Carcinogenic Potency Database
Available Experimental Results to Examine Possible Adjustment of TTC Exposure Limits for Short or Intermittent Exposures

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NTP Stop Exposure Studies in CPDB

NTP analysis (Halmes et al.) of 11 NTP bioassays with stop exposure groups found that for some chemicals stop exposures had more target sites, and that for others there was no difference.

- **Results added to Halmes table (next slide):**
  - When doses (in ppm) were the same, stop groups did not have more target sites (exception is Butadiene by inhalation).
  - The greater number of target sites occurred when doses in stop groups were higher than full and exceeded the MTD by up to 9 fold.
  - Conclusion: Experimental design does not permit analysis of target sites in stop vs full exposures due to exceeding the MTD.
- ***o*-Nitroanisole example from CPDB analyses (2 slides of lifetables):**
  - Results: body weights vastly reduced at 13 weeks in stop groups, and rats with tumors were dead early. Full exposure groups at the MTD did not develop any of those tumors.

NTP: 11 Chemicals with Stop Exposure Studies
Added results to Table 3 of Halmes et al.

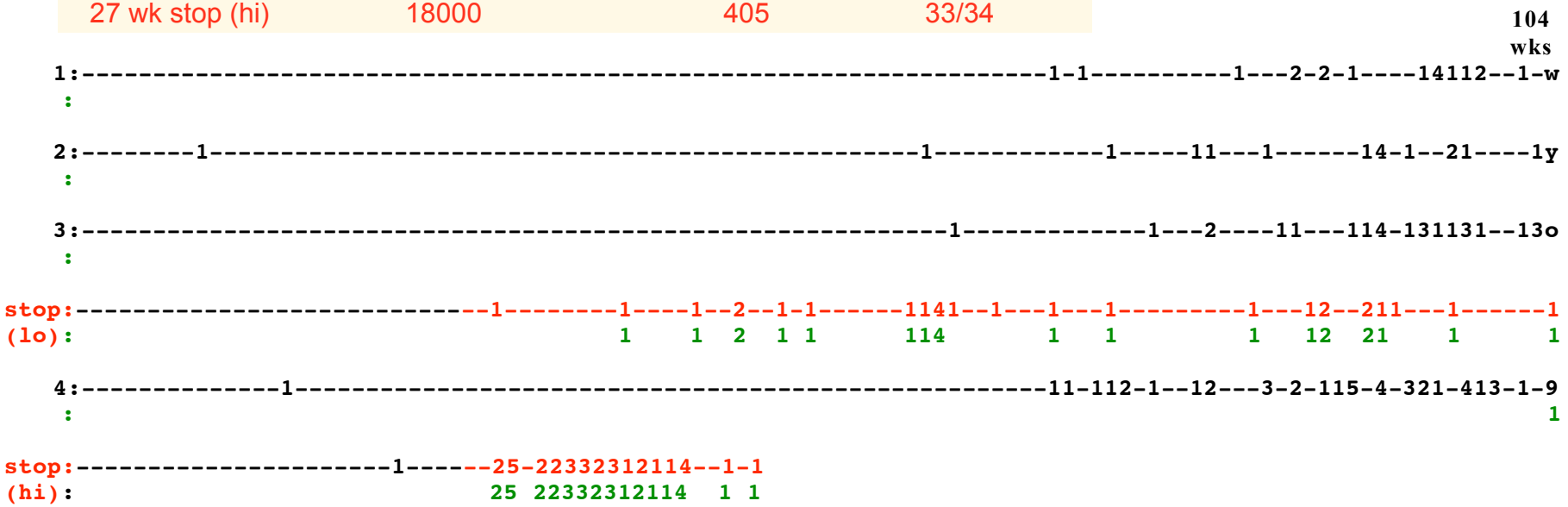
Chemical	Number of sites Stop>Full	Highest administered ppm Stop/Full	Weeks dosed in stop	Added: Body weight 13 week sacrif. (% of control)
1-Amino-2,4-dibromoanthraquinone	0	=	36, 66	
Coumarin (gav)	0	=	39, 65	
3,4-Dihydrocoumarin (gav)*	0	=	40, 65	
Salicylazosulfapyridine*	0	=	26	
1,3-Butadiene (inh)	5	=	26 (<hi 40, 52)	
Oxazepam*	0	2x	26	
2,2-Bis(bromomethyl)-1,3-propanediol	12	2x	13	76%
o-Nitroanisole	**5**	**3x, 9x**	**27**	**86%, 48%**
Methyleugenol*	2	2x	52	
Pentachlorophenol*	2	1.66x	52	
Furan (gav)*	1	3.75x	13	

Notes: * = Not mutagenic in Salmonella
Administered by diet, except where indicated.
Male rats, except 1,3-Butadiene is male mice.

Source: Halmes NC et al., Toxicol. Sci. (2000) 58:32-42; NTP Technical Reports

NTP: *o*-Nitroanisole - Male Rats, Urinary Bladder Transitional Epithelium Carcinoma

Group	Administered ppm	Average mg/kg/day	Tumors
1 control [stop]	0	0 [0]	0/50 [0/21]
2	222	8.75	0/50
3	666	26.2	0/50
27 wk stop (lo)	6000	62.3	23/27
4	2000	79.0	1/51
27 wk stop (hi)	18000	405	33/34



Stop, Clear evidence: urinary bladder, kidney, large intestine
Full, Some evidence: mononuclear cell leukemia only

Each dash = a week on test; number on line = number dead; number below line (green) is number with bladder carcinoma.
Number sacrificed at 104 weeks: 9 + numerical-equivalent in alphabet (e.g., “y” = 34 animals sacrificed)

Source: Carcinogenic Potency Database.

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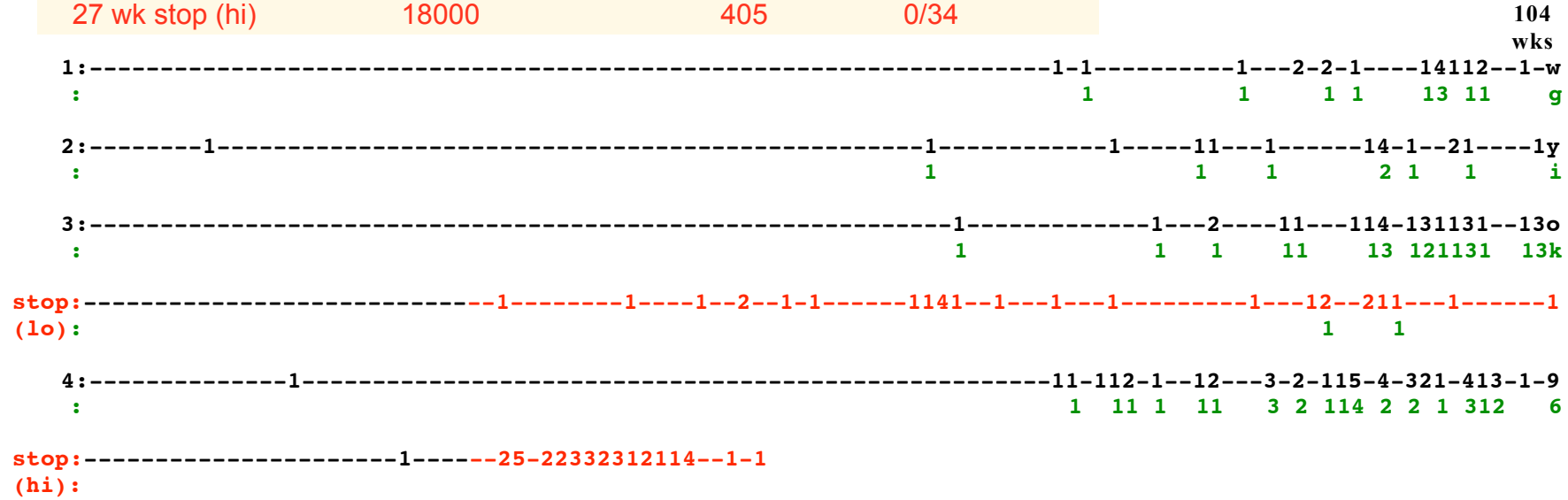

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Available results in CPDB from General Literature

Both stop and full exposure in same paper, species, strain, sex and route with same experiment length

	Mutagenicity in Salmonella		
	+	-	?
Positive chemicals (N=24)	16	4	4

Examples	
Equal doses stop and full (N=15)	HC Blue No. 1, Potassium bromate, BHA, Catechol, Hexachlorocyclohexane, Methylene chloride, Phenobarbital
Unequal doses stop and full (N=9)	Acrylonitrile, 1,4-Dichlorobutene, Dinitrosopiperazine, DEN

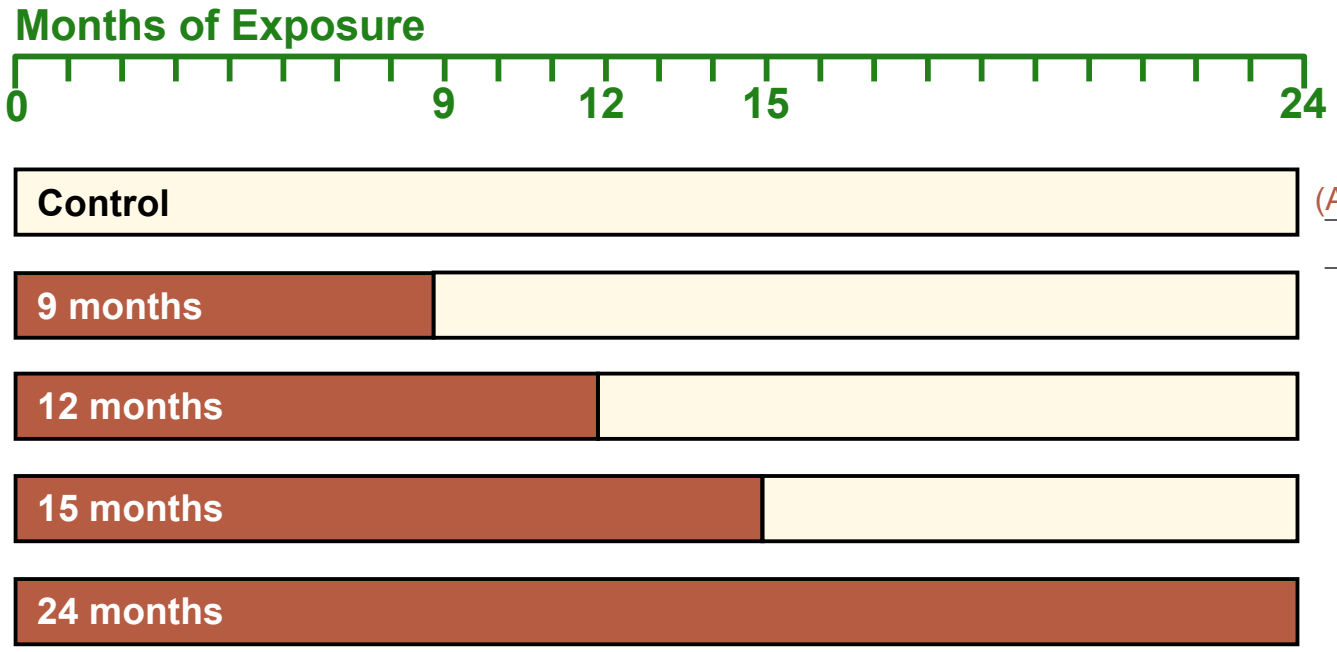
CPDB general literature experiments limited to at least 6 months dosing and 1-year experiment length.

Source: Carcinogenic Potency Database. http://potency.berkeley.edu

Example: 2-AAF Megamouse

Female Mice, Highest Administered Dose, 24-month sacrifice
Hepatocellular Carcinoma and Urinary Bladder

Result: Haber's Rule underestimates liver carcinoma. Incidence greater than expected at shorter exposures.



% Liver Tumors
(Administered Dose in ppm)

	0	60	75	100	150
9 months	2	12	15	14	27
12 months	2	9	19	15	31
15 months	2	13	16	17	21
24 months	2	17	20	29	43

Starting age: 3-4 weeks

Design: 4 Equal administered dose levels all exposure periods plus
3 extra lower dose levels in 24 month exposure period

Source: Littlefield NA et al., J. Environ. Pathol. Toxicol. (1980) 3:17-34

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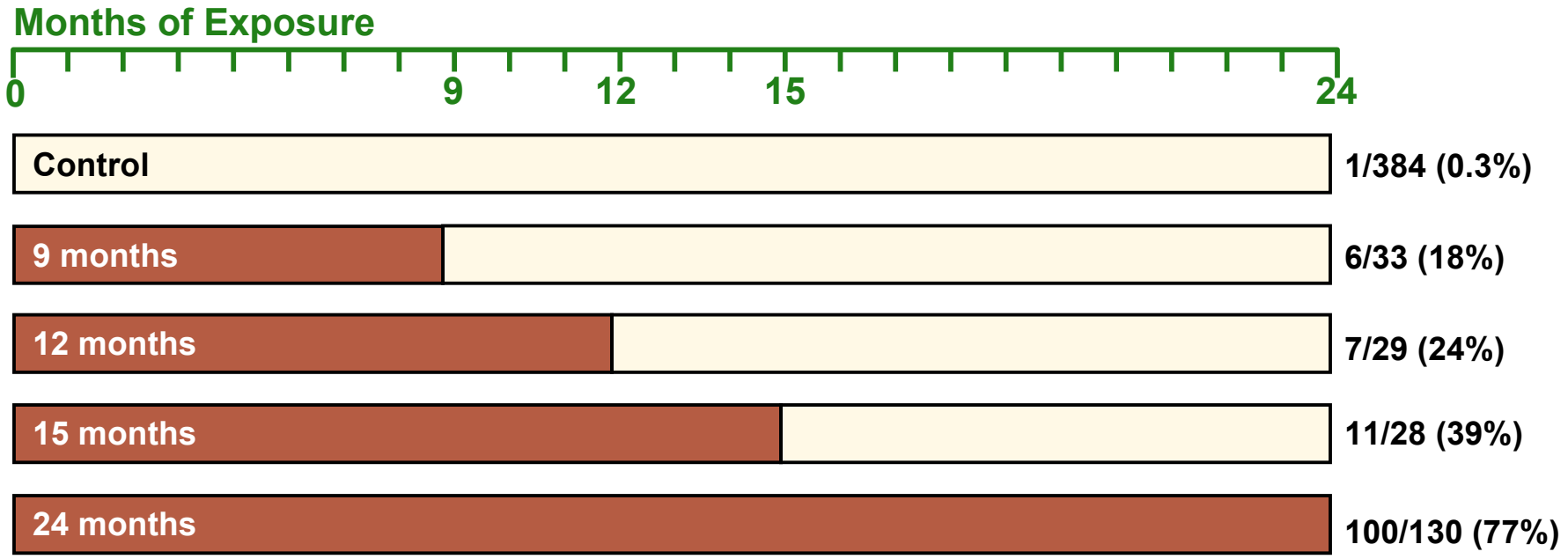

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NCI: 25 Chemicals Tested in Monkeys in CPDB

Design: 6-13 animals per experiment, colony controls
Length of experiment: up to 32 years

Carcinogenicity Results: Mutagens 11/21. Nonmutagens 0/4.

Stop exposure design: 6 Model rodent carcinogens with exposure stopped at 5 years
Length of experiment 20-32 years

6 Mutagens* - dosing stopped after 5 years	Experiment length	Carcinogenicity
2-Acetylaminofluorene	26	-
2,7-Acetylaminofluorene	32	-
N,N-Dimethyl-4-aminoazobenzene	20	-
3-Methyl-4-dimethylaminoazobenzene	24	-
3-Methylcholanthrene	26	-
Urethane	25	+

* Results may be due to lack of power, differences in metabolism between rodents and monkeys, or short dosing period.

IQ induced hepatocellular carcinoma in 100% of monkeys in 6 years with 6 years of dosing.

Sources: Carcinogenic Potency Database. http://potency.berkeley.edu; Gold et al., Envir. Health Perspect. (1999) 107(S4): 527-600

Chemicals in Both CPDB and Single Exposure Carcinogenicity Database (SECD of Calabrese)

SECD 800 chemicals: 426 carcinogenic
CPDB 1523 chemicals: 786 carcinogenic

	Number of Chemicals
All chemicals in both databases	176
++ Both databases	80
++ Same species, route	25
++ Same species, route, strain, sex	11

SECD is not publicly available; however, Dr. Calabrese has offered to collaborate.

Source: Carcinogenic Potency Database. http://potency.berkeley.edu; Single Exposure Carcinogenicity Database (Calabrese EJ, Blain RB, Toxicol Sci. 1999;50(2):169-85.

Chemicals in CPDB from General Literature

Dosing 1x or 2x per week by gavage, intravenous or intraperitoneal injection

Chemicals	1x/Week	2x/Week
Positive	56	39
Not positive	42	14

Experiments	1x/Week	2x/Week
Positive	80	53
Not positive	63	32

Examples of positive chemicals	
1x per week	16 Nitroso Compounds Beta-butyrolactone, 2-Nitrobutane, 5-Azacytadine, Procarbazine
2x per week	17 Nitroso Compounds Carbon tetrachloride, 1-Nitropyrene, 1,2-Propylene oxide, Safrole

Source: Carcinogenic Potency Database. http://potency.berkeley.edu

CPDB Chemicals Among 768 Used for TTC

Chemicals Having an Experiment with Exposure Stopped at Half the Experiment Length or Earlier

Mutagenicity in Salmonella	Number
Mutagens	54
Non mutagens	11
Mutagenicity unknown	46

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