Supporting Information for:

A Practical and Science-Based Strategy for Establishing Acceptable Intakes for Drug Product *N*-Nitrosamine Impurities

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Table S1. Structural Group 3 Nitrosamines: Details of Carcinogenicity Studies from which TD_{50} Values were Derived.

CAS Number	Duration of exposure (experiment)[a]	Species, sex, animal number	Dose route	Endpoint selected	Dose (mg/kg/day): tumor incidence[b]	TD_{50} (mg/kg/day)[c]	Reference[d]
614-00-6	104 weeks	Rat, mixed sex, 48 per group	Drinking water	Esophagus, multiple tumor types	0: 0/48 0.0838: 39/48 0.319: 42/48	0.106	LCDB[1]
145438-97-7	41 (52) weeks	Rat, mixed sex, 43 control, 42 treated	Gavage	Forestomach, squamous cell carcinoma	0: 0/43 1.71: 42/42 9.13: 40/42	0.185	LCDB[1]
937-25-7	50 (114) weeks	Rat, male, 20 per group	Drinking water	Esophagus, multiple tumor types	0: 0/20 0.714: 18/20	0.255	LCDB[1]
16699-10-8	34 (52) weeks	Rat, female, 20 per group	Diet	Liver, hyperplastic nodules	0: 0/20 1.63: 9/20	0.468	LCDB[1]
145438-96-6	73 (79) weeks	Rat, mixed sex, 66 control, 41-45 treated	Drinking water	Nasal cavity, multiple tumor types	0: 0/66 2.14: 31/41 3.57: 28/45 10.7: 32/43	1.01	LCDB[1]
99-80-9	26 (86) weeks	Rat, male, 10 control, 14 treated	intraperitoneal	Peritoneal cavity, multiple tumor types	0: 0/10 0.429: 2/14	1.3[e]	LCDB[1]
No CAS #	104 weeks	Mouse, female, 16 control, 20 treated	Drinking water	Reproductive tract, multiple tumor types	0: 1/16 35.7: 16/20	15.8	LCDB[1]

N^6-(methylnitroso)adenosine[f]							
21928-82-5[g] N^6-(methylnitroso)adenine	104 weeks	Mouse, male, 21 control, 19 treated	Drinking water	Lung, type not specified	0: 4/21 17.0[h]: 11/19	18.1	Anderson *et al*[2]
69658-91-9	116 weeks	Rat, female, 5 control, 26 treated	Gavage	NA	0 0.571	Not carcinogenic	LCDB[1]
943-41-9	50 (114) weeks	Rat, male, 20 per group	Drinking water	NA	0 0.840	Not carcinogenic	LCDB[1]
16219-99-1	101 weeks	Rat, female, 5 controls, 15 treated	Gavage	NA	0 2.86	Not carcinogenic	LCDB[1]
62018-88-6	Not available[i]	Not available[i]	Not available[i]	NA	Not available[i]	Not carcinogenic	Nagao *et al*[3]

TD_{50} = dose resulting in tumors in 50% of animals; LCDB = Lhasa Carcinogenicity Database; NA = Not applicable.

[a]Experiment length if different than treatment duration.

[b]Tumor incidence (number of animal with tumors in selected endpoint/total number of animals analyzed for selected endpoint) is provided for each dose for compounds deemed as carcinogenic. Incidence is not provided for compounds evaluated as non-carcinogenic.

[c]When reference is not LCDB, TD_{50} was calculated internally using R-code adapted from Thresher *et al*[4] based on the data from cited reference.

[d]Source of carcinogenicity study data reviewed and from which the presented data was selected.

[e]Gold TD_{50} reported in LCDB, but results are not statistically significant.

[f]When a user enters CAS number 21928-82-5 into LCDB, it will pull back a record associated with N^6-methyladenosine. It should be noted that the CAS number provided in CPDB and LCDB corresponds to the structure for N^6-methylnitrosoadenine in CAS (though CAS does list both names). There is no unique CAS number provided for N^6-(methylnitroso)adenosine. The data presented in LCDB does correspond to that for N^6-(methylnitroso)adenosine from Anderson et al, 1979.

[g]When a user enters CAS number 21928-82-5 into LCDB, it will pull back a record of carcinogenicity data associated with N^6-methyladenosine. However, this CAS number is associated to N^6-methylnitrosoadenine in CAS and one must refer to the source document, Anderson *et al*[2] to find the relevant carcinogenicity data for N^6-methylnitrosoadenine.

[h]Dose reported as 1 mM solution in drinking water 4 days per week until death. At a molecular weight of 178.16 g/mol, this is equivalent to 178.16 mg/L Assuming a male mouse weight of 0.030 kg and daily water intake of 5 mL, the daily dose is 17.0 mg/kg when corrected for dosing 4 days per week.

[i]No data reported in the LCDB or the CPDB. The literature reference (review article) did not report study details.

Table S2. Structural Group 4 Nitrosamines: Details of Carcinogenicity Studies from which TD_{50} Values were Derived.

CAS Number	Duration of exposure (experiment)[a]	Species, sex, animal number	Dose route	Endpoint selected	Dose (mg/kg/day): tumor incidence[b]	TD_{50} (mg/kg/day)	Reference[c]
75411-83-5	30 (75) weeks	Rat, male, 20 per group	Drinking water	Nasal cavity, multiple tumor types	0: 0/20 0.286: 18/20	0.0442	LCDB[1]
86451-37-8	40 (110) weeks	Rat, female, 20 per group	Drinking water	Lung, multiple tumor types	0: 0/20 0.430: 8/20	0.646	LCDB[1]

TD_{50} = dose resulting in tumors in 50% of animals; LCDB = Lhasa Carcinogenicity Database.

[a]Experiment length if different than treatment duration.

[b]Tumor incidence (number of animal with tumors in selected endpoint/total number of animals analyzed for selected endpoint) is provided for each dose for compounds deemed carcinogenic.

[c]Source of carcinogenicity study data reviewed, and from which the presented data was selected.

Table S3. Structural Group 5 Nitrosamines: Details of Carcinogenicity Studies from which TD_{50} Values were Derived.

CAS Number	Duration of exposure (experiment)[a]	Species, sex, animal number	Dose route	Endpoint selected	Dose (mg/kg/day): tumor incidence[b]	TD_{50} (mg/kg/day)[c]	Reference[d]
55556-85-9	36 (50) weeks	Rat, male, 15 treated	Drinking water	Nasal cavity, squamous cell tumors and adenocarcinomas	2.38[e]: 13/15	0.819[f]	Lijinsky and Taylor[5].
88208-16-6	50 (55) weeks	Rat, female, 20 per group	Drinking water	Esophagus, multiple tumor types	0: 0/20 8.16: 17/20	0.825	LCDB[1]
53609-64-6	45 (52) weeks	Rat, male, 12 controls, 9-10 treated	Drinking water	Lung, adenoma	0: 0/12 5: 6/10 25: 9/9	0.891	LCDB[1]
75896-33-2	50 (75) weeks	Rat, female, 20 per group	Drinking water	Liver, hepatocellular carcinoma	0: 0/20 5.44: 17/20	1.02	LCDB[1]
61499-28-3	21 or 40 weeks	Rat, female 20 per group	Drinking water	Esophagus, papilloma	0: 0/20 8.9[g]: 19/20 2.2[h]: 18/20	1.1	Lijinksy *et al*[6]
89911-78-4	75 (120) weeks	Rat, female, 20 per group	Drinking water	Liver, multiple tumor types	0: 3/20 1.87: 8/20	6.04	LCDB[1]

					3.74: 10/20		
56222-35-6	112 weeks	Rat, mixed sex, 24 controls, 23 treated	Drinking water	Liver, hepatocellular carcinoma	0: 0/24 2.5: 5/23	8.11	LCDB[1]
30310-80-6	75 (104) weeks	Rat, female, 15 per group	Drinking water	NA	0 4.42	Not carcinogenic	LCDB[1]
75195-74-3	3X per week for 7.3 (37.3) weeks	Mouse, female, 25 per group	ip injection	NA	0 3.6[i]	Not carcinogenic	Castonguay *et al*[7]
75195-75-4	3X per week for 7.3 (37.3) weeks	Mouse, female, 25 per group	ip injection	Lung tumors	0: 10/25 3.6[i]: 19/25	Study design does not allow for a reliable estimate of TD_{50}	Castonguay *et al*[7]

TD_{50} = dose resulting in tumors in 50% of animals; LCDB = Lhasa Carcinogenicity Database; NA = Not applicable; ip = intraperitoneal.

[a]Experiment length if different than treatment duration.

[b]Tumor incidence (number of animal with tumors in selected endpoint / total number of animals analysed for selected endpoint) is provided for each dose for compounds deemed carcinogenic. Incidence is not provided for compounds evaluated as non-carcinogenic.

[c]When reference is not LCDB, TD_{50} was calculated internally using R-code adapted from Thresher *et al*[4] based on the data from cited reference.

[d]Source of carcinogenicity study data reviewed and from which the presented data was selected.

[e]Total dose reported as 3.2 mmol. At a molecular weight of 130.15 g/mol, this is equivalent to 416 mg over the course of the study. Animals were dosed for 36 weeks (1.65 mg/day), and the total study duration was 50 weeks (1.19 mg/day). Assuming a male rat weight of 0.50 kg, the daily dose is 2.38 mg/kg/day.

[f]TD_{50} was calculated assuming a control group tumor incidence of 0/15, as the study did not include control animals.

[g]Total dose was 460 mg over 21 weeks with treatment 5X per week. Daily dose was calculated by dividing total dose by 21 weeks x 7 days/week for a daily average dose of 3.1 mg/day and divided by average female rat weight of 0.35 kg.

[h]Total dose was 220 mg over 40 weeks with treatment 5X per week. Daily dose was calculated by dividing total dose by 40 weeks x 7 days/week for a daily average dose of 0.79 mg/day and divided by average female rat weight of 0.35 kg.

[i]Total dose reported as 0.12 mmol/mouse. At a molecular weight of 193.2 mg/mmol, this is equivalent to 23 mg total over 7.3 week. Animals were examined 30 weeks after treatment stopped for a total experiment duration of 37.3 weeks after treatment ended (0.089 mg/day). Assuming a female mouse weight of 0.025 kg, the daily dose is 3.6 mg/kg/day.

Table S4. Structural Group 7 Nitrosamines: Details of Carcinogenicity Studies from which TD_{50} Values were Derived.

CAS Number	Duration of exposure (experiment)[a]	Species, sex, animal number	Dose route	Endpoint selected	Dose (mg/kg/day): tumor incidence[b]	TD_{50} (mg/kg/day)[c]	Reference[d]
55984-51-5	67 (76) weeks	Rat, female, 15 per group (14 for high dose)	Gavage	Nasal/paranasal cavity, multiple tumor types	0: 0/15 0.129: 14/15 0.257: 15/15 0.500: 9/14	0.017	LCDB[1]
92177-50-9	31 (55) weeks	Rat, female, 20 per group	Drinking water	Esophagus, multiple tumor types	0: 0/20 0.349: 17/20	0.0352	LCDB[1]
91308-71-3	50 (85) weeks	Rat, female, 20 per group	Drinking water	Liver, hepatocellular carcinoma	0: 0/20 1.18: 16/20	0.335	LCDB[1]
60599-38-4	73 (77) weeks	Rat, female, 15 per group	Gavage	Liver, multiple tumor types	0: 0/15 0.357: 0/15 0.714: 12/15 1.43: 14/15	0.286	LCDB[1]
92177-49-6	50 (65) weeks	Syrian hamster, female, 20 per group	Gavage	Liver, multiple tumor types	0: 0/20 5.99: 16/20	0.997	LCDB[1]
61499-28-3	21 or 40 weeks	Rat, female, 20 per group	Drinking water	Esophagus, papilloma	0: 0/20 8.9[f]: 19/20 2.2[g]: 18/20	1.1	Lijinksy *et al*[6]

39603-54-8	1X per week for 52 weeks[e]	Syrian hamster, mixed sex, controls 15 per sex; treated 10 per sex per group	Subcutaneous injection	Laryngo-bronchial tract	0: 0/30 4.1[h]: 18/18[i] 8.2[h]: 13/16[i] 16[h]: 18/19[i]	Study design does not allow for a reliable estimate of TD_{50}	Pour *et al*[8]
51938-15-9	4-13 weeks or 10-17 (20-27) weeks[j]	Rat, male, no controls, 5-8 per treated group	Drinking water	Liver, hepatocellular carcinoma	~26.8-34.3[k]: 1/8 ~13.4-16.5[l]: 3/5	Study design does not allow for a reliable estimate of TD_{50}	Okada and Hashimoto[9]

TD_{50} = dose resulting in tumors in 50% of animals; LCDB = Lhasa Carcinogenicity Database.

[a]Experiment length if different than treatment duration.

[b]Tumor incidence (number of animal with tumors in selected endpoint/total number of animals analyzed for selected endpoint) is provided for each dose for compounds deemed carcinogenic. Incidence is not provided for compounds evaluated as non-carcinogenic.

[c]When reference is not LCDB, TD_{50} was calculated internally using R-code adapted from Thresher *et al*[4] based on the data from cited reference.

[d]Source of carcinogenicity study data reviewed and from which the presented data was selected.

[e]Surviving control animals were sacrificed after the last experimental animal had died (52 weeks). Survival was impacted by treatment with average survival of 43, 30, and 28 weeks for low, mid, and high doses, respectively.

[f]Total dose was 460 mg over 21 weeks with treatment 5X per week. Daily dose was calculated by dividing total dose by 21 weeks x 7 days/week for a daily average dose of 3.1 mg/day and divided by average female rat weight of 0.35 kg.

[g]Total dose was 220 mg over 40 weeks with treatment 5X per week. Daily dose was calculated by dividing total dose by 40 weeks x 7 days/week for a daily average dose of 0.79 mg/day and divided by average female rat weight of 0.35 kg.

[h]Doses were 0.025, 0.05, and 0.1 of LD_{50}, which was defined as 1100 and 1200 mg/kg in males and females, respectively. Tumor incidence was combined for males and females so the daily doses are estimates calculated by averaging the LD_{50} to 1150 mg/kg, multiplying by the factors of 0.025, 0.05 and 0.1 and dividing by 7 to get at the daily doses of 4.1, 8.2, and 16 mg/kg/day, respectively, over the treatment period.

[i]Tumor incidence (%) was reported and was converted to incidence (number of animal with tumor/total number of animals) by multiplying the effective number of animals reported by the % incidence.

[j]10 rats were treated daily for 4-13 weeks until death (5) or sacrifice (5). An additional 5 rats were added, which were treated every other week for 10-17 weeks and sacrificed 10 weeks later.

[k]Total dose in rats treated continuously for 4-13 weeks is reported as 0.3-0.5 g. 5 of 10 rats died within 10 weeks and 5 were sacrificed after 13 weeks so daily corrected dose was calculated as 0.3 g/70 days or 0.5g/91days for daily dose of 4.3 mg/day or 5.5 mg/day, respectively. Male ACI/N rats used in the study typically weighed ~150-275 g during the study based on the data presented, but rats treated with this compound weighed about 140-190 g based on the data presented. Average body weight is estimated to be about 160 g for these rats over the course of the study, resulting in estimated average daily doses of 26.8-34.3 mg/kg/day. Only 8 of the 10 dosed rats were analysed for tumors.

[l]Total dose in rats treated every other week for 10-17 weeks and then maintained on tap water for 10 weeks is reported as 0.3-0.5 g, so daily corrected dose was calculated at 0.3 g/140 days or 0.5 g/189 days. Body weight of 160 g was used as in footnote *k*, resulting in estimated average daily doses of 13.4-16.5 mg/kg/day.

Table S5. Structural Group 9 Nitrosamines: Details of Carcinogenicity Studies from which TD_{50} Values were Derived.

CAS Number	Duration of exposure (experiment)[a]	Species, sex, animal number	Dose route	Endpoint selected	Dose (mg/kg/day): tumor incidence[b]	TD_{50} (mg/kg/day)[c]	Reference[d]
55556-91-7	36 (60) weeks	Rat, male, 15 treated, no control animals	Drinking water	Nasal cavity, adenocarcinomas	1.96[e]: 14/15	0.499[f]	Lijinsky and Taylor[5]
55556-93-9	36 (60) weeks	Rat, male and female, 15 per sex, no control animals	Drinking water	Nasal cavity, squamous cell tumors and adenocarcinomas	2.33[g]: 13/15 (male) 2.33[g]: 15/15 (female)	0.596[f,h]	Lijinsky and Taylor[5]
15104-03-7	40 (70) weeks	Rat, females, 15 treated, no control animals	Drinking water	Upper gastrointestinal tract tumors	2.60[i]: 14/15	0.665[f]	Lijinksy and Taylor[10]
13603-07-1	50 (70) weeks	Rat, male and female, 14 per sex, no control animals	Drinking water	Upper gastrointestinal tract tumors	2.71[j]: 14/14 in both males and females	0.665[k]	Lijinksy and Taylor[10]
55556-85-9	36 (50) weeks	Rat, male, 15 treated	Drinking water	Nasal cavity, squamous cell tumors and adenomcarcinomas	2.38[l]: 13/15	0.819[f]	Lijinsky and Taylor[5]
100-75-4	116 (141) weeks	Rat, mixed sex, 34-78 per group	Drinking water	Liver, multiple tumor types	0: 0/40 0.0171: 3/78 0.0857: 5/75 0.429: 16/34 2.14: 11/34	0.974	LCDB[1]

37620-20-5	78 weeks	Rat, male, 16 per group	Drinking water	Esophagus, benign and malignant tumors	0: 0/16 10[m]: 13/16	4.14	Boyland *et al*[11]
14026-03-0	104 weeks	Rat, mixed sex, 20 per group	Drinking water	Olfactory nerve ependymo-blastoma	0: 0/20 25.7: 11/20	22.1	LCDB[1]
36702-44-0	104 weeks	Rat, mixed sex, 20 per group	Drinking water	Liver, multiple tumor types	0: 0/20 25.7: 6/20	49.4	LCDB[1]
17721-95-8	50 (120) weeks	Rat, male and female, 15 per sex, no control group	Drinking water	NA	1.74[n]	Not carcinogenic	Lijinksy and Taylor[10]
55557-03-4	73 (106) weeks	Mouse, female, 43 control, 31 treated	Drinking water	NA	0 8.05	Not carcinogenic	LCDB[1]
6130-93-4	50 (120) weeks	Rat, male and female, 15 per sex	Drinking water	NA	2.10[o]	Not carcinogenic	Lijinksy and Taylor[10]
6238-69-3	50 (130) weeks	Rat, male and female, 15 per sex	Drinking water	NA	1.81[p]	Not carcinogenic	Lijinsky and Taylor[12]
4515-18-8	75 (104) weeks	Rat, female, 15 treated	Drinking water	NA	0 4.42	Not carcinogenic	LCDB[1]

TD_{50} = dose resulting in tumors in 50% of animals; LCDB = Lhasa Carcinogenicity Database; NA = Not applicable.

[a]Experiment length if different than treatment duration.

[b]Tumor incidence (number of animal with tumors in selected endpoint/total number of animals analyzed for selected endpoint) is provided for each dose for compounds deemed carcinogenic. Incidence is not provided for compounds evaluated as non-carcinogenic.

[c]When reference is not LCDB, TD_{50} was calculated internally using R-code adapted from Thresher *et al*[4] based on the data from cited reference.

[d]Source of carcinogenicity study data reviewed and from which the presented data was selected.

[e]Total dose reported as 3.2 mmol. At a molecular weight of 128 g/mol, this is equivalent to 410 mg over the course of the study. Animals were dosed for 36 weeks (1.63 mg/day) and the total study duration was 60 weeks (0.98 mg/day). Assuming a male rat weight of 0.50 kg, the daily dose is 1.96 mg/kg/day.

[f]As there were no control animals included in the study a tumor incidence of 0 in 15 was assumed to allow a TD_{50} value to be estimated.

[g]Total dose reported as 3.2 mmol. At a molecular weight of 130 g/mol, this is equivalent to 416 mg over the course of the study. Animals were dosed for 36 weeks (1.65 mg/day) and the total study duration was 60 weeks (0.99 mg/day). Assuming a combined sex weight of 0.425 kg, the daily dose is 2.33 mg/kg/day.

[h]Given that there was a 100% tumor incidence in female rats, it is not possible to calculate a reliable TD_{50} value for females, therefore the tumor incidence of male and female rats was combined to estimate the TD_{50}.

[i]Total dose reported as 3.5 mmol. At a molecular weight of the compound is 128 g/mol, this is equivalent to 448 mg over the course of the study. Animals were dose for 50 weeks (1.28 mg/day) and the total study duration was 70 weeks (0.91 mg/day). Assuming a female rat weight of 0.350 kg, the daily dose is 2.60 mg/kg/day.

[j]Total dose reported as 4.4 mmol. At a molecular weight of 128 g/mol, this is equivalent to 563 mg over the course of the study. Animals were dosed for 50 weeks (1.61 mg/day) and the total study duration was 70 weeks (1.15 mg/day). Assuming a mixed rat sex weight of 0.425 kg, the daily dose is 2.71 mg/kg/day.

[k]As all animals treated with 3-methylnitrosopiperidine had gastrointestinal tumors, it is not possible to calculate a reliable TD_{50}. However, examination of the overall tumor incidence reveals a pattern like that reported for 4-methylnitrosopiperidine. Therefore, the TD_{50} of 3-methylnitrosopiperidine is predicted to be like that of 4-methylnitrosopiperidine.

[l]Total dose reported as 3.2 mmol. At a molecular weight of 130 g/mol, this is equivalent to 416 mg over the course of the study. Animals were dosed for 36 weeks (1.65 mg/day) and the total study duration was 50 weeks (1.19 mg/day). Assuming a male rat weight of 0.50 kg, the daily dose is 2.38 mg/kg/day.

[m]Dose reported as 5 mg/day. Animals were dosed for 78 weeks and the total study duration was 78 weeks. Assuming a male rat weight of 0.50 kg, the daily dose is 10 mg/kg/day.

[n]Total dose reported as 4.4 mmol. At a molecular weight of 142 g/mol, this is equivalent to 625 mg over the course of the study. Animals were dose for 50 weeks (1.79 mg/day) and the total study duration was 120 weeks (0.74 mg/day). Assuming a mixed rat sex weight of 0.425 kg, the daily dose is 1.74 mg/kg/day.

[o]Total dose reported as 4.4 mmol. At a molecular weight of 170 g/mol, this is equivalent to 748 mg over the course of the study. Animals were dose for 50 weeks (2.14 mg/day) and the total study duration was 120 weeks (0.89 mg/day). Assuming a mixed rat sex weight of 0.425 kg, the daily dose is 2.10 mg/kg/day.

[p]Total dose reported as 700 mg over the course of the study. Animals were dose for 50 weeks (2 mg/day) and the total study duration was 130 weeks (0.77 mg/day). Assuming a mixed rat sex weight of 0.425 kg, the daily dose is 1.81 mg/kg/day.

Table S6. Structural Group 10 Nitrosamines: Details of Carcinogenicity Studies from which TD_{50} Values were Derived.

CAS Number	Duration of exposure (experiment)[a]	Species, sex, animal number	Dose route	Endpoint selected	Dose (mg/kg/day): tumor incidence[b]	TD_{50} (mg/kg/day)[c]	Reference[d]
16339-07-4	74 days over 7.5 months	Rat, female, 7 control, 10 treated	Inhalation	Nasal cavity tumors	0: 0/7 4.6: 10/10	0.140[e]	Klein *et al*[13]
75881-18-4	30 (85) weeks	Rat, female, 20 per group	Drinking water	Nasal cavity carcinoma - olfactory	0: 0/20 0.259: 13/20 0.980: 18/20	0.153	LCDB[1]
67774-31-6	29 (50) weeks	Rat, female, 20 per group	Drinking water	Thymus, lymphoma, or leukaemia	0: 0/20 2.37[f]: 17/20	0.866	Singer *et al*[14]
75881-17-3	30 (40) weeks	Rat, female, 20 per group	Drinking water	Esophagus multiple tumor types	0: 0/20 3.98[g]: 19/20	0.921	Singer *et al*[14]
55380-34-2	35 (76) weeks	Syrian hamster, male, 20 per group	Gavage	Forestomach papilloma	0: 3/20 3.68: 9/20	3.1	LCDB[1]
140-79-4	52 (100) weeks	Mouse, male, 50 control, 22 treated	Drinking water	Lung adenoma	0: 3/50 8.67: 11/22	8.7	LCDB[1]
61034-40-0	50 (125) weeks	Rat, female, 20 per group	Drinking water	Liver, multiple tumor types	0:1/20 2.81: 6/20	9.1	LCDB[1]
5632-47-3[h]	Lifetime	Rat, female, 69 controls, 27 or 29 treated	Drinking water	Nasal cavity multiple tumor types	0: 0/69 16.3[i]: 8/29 32.6[i]: 13/27	34.6	Love *et al*[15]

TD_{50} = dose resulting in tumors in 50% of animals; LCDB = Lhasa Carcinogenicity Database.

[a]Experiment length if different than treatment duration.

[b]Tumor incidence (number of animal with tumors in selected endpoint/total number of animals analyzed for selected endpoint) is provided for each dose for compounds deemed carcinogenic. Incidence is not provided for compounds evaluated as non-carcinogenic.

[c]When reference is not LCDB, TD_{50} was calculated internally using R-code adapted from Thresher *et al*[4] based on the data from cited reference.

[d]Source of carcinogenicity study data reviewed, and from which the presented data was selected.

[e]100% tumor incidence observed in the only treatment group included on study, therefore does not result in a reliable estimate of $TD_{50.}$ This TD_{50} value was not considered in derivation of the AI for the structural class due to the limitation of the estimate.

[f]Total dose reported as 290 mg. Animals were dosed for 29 weeks (1.43 mg/day) and the total study duration was 50 weeks (0.83 mg/day). Assuming a female rat weight of 0.35 kg, the daily dose is 2.37 mg/kg/day.

[g]Total dose reported as 390 mg. Animals were dosed for 30 weeks (1.86 mg/day) and the total study duration was 40 weeks (1.39 mg/day). Assuming a female rat weight of 0.35 kg, the daily dose is 3.98 mg/kg/day.

[h]Data is summarized in LCDB for another carcinogenicity study conducted in male and female rats.[16] However, the study is considered less robust than the Love *et al* study[15] summarized in the table above. The study[16] included two treatment groups, had 10 animals in the treatment groups and the duration of administration was more limited (60 weeks). In addition, there was no specific site of carcinogenicity that was reported to have a significant increase in tumors. It was only when all tumor sites were considered that a statistically significant increase in tumors was observed.

[i]Animals were dosed 5 days a week in drinking water for life, with 20 mL of a 400 or 800 mg/L solution of 1-nitrosopiperazine. Assuming a mean body weight of 0.35 kg for female rats and adjusting for 7 days in a week, average daily doses of 16.3 and 32.6 mg/kg/day were administered.

Table S7. Structural Group 11 Nitrosamines: Details of Carcinogenicity Studies from which TD_{50} Values were Derived.

CAS Number	Duration of exposure (experiment)[a]	Species, sex, animal number	Dose route	Endpoint selected	Dose (mg/kg/day): tumor incidence[b]	TD_{50} (mg/kg/day)[c]	Reference[d]
53759-22-1	87 weeks	Rat, male, 9 control, 14 treated	Drinking water	Esophagus, squamous cell papilloma	0: 0/9 0.250: 10/14	0.0957	LCDB[1]
78246-24-9	36 (104) weeks	Rat, male, 12 per group	Drinking water	Nasal cavity, multiple tumor types	0: 0/12 2.08: 11/12	0.573	LCDB[1]
930-55-2	159 (164) weeks	Rat, male, 500 control, 80 per treated group	Drinking water	Liver, multiple tumor types	0: 3/500 0.0286: 1/80 0.095: 4/80 0.286: 17/80	2.47	LCDB[1]
56222-35-6	112 weeks	Rat, mixed sex, 24 control, 23 treated	Drinking water	Liver, hepatocellular carcinoma	0: 0/24 2.50: 5/23	8.11	LCDB[1]
55556-86-0	50 (130) weeks	Rat, no control, 15 males, 14 females	Drinking water	Hepatocellular	3.23[e]: 2/29	31.3[f]	Lijinsky and Taylor[17]
75195-75-4	3X per week for 7.3 (37.3) weeks	Mouse, female, 25 per group	ip injection	Lung tumors	0: 10/25 3.6[g]: 19/25	Study design does not allow for a reliable estimate of TD_{50}	Castonguay *et al*[7]
75195-74-3	3X per week for 7.3 (37.3) weeks	Mouse, female, 25 per group	ip injection	NA	0: 10/25 3.6[g]:12/25	Not carcinogenic	Castonguay *et al*[7]

7519-36-0	75 (104) weeks	Rat, female, 15 per group	Drinking water	NA	0 4.42	Not carcinogenic	LCDB[1]
30310-80-6	75 (104) weeks	Rat, female, 15 per group	Drinking water	NA	0 4.42	Not carcinogenic	LCDB[1]

TD_{50} = dose resulting in tumors in 50% of animals; CI: Confidence Interval of TD_{50}; LCDB = Lhasa Carcinogenicity Database; NA = Not applicable; ip = intraperitoneal.

[a]Experiment length if different than treatment duration.

[b]Tumor incidence (number of animal with tumors in selected endpoint/total number of animals analyzed for selected endpoint) is provided for each dose for compounds deemed carcinogenic. Incidence is not provided for compounds evaluated as non-carcinogenic.

[c]When reference is not LCDB, TD_{50} was calculated internally using R-code adapted from Thresher *et al*[4] based on the data from cited reference.

[d]Source of carcinogenicity study data reviewed and from which the presented data was selected.

[e]Dosed 20/ml/rat/day (5 days/week) of a 250 mg/L dosing solution for 50 weeks for a total dose of 1250 mg/rat. Assuming an average rat weight of 0.425 kg and correcting for experimental duration of 130 weeks, the daily dose is 3.23 mg/kg/day.

[f]Calculated internally assuming zero tumors for controls since there were no controls included.

[g]Total dose reported as 0.12 mmol/mouse. At a molecular weight of 193.2 mg/mmol, this is equivalent to 23 mg total over 7.3 week. Animals were examined 30 weeks after treatment stopped for a total experiment duration of 37.3 weeks after treatment ended (0.089 mg/day). Assuming a female mouse weight of 0.025 kg, the daily dose is 3.6 mg/kg/day.

Table S8. Structural Group 12 Nitrosamines: Details of Carcinogenicity Studies from which TD_{50} Values were Derived.

CAS Number	Duration of exposure (experiment)[a]	Species, sex, animal number	Dose route	Endpoint selected	Dose (mg/kg/day): tumor incidence[b]	TD_{50} (mg/kg/day)	Reference[c]
55557-00-1	30 (133) weeks	Rat, female, 20 per group	Drinking water	Gastrointestinal tract-upper, carcinoma	0: 0/20 0.0101: 1/20 0.0264: 3/20 0.072: 7/20 0.269: 13/20 1.18: 10/20 2.93: 14/20	0.242	LCDB[1]
932-83-2	32 (60) weeks	Mouse, male, 194 in control, 10 in treatment group	Drinking water	Esophagus, multiple tumor types	0: 0/194 3.16: 9/10	0.313	LCDB[1]

TD_{50} = dose resulting in tumors in 50% of animals; LCDB = Lhasa Carcinogenicity Database/

[a]Experiment length if different than treatment duration.

[b]Tumor incidence (number of animal with tumors in selected endpoint/total number of animals analysed for selected endpoint) is provided for each dose for compounds deemed carcinogenic. Incidence is not provided for compounds evaluated as non-carcinogenic.

[c]Source of carcinogenicity study data reviewed and from which the presented data was selected.

Table S9. Structural Group 13 Nitrosamines: Details of Carcinogenicity Studies from which TD_{50} Values were Derived.

CAS Number	Duration of exposure (experiment)[a]	Species, sex, animal number	Dose route	Endpoint selected	Dose (mg/kg/day): tumor incidence[b]	TD_{50} (mg/kg/day)	Reference[c]
59-89-2	100 (126) weeks	Rat, female, 24 to 100 per group	Drinking water	Liver, multiple tumor types	0: 1/80 0.00227: 6/100 0.00583: 5/99 0.0146: 7/47 0.0356: 9/48 0.0842: 22/48 0.249: 23/24	0.129	LCDB[1]
1456-28-6	66 (87) weeks	Syrian hamster, male, 15 per group	Gavage	Lung, multiple tumor types	0: 0/15 1.31: 7/15 2.63:9/15 5.24: 5/15 10.5:5/15	1.22	LCDB[1]
67587-52-4[e]	50 (122) weeks	Rat, female, 20 per group	Drinking water	NA	0 0.265 0.530	Not carcinogenic	LCDB[1]
34993-08-3	50 (140) weeks	Rat, female, 30 control, 15 treated	Drinking water	NA	0 2.62[d]	Not carcinogenic	Lijinsky and Taylor[18]

TD_{50} = dose resulting in tumors in 50% of animals; LCDB = Lhasa Carcinogenicity Database; NA=Not applicable.

[a]Experiment length if different than treatment duration.

[b]Tumor incidence (number of animal with tumors in selected endpoint/total number of animals analyzed for selected endpoint) is provided for each dose for compounds deemed carcinogenic. Incidence is not provided for compounds evaluated as non-carcinogenic.

[c]Source of carcinogenicity study data reviewed and from which the presented data was selected.

[d]Total dose reported as 900 mg. Animals were dosed for 50 weeks (2.57 mg/day) and the total study duration was 140 weeks (0.92 mg/day). Assuming a female rat weight of 0.35 kg, the daily dose is 2.62 mg/kg/day.

[e]There is a carcinogenicity study conducted in mice that concludes that 4-nitrosomorpholin-2-ol is weakly carcinogenic (Hecht et al., 1989). However, due to the limited duration of the study (animals exposed for 10 weeks and total duration of study 30 weeks) a TD_{50} value was not calculated. In this study the incidence of lung adenomas was 40% in control animals and 60% in treated animals.

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