosoranitidine 16-22 µM	+	(97)
DNA strand breaks, rat liver *in vivo*	Ranitidine 175 mg/kg + NaNO2 80 mg/kg p.o.	+	(98)
DNA strand breaks, rat gastric mucosa *in vivo*	Ranitidine 175 mg/kg + NaNO2 80 mg/kg p.o.	+	(98)
SCE, mice bone-marrow cells *in vivo*	Ranitidine 175 mg/kg + NaNO2 80 mg/kg p.o.	+	(98)
Salbutamol			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (80 µg/ml)	(+)	(48)
Sertraline			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (0.14 mg/ml)	-	(48)
Sotalol[3]			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (6.0 mg/ml)	(+)	(48)
DNA strand breaks, Chinese hamster lung V79 cells, *in vitro*	N-nitrososotalol 1.0 mM	+	(22)
DNA strand breaks, rat primary hepatocytes	N-nitrososotalol 0.3 mM	+	(22)

UDS, rat primary hepatocytes	N-nitrososotalol 0.3 mM	+	(22)
DNA strand breaks, human hepatocytes	N-nitrososotalol 3 mM	+	(22)
UDS, human primary hepatocytes	N-nitrososotalol 3 mM	+	(22)
Micronucleus test, rats *in vivo*	N-nitrososotalol 1000 mg/kg p.o.	-	(62)
Micronucleus test, rat spleen cells *in vivo*	N-nitrososotalol 1000 mg/kg p.o.	-	(62)
Micronucleus test, rat liver cells *in vivo*	N-nitrososotalol 1000 mg/kg p.o.	+	(62)
Sulfadimidine[3]			
S. typhimurium TA97, TA98, TA100, reverse mutation	Nitrosation reaction product (1 mg/plate)	-	(47)
Drosophila melanogaster, somatic mutation	Nitrosation reaction product (10 mM)	-	(47)
Drosophila melanogaster, recombination test	Nitrosation reaction product (10 mM)	-	(47)
Terbutaline			
S. typhimurium TA1535, *umu*-test	Drug-nitrite interaction product (80 µg/ml)	+	(48)
Tetracycline[3]			
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (0,5 µg tetracycline + 200 µg NaNO2/plate)	(+)	(99)
Thenyldiamine			
S. typhimurium TA98, TA100, TA1535, TA1538, reverse mutation	Nitrosation reaction mixture (1 mg of parent drug)	-	(86)
S. typhimurium TA98, TA100, reverse mutation	Nitrosation reaction mixture (0.5 mg of parent drug)	-	(100)
Tolazamide[3]			
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, reverse mutation	Nitrosation reaction mixture (1 mg of parent drug)	(+)	(49)
Long-term carcinogenesis assay, rats	Tolazamide 1000 ppm + NaNO2 2000 ppm in drinking water	-	(55)
Tolazoline[3]			
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitroso derivative(s) 49.5 µM	+	(7)
Tolbutamide[3]			
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, reverse mutation	Nitrosation reaction mixture (1 mg of parent drug)	-	(49)
Tripelennamine[3]			
DNA strand breaks, Chinese hamster ovary cells *in vitro*	N-nitroso derivative(s) 38 µM	+	(7)
Verapamil[3]			
DNA strand breaks, rat liver *in vivo*	Verapamil 54 mg/kg + NaNO2 80 mg/kg p.o.	-	(35)

should be compared with the therapeutic benefit, but it should be taken into account that the drug-nitrite interaction can be to a large extent reduced by administering the nitrosatable drug with ascorbic acid that rapidly reacts with nitrite to give nitric oxide and dihydroascorbic acid.

6. REFERENCES

1. P Bogovski , S Bogovski : Animal species in which N-nitroso compounds induce cancer. *Int J Cancer 27,* 471-474 (1981)

2. S S Mirvish. Formation of N-nitroso compounds: chemistry, kinetics and *in vivo* occurrence. *Toxicol Appl Pharmacol* 31, 325-351 (1975)

3. G Brambilla, A Martelli : Genotoxic and carcinogenic risk to humans of drug-nitrite interaction products. *Mutat Res* 635, 17-52 (2007)

4. Martindale The Complete Drug Reference, 35th edition, *Pharmaceutical Press*, London, 2007

5. WHO: Informal consultation on the potential carcinogenicity of nitrosatable drugs. In: Proceedings of the Report of a WHO meeting, Geneva, June 12-16, 1978

6. T Ohta, H Oribe, T Kameyama, Y Goto, S Takitani: Formation of a diazoquinone-type mutagen from acetaminophen treated with nitrite under acidic conditions. *Mutat Res* 209, 95-98 (1988)

7. G Brambilla, E Cajelli, R Finollo, A Maura, A Pino, L Robbiano: Formation of DNA-damaging nitroso compounds by interaction of drugs with nitrite. A preliminary screening for detecting potentially hazardous drugs. *J Toxicol Environ Health* 15, 1-24 (1985)

8. K Kikugawa, T Cato, Y Takeda : Formation of a highly mutagenic diazo compound from the bamethan-nitrite reaction. *Mutat Res* 177, 35-43 (1987)

9. D Ziebarth, B Spiegelhalder, H Bartsch : N-nitrosation of medicinal drugs catalyzed by bacteria from human saliva and gastrointestinal tract, including *Helicobacter pylori. Carcinogenesis* 18, 383-389 (1997)

10. A Sakai, T Inoue, A Tanimura : Formation of volatile nitrosamines by drug-nitrite interactions under physiological conditions. *Gann* 75, 245-252 (1984)

11. W Lijinsky : Reaction of drugs with nitrous acid as a source of carcinogenic nitrosamines. *Cancer Res* 34, 255-258 (1974)

12. D Ziebarth. : Nitrosierbare Arzneimittel. *Arch Geschwulstforsch* 51, 587-595 (1981)

13. G S Rao, G Krishna : Drug-nitrite interactions: formation of N-nitroso, C-nitroso, and nitro compounds from sodium nitrite and various drugs under physiological conditions. *J Pharm Sci* 64, 1579-1581 (1975)

14. Y Takeda, K Kanaya : Formation of nitroso compounds and mutagens from cinnarizine, ethambutol, piromidic acid, pyridinol, carbamate and tiaramide by drug-nitrite interaction. *Cancer Lett* 15, 53-59 (1982)

15. D Ziebarth, B Teichmann : Nitrosation of orally administered drugs under simulated stomach conditions. In : N-Nitroso Compounds: Analysis, Formation and Occurrence. Eds : E A Walker, L Castegnaro, H Börzsönyi, M, Griciute : IARC Scientific Publication No. 31, *International Agency for Research on Cancer, Lyon, France* , pp. 231-244 (1980)

16. D Ziebarth: Bildung flüchtinger kanzerogener N-Nitrosoverbindungen aus Arzneimitteln unter simulierten Bedingungen des menschlichen Magens. *Arch Geschwulstforsch* 55, 315-326 (1985)

17. D Ziebarth: Vergleichende Untersuchungen des Nitrosierungverhaltens von Arzneimitteln bei konstanten pH-Wert und unter simulierten Magenbedingungen. *Arch Geschwulstforsch* 52, 429-442 (1982)

18. C L Walters, P N Gillat, R C Palmer, P L R Smith, P I Reed : Nitrosation of drugs under in-vivo conditions. In: The Relevance of N-nitroso Compounds to Human Cancer, Exposure and and Mechanism. Eds : H Bartsch, I O'Neill, R Shultz-Hermann : IARC Scientific Publication No. 84. *International Agency for Research on Cancer, Lyon, France* , pp.351-354 (1987)

19. P N Gillat, R J Hart, C L Walters , P I Reed : Susceptibilities of drugs to nitrosation under standardized chemical conditions. *Food Chem Toxicol* 22, 269-274 (1984)

20. P N Gillat, R C Palmer, P L R Smith, C L Walters, P I Reed : Susceptibilities of drugs to nitrosation under simulated gastric conditions. *Food Chem Toxicol* 23, 849-855 (1985)

21. W Lijinsky : Formation of nitrosamines from tertiary amines and related compounds. *Proc Am Assoc Cancer Res* 13, 68 (1972)

22. L Robbiano, A Martelli, A Allavena, M Mazzei, G M Cazzaniga, G Brambilla: Formation of the N-nitroso derivatives of six ß-adrenergic-blocking agents and their genotoxic effects in rat and human hepatocytes. *Cancer Res* 51, 2273-2279 (1991)

23. M Arriaga Alba, J Espinosa, C Cortinas de Nava : Mutagenicity of products generated by the reaction between several antiparasitic drugs and nit nitrite. *Environ Mol Mutagen* 12, 65-73 (1988)

24.Y Takeda, H Kanaya: Formation of nitroso compounds and mutagens from tranquilizers by drug/nitrite interaction. *Cancer Lett* 12, 81-86 (1981)

25. J Schmid, K Danek, F W Koss, G Eisenbrand, K H Schlemmer : Kinetic and analytic investigation on the formation of N-nitroso-N-methyl-N-cyclohexylamine from bromhexine and nitrite. *Arzneimittel-Forsch* 38, 1355-1358 (1988)

26. J Schmid, E Bauer, K Danek, H Franke , F W Koss : Lack of detectable N-nitroso-N-methyl-N-cyclohexylamine in humans after administration of bromhexine. *Arzneimittel-Forsch* 38, 1359-1364 (1988)

27. K H Schlemmer, G Eisenbrand : Nitrosation of bromhexine and aminophenazone in gastric juice after high nitrate loading in the diet. An ex-vivo/*in vitro* study in humans. *Arzneimittel-Forsch* 38, 1365-1368 (1988)

28. K H Schlemmer , G Eisenbrand : In-vitro and in-vivo formation of N-nitrosomethylcyclohexylamine from bromhexine and sodium nitrite in rats. In: The Relevance of N-nitroso Compounds to Human Cancer, Exposure and and Mechanisms. Eds: H Bartsch, I O'Neill , R Schulte-Hermann. IARC Scientific Publication No. 84. *International Agency for Research on Cancer, Lyon, France* , pp.355-359 (1987)

29. D Ziebarth, T Schramm, A Töppel : Unter simulierten Bedingungen des menschlichen Magens nitrosierbare Arzneimittel den Gruppen der trizyklischen Antidepressiva und Antiepileptika. *Arch Geschwulstforsch* 59, 257-263 (1989)

30. G Brambilla, L Robbiano, A Martelli, E Cajelli, A Allavena , M Mazzei : Genotoxicity of N-nitrosochlordiazepoxide in cultured mammalian cells. *Toxicol Appl Pharmacol* 97, 480-488, (1989)

31. M Mazzei, A Balbi, G Roma, M Di Braccio, L Robbiano : HPLCanalysis of the nitrosation product of chlordiazepoxide. *Il Farmaco-Ed Sci* 44, 883-891 (1989)

32. A Kinawi, A Onken, B Rozyczka , W König : Untersuchungen zur Nitrosierbarkeit von Chlordiazepoxid unter physiologischen Bedingungen. *Arzneimittel-Forsch* 27, 363-367 (1977)

33. Röper, K Heyns : Possible nitrosodimethylamine formation in comparative in vitro nitrosation experiments with six different tetracycline antibiotics. In: Environmental Aspects of N-Nitroso Compounds. Eds : E A Walker, M Castegnaro, L Griciute , R E Lyle. IARC Scientific Publication No. 19. International Agency for Research on Cancer, Lyon, France pp. 219-237 (1978)

34. L M Anderson, A Giner-Sorolla, I M Haller, J M Budinger: Effects of cimetidine, nitrite, cimetidine plus nitrite, and nitrosocimetidine on tumours in mice following transplacental plus chronic lifetime exposure. Cancer Res 45, 3561-3566 (1985)

35. A Martelli, C Garbero, M Gosmar, G Brambilla : Formation of DNA-damaging N-nitroso derivatives from calcium channel antagonists by interaction with nitrite. Toxicology 238, 211-215 (2007)

36. M Mazzei, G Roma, A Balbi, E Sottofattori, L Robbiano : Formation of 2,6-dimethoxy-1,4-benzoquinone, a higly genotoxic compound, from the reaction of sodium nitrite with the sympathomimetic drug dimetofrine in acidic aqueous solution. *Il Farmaco.Ed Sci* 43, 523-538 (1988)

37. Kikugawa, T Kato ,T Tukeda : Formation of a direct mutagen, diazo-N-nitrosoetilefrin, by interaction of etilefrin with nitrite. *Chem Pharm Bull* 37, 1600-1603 (1989)

38. B Gold, S S Mirvish : N-Nitroso derivatives of hydrochlorothiazide, niridazole, and tolbutamide. *Toxicol Appl Pharmacol* 40, 131-136 (1977)

39. H Shimizu, N Takemura, H Ando, M Morita, K Machida : Mutagenic activity of N-nitrosomethamphetamine and N-nitrosoephedrine. *Cancer Lett* 21, 63-68 (1983)

40. S S Mirvish, L Wallcave, M Eagen, P Shubik : Ascorbate-nitrite reaction: possible means of blocking the formation of carcinogenic N-nitroso compounds. *Science* 177, 65-67 (1972)

41. G Eisenbrand, R Preussmann : Nitrosation of phenacetin. Formation of N- nitroso-2-nitro-4-ethoxyacetanilide as an unstable product of the nitrosation in dilute aqueous-acidic solution. *Arzneimittel-Forsch* 25, 1472-1475 (1975)

42. J Chen, I H Raisfeld-Danse : Drug interactions. Part II. Formation of nitrosamines from therapeutic drugs. Properties and kinetics of the formation of N-nitrosopropranolol from nitrite and the secondary amine propranolol hydrochloride. *J Pharmacol Exp Ther* 225, 705-712 (1983)

43. I H Raisfeld-Danse , J Chen : Drug interactions. Part III. Formation of nitrosamines from therapeutic drugs. Formation, mutagenic properties and safety assessment of propranolol hydrochloride with respect to the intragastric formation of N-nitrosopropranolol under conditions found in patients. *J Pharmacol Exp Ther* 225, 713-719 (1983)

44. E Sottofattori, M Anzaldi, A Balbi, A Martelli : High-performance liquid chromatographic study of formation of N-nitroso- propranolol in simulated gastric juice. *Il Farmaco-Ed Sci* 52, 123-125 (1997)

45. G Brambilla, Martelli, E Sottofattori : Nitrosation of propranolol under simulated gastric conditions. *Carcinogenesis* 16, 1239-1242 (1995)

46. A Maura, A Pino, L Robbiano, E Cajelli, , R Finollo, M Capanna, G Brambilla : DNA damage induced by nitrosated ranitidine in cultured mammalian cells. *Toxicol Lett* 18, 97-102 (1983)

47. L A P Hoogenboom, P W Van Der Steeg, H A Kuiper, P G N Kramers : *In vitro* formation of a triezene compound by reaction of sulphadimidine and nitrite. *Food Chem Toxicol* 25, 373-377 (1987)

48. G Özhan, B Alpertunga : Genotoxic activity of drug-nitrite interaction products. *Drug Chem Toxicol* 26, 295-308 (2003

49. A W Andrews, J A Fornwald , W Lijinsky : Nitrosation and mutagenicity of some amine drugs. *Toxicol Appl Pharmacol* 52, 237-244 (1980)

50. V Boido, C Bennicelli, P Zanacchi , S De Flora : Formation of mutagenic derivatives from nitrite and two primary amines. *Toxicol Lett* 6, 379-383 (1980)

51. R Braun, J Schoneich, D Ziebarth : Testing of drugs for combined mutagenesis with sodium nitrite in the host-mediated assay. *Arch Toxicol* 4 (Suppl), 49-53, 1980

52. S Parodi, M Taningher, M Pala, G Brambilla, M Capanna : Detection by alcaline elution of rat liver DNA damage induced by simultaneous subacute administration of nitrite and aminopyrine. *J Toxicol Environ Health* 6, 167-174 (1980)

53. W Lijinsky, H W Taylor, C Snyder, P Nettesheim : Malignant tumors of liver and lug in rats fed aminopyrine o heptamethyleneimine with nitrite. *Nature* 244, 176-178 (1973)

54. H W Taylor , W Lijinsky : Tumour induction in rats by feeding aminopyrine or oxytetracycline with nitrite. *Int J Cancer* 16, 211-215 (1975)

55. W Lijinsky, H W Taylor : Nitrosamines and their precursors in food. In: Origins of Human Cancer, Book C, Human Risk Assessment. Eds : H H Hiatt, J D Watson, J A Winsten . *Cold Spring Harbor Laboratory* , pp. 1579-1590 (1977)

56. W Thamavit, M A Moore, Y Hiasa, N Ito : Generation of high yields of Syrian hamster cholangiocellular carcinomas and hepatocellular nodules by combined nitrite and aminopyrine administration and *Opisthorchis viverrini* infection. *Jpn J Cancer Res* 79, 909-916 (1988)

57. N Inui, Y Nishi, A Tanimura : Induction of 8-azaguanine-resistant mutation and neoplastic transformation of hamster embryonic cells by coadministration of sodium nitrite and aminopyrine. In : N-nitroso Compounds: Occurrence and Biological Effects, IARC Scientific Publication No. 41. Eds : H Bartsh, , I K O'Neill, M Castegnaro, M Okada. *International Agency for Research on Cancer, Lyon, France* (1982) pp.585-590

58. T Kawanishi, Y Ohno, M Sunouki, K Onoda, A Takahashi, Y Kasuya, Y Omori : Studies on nitrosamine formation by the interaction between drugs and nitrite. Part II. Hepatotoxicity by the simultaneous administration of several drugs and nitrite. *J Toxicol Sci* 6, 271-286 (1981)

59.B Farmer, D E G Shuker, I Bird : DNA and protein adducts as indicators of *in vivo* methylation by nitrosatable drugs. *Carcinogenesis* 7, 49-52 (1986)

60. C T Gombar, J Zubrtoff, G D Straham, P N Magee : Measurement of 7-methylguanine as an estimate of the amount of dimethylnitrosamine formed following administration of aminopyrine and nitrite to rats. *Cancer Res* 43, 5077-5080 (1983)

61. D M Parisi, G S Rao : Mutagenicity of 4-aminoantipyrine and 4-nitroso antipyrine, the C-nitroso derivative of antipyrine. *Mutat Res* 206, 317-326 (1988)

62. A Martelli, A Allavena, E Sottofattori, G Brambilla : Low clastogenic activity *in vivo* of the N-nitrosoderivatives of 5 ß-adrenergic-blocking drugs proved to be potent genotoxins *in vitro*. *Toxicol Lett* 73, 185-191 (1994)

63. M Arriaga Alba, J Espinosa Aguirre, J Ramirez, J Cortinas de Nava : Mutagenicity of urine from mice exposed orally to nitrite and various aminated antiparatsitic drugs. *Environ Mol Mutagen* 14, 13-19 (1989)

64. P B Farmer, A Parry, H Franke, J Schmid : Lack of detectable DNA alkylation from bromhexine in man. *Arzneimittel-Forsch* 38, 1351-1354 (1988)

65. S Kraft, A Onken : Induction of mitotic gene conversion in *Saccharomyces cerevisiae* with chlordiazepoxide and its N-nitroso derivative in a host-mediated assay. *Mutat Res* 34. 333-336 (1976)

66. L Robbiano, P Carlo, R Finollo, G Brambilla : DNA damage induced in rats by oral administration of chlordiazepoxide plus sodium nitrite or of N-nitrosochlordiazepoxide. *Toxicol Appl Pharmacol* 102, 186-190 (1990)

67. A Giner-Sorolla, J Greenbaum, K Last-Barney, L M Anderson, J M Budinger: Lack of carcinogenic effect of nitrosochlordiazepoxide and nitrosomethylphenidate given orally in mice. *Food Cosmet Toxicol* 18, 81-83 (1980)

68. W Lijinsky, H W Taylor : Feeding tests in rats on mixtures of nitrite with secondary and tertiary amines of environmental importance. *Food Cosmet Toxicol* 15, 269-274 (1977)

69. S De Flora, A Picciotto : Mutagenicity of cimetidine in nitrite-enriched human gastric juice. *Carcinogenesis* 1, 925-930 (1980)

70. B L Pool, G Eisenbrand : Biological activity of nitrosated cimetidine. *Mutat Res* 74, 243 (1980)

71. M Schwarz, J Hummel, G Eisenbrand : Induction of DNA strand breaks by nitrosocimetidine. *Cancer Lett* 10, 223-228 (1980)

72. L R Barrows, C T Gombar, P N Magee : Mutation, DNA labelling and transformation of BHK-21/CL13 cells by MNNG, and nitrosocimetidine. *Mutat Res* 102, 145-158 (1982)

73. K Athanasiou, S A Kyrtopoulos : Induction of sister chromatid exchances and chromosome aberrations in cultured mammalian cells by N-nitrosocimetidine. *Cancer Lett* 14, 71-75 (1981)

74. D Ichinotsubo, E A MacKinnon, C Liu, S Rice, H F Mower : Mutagenicity of nitrosated cimetidine. *Carcinogenesis* 2, 261-264 (1981)

75. E E Henderson, R Basilio, R M Davis : Cellular DNA damage by nitrosocimetidine: a comparison with N-methyl-N'nitrosonitroguanidine and X- irradiation. *Chem Biol Interact 38, 87-98 (1981)*

76. K Inoue, T Shibata, H Kosaka, M Uozumi, S Tsuda, T Abe : Induction of sister-chromatid exchanges by N-nitrosocimetidine in cultured human lymphocytes and its inhibition by chemical compounds. *Mutat Res* 156, 117-121 (1985)

77. G Brambilla, M Cavanna, A Maura, A Pino, L Robbiano, P Carlo, F Biassoni, R Ricci : Absence of DNA damage in liver of rats given high doses of cimetidine and sodium nitrite. *J Pharmacol Exp Ther* 221, 222-227 (1982)

78. A Pino, L Robbiano : Absence of DNA fragmentation in gastric mucosa of rats treated with high doses of cimetidine and nitrite. *IRCS Med Sci* 11, 172 (1983)

79. W Lijinsky, M D Reuber : Comparison of nitrosocimetidine with nitrosomethylnitroguanidine in chronic feeding tests in rats. *Cancer Res* 44, 447-449, (1984)

80. M Habs, G Eisenbrand , H Habs, D Schmahl : No evidence of carcinogenicity of N-nitrosocimetidine in rats. *Hepatogastroenterolgy* 29, 265-266 (1982)

81. D E Jensen, P N Magee : Methylation of DNA by nitrosocimetidine *in vitro. Cancer Res* 41, 230-236 (1981)

82. S A Kyrtopoulos, E Hadjiloucas, B Vrotsou : Non detection of O6-methylguanine in rat DNA following *in vivo* treatment with large doses of cimetidine alone or in combination with sodium nitrite. *Cancer Res* 42, 1962-1966 (1982)

83. D E Jensen : Denitrosation as a determinant of nitrosocimetidine *in vivo* activity. *Cancer Res* 43, 5258-5267 (1983)

84. C T Gombar, P N Magee : DNA-methylation by nitrosocimetidine and N-methyl-N'-nitro-N-nitrosoguanidine in the intact rat. *Chem Biol Interact* 40, 149-157 (1982)

85. G Brambilla, L Robbiano, E Cajelli, A Martelli, F Turmolini, M Mazzei : Cytotoxic, DNA-damaging and mutagenic properties of 2,6-dimethoxy-1,4-benzoquinone,

formed by dimethophrine-nitrite interaction. *J Pharmacol Exp Ther* 244, 1011-1015 (1988)

86. A W Andrews, W Lijinsy, S W Snyder : Mutagenicity of amine drugs and their products of nitrosation. *Mutat Res* 135, 105-108 (1984)

87. A Sakai, K Yoshikawa, A Tanimura, I Tomita : Mutagenicity of reaction products of sulpyrine with nitrite. *Mutat* Res 90, 57-65 (1981)

88. G N Wogan, S Paglialunga, M C Archer, S R Tannenbaum : Carcinogenicity of nitrosation products of ephedrine, sarcosine, folic acid, and creatinine. *Cancer Res* 35, 1981-1984 (1975)

89. G Eisenbrand, R Preussmann, D Schmahl : Carcinogenicity of N-nitrosoephedrine in rats. *Cancer Lett* 5, 103-106 (1978)

90. J Schneider, R Warzok, H Schwarz : Endogenous formation of carcinogenic N-nitroso compounds in rats after application of drugs and nitrite. *Exp Pathol* 13, 32-43 (1977)

91. A Martelli, R Canonero, A Allavena, E Sottofattori, G Brambilla : *In vitro* and *in vivo* evaluation of the genotoxicity of N-nitrosooxprenolol. *Pharmacol Toxicol* 70, 1-6 (1992)

92. J-K Lin, J-Y Yen, H-W Chang, S-Y Lin-Shiau : N-nitrosophenacetin: its sy6nthesis, characterisation, mutagenicity, and teratogenicity. *J Natl Cancer Inst* 72, 863-869 (1984)

93. W Lijinsky, H W Taylor : Carcinogenicity tests of N-nitroso derivatives of two drugs, phenmetrazine and methylphenidate. *Cancer Lett* 1, 359-363 (1976)

94. T Ono-Ogata, T Ogino, M Nishikawa, T Ohta, H Yamagata : Mutagenic activity and mutational specificità of antiprotozoals drugs with and without nitrite treatment. *Environ Mol Mutagen* 39, 43-48 (2002)

95. S De Flora, C Bennicelli, A Camoirano, P Zanacchi : Genotoxicity of nitrosated ranitidine. *Carcinogenesis* 4, 255-260 (1983)

96. J Franekic, S Skupnjak, Z Matijasevic : Genotoxicity of nitrosated ranitidine. *Mutat Res* 227, 13-16 (1989)

97. A Martelli, E Fugassa, A Voci, G Brambilla : Unscheduled DNA synthesis induced by nitrosated ranitidine in primary cultures of rat hepatocytes. *Mutat Res* 122, 373-376 (1983)

98. G Brambilla, M Cavanna, P Faggin, A Maura, A Pino, R Ricci, L Robbiano : Genotoxic effects in rodents given high oral doses of ranitidine and sodium nitrite. *Carcinogenesis* 4, 1281-1285 (1983)

99. A Kasamaki, S Urasawa : Induction of mutagenic activity of tetracycline by synergistic action with nitrite. *J Toxicol Sci* 12, 73-85 (1987)

100. R C Kammerer, J R Froines, T Price : Mutagenicity studies of selected antihistamines, their metabolites and products of nitrosation. *Food Chem Toxicol* 24, 981-985 (1986)

101.International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol.17, Some N-Nitroso Compounds. *IARC, Lyon, France* (1978)

102.International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, suppl. 7, Overall Evaluation of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. *IARC, Lyon, France* (1987)

103.L Müller, Y Kikuchi, G Probst, L Schechtman, H Shimada, T Sofuni, D Tweats : ICH-harmonised guidance on genotoxicity testing of pharmaceuticals: evolution, reasoning and impact. *Mutat Res* 436, 195-225 (1999)

104.R Preussmann : Dose-response studies and “no-effect levels” of N-nitroso compounds : some general aspects. *Oncolgy* 37, 243.250 (1980)

Key Words: Arylamine drugs, NO-derivatives, Genotoxic-carcinogenic activity, Review

Send correspondence to: Antonietta Martelli, Sezione di Farmacologia, Viale Benedetto XV, 2, I-16132 Genova, Italy, Tel: 39-010-3538850, Fax: 39-010-353.8232, E-mail: Antonietta.Martelli@unige.it

http://www.bioscience.org/current/vol4E.htm