

Supplemental Table 1

Mitochondria as a Target of Environmental Toxicants

Joel N. Meyer, Maxwell C.K. Leung, John P. Rooney, Ataman Sendoel, Michael O. Hengartner,

Glen E. Kisby, Amanda S. Bess

This Supplemental Table is a compilation of studies that have directly compared nDNA to mtDNA damage after chemical exposure, or by other means provided data supporting the importance of mtDNA damage for the toxicity of those chemicals (or, in a few cases, nonchemical stressors). Earlier (pre-1970) reports exist but are not included due to difficulties in interpreting earlier methodologies. Similarly, early reports comparing oxidative damage in mtDNA and nDNA before understanding the importance of artefactual oxidation during DNA isolation (Anson *et al.*, 2000) have not been included.

Chemical or Stressor	Model	Approach	mtDNA/nDNA damage ratio	Citation
2-Acetylaminofluorene (2AAF)	male rats	³² P postlabeling	~2	Balansky et al. 1996
Aflatoxin B ₁	rat liver	LSC	~4-6	Niranjan et al 1982
	rat, mouse, and hamster liver	LSC	2-20 (no damage detected in mice)	Niranjan et al., 1986
	rat liver	LSC	0.47	Shamsuddin et al. 1987
5-aminolevulinic acid	cell culture (various cell types)	QPCR	~1-2	Onuki et al., 2004
2-Amino-3-methylimidazo[4,5-f]quinoline (IQ)	rat liver	³² P postlabeling	0.5 after one dose, ~1 after 10 doses	Davis et al. 1994
2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)	rat liver	³² P postlabeling	~1 after one dose, ~2 after 10 doses	Davis et al. 1994
Benzo(a)pyrene	MCL-5 cells	Chemoiluminescent immunoassay	~10	Divi et al. 2002
	killifish (larvae and adult tissues)	QPCR	~1-4	Jung et al. 2009a, 2009b, 2010
	male rats	³² P postlabeling and SFS	1.5-2	Balansky et al. 1996

BPDE; BPDE/BaP; BaP	various cell lines	LSC	40-100 (Backer and Weinstein papers); 4.8-16.5 (Stairs et al.); 1 (Ayala-Torres et al.)	Backer and Weinstein 1980, 1982; Stairs et al., 1983; Ayala-Torres et al., 2000
Bleomycin	A549 cells	QPCR	~2	Brar et al., 2012
Butadiene diepoxide	human fibroblasts	QPCR	>1	Ayala-Torres et al., 2000
Carcinogens (multiple; benzidine and 4-Nitroquinoline- N-oxide especially)	yeast	induction of petites and growth on a nonfermentable medium	not directly measured	Egilsson et al., 1979
Cigarette Smoke	male rats	³² P postlabeling	0.65-15	Balansky et al. 1996
	bronchoalveolar lavage cells (human)	QPCR	13; mtDNA deletions also noted	Ballinger et al., 1996
Cisplatin	CHO cells	Southern Blot	0.64-0.84	LeDoux et al. 1992
	CHO cells	Dissociation- enhanced lanthanide fluoroimmunoassay (DELFI A)	~4-6	Olivero et al. 1995
	Exposure of young adult (12 h post-L4) <i>C. elegans</i> to 1 mM in NGM plates for 12 h resulted in ~0.7 nDNA lesions/10 kb, vs ~0.3 mtDNA lesions.	QPCR	~0.5	unpublished data: Meyer JN, Sendoel A, Hengartner MO, Van Houten B
	pregnant rats dosed; maternal and fetal tissues examined	DELFI A	<<1 to 40 or more; highly variable by tissue	Giurgiovich et al. 1997
	rat gastric and intestinal tissue	QPCR	nDNA damage not detected	Yañez et al., 2003
	HNSCC cells	Atomic absorption spectroscopy of isolated DNA	~200-600	Yang et al. 2006
	L1210 cells	QPCR	~0.4	Kalinowski 1992
tumors in mice	Atomic absorption spectroscopy of isolated DNA	~50	Murata et al., 1990	
Decarbamoyl mitomycin C	MCF-7 cells	QPCR	~0.4	Boamah et al., 2010
7H-Dibenzo(c,g)- carbazole and derivatives	mouse liver	³² P postlabeling	0.2-1.1	Périn-Roussel et al. 1995
Diepoxybutane	6C2 chicken cells	QPCR	~1	LaRiviere et al. 2009
Diethylstilbestrol	rat liver and kidney	³² P postlabeling	~7 (liver) and ~15 (kidney)	Thomas and Roy, 2001

Dimethylnitrosamine	rat liver	gel electrophoresis, isopycnic centrifugation	1.7-2.8	Wilkinson et al. 1975
	rat liver	HPLC/RIA	1.4	Myers et al. 1988
	rat liver	LSC	2.2-7.7	Wunderlich et al. 1972
	hamster liver	LSC	3.8-6.0	Wunderlich et al. 1972
Dioxin	mouse liver	Gel electrophoresis with enzyme (formamide-pyrimidine DNA N-glycosylase) digestion	~2	Shen et al., 2005
Doxorubicin (adriamycin)	male rat heart and liver	LC/ESI/MS/MS for 8-oxo-dG	~ 2	Palmeira et al. 1997
	MCF-7 cells	gel electrophoresis for interstrand crosslinks	~0.7	Cullinane et al., 2000
	human autopsy samples	PCR	mtDNA depletion and deletions/mutations observed; nDNA damage not directly measured	Lebrecht et al., 2005
	Exposure of young adult (12 h post-L4) <i>C. elegans</i> to 1 mM in NGM plates for 12 h resulted in ~0.7 nDNA lesions/10 kb, vs ~0.3 mtDNA lesions.	QPCR	~1	unpublished data: Meyer JN, Sandoel A, Hengartner MO, Van Houten B
Epichlorohydrin	6C2 chicken cells	QPCR	~0.28	LaRiviere et al. 2009
Epibromohydrin	6C2 chicken cells	QPCR	~0.38	LaRiviere et al. 2009
Ethanol	rat liver	QPCR	no direct comparisons to nDNA	Bailey et al., 2006; Cakir et al., 2007
Etoposide	Exposure of young adult (12 h post-L4) <i>C. elegans</i> to 1 mM in NGM plates for 12 h resulted in ~0.7 nDNA lesions/10 kb, vs ~0.3 mtDNA lesions.	QPCR	<1 (no mtDNA damage detected)	unpublished data: Meyer JN, Sandoel A, Hengartner MO, Van Houten B
5-Fluorouracil	rat gastric and intestinal tissue	QPCR	nDNA damage not detected	Yañez et al., 2003

H ₂ O ₂	cell culture (various cell types), <i>C. elegans</i>	QPCR	2-3 fold or more	Yakes and Van Houten 1997; Salazar and Van Houten, 1997; Ballinger et al., 1999; Ballinger et al., 2000; Santos et al., 2003, 2004, 2006; Hunter et al., 2012; Furda et al., 2012; Ayala-Torres et al., 2000
Hypoxia	rat brain	QPCR	greater in mtDNA (not quantified precisely)	Englander et al., 1999
Hypoxia caused by cobalt chloride	PC12 cells	QPCR	greater in mtDNA (not quantified precisely)	Wang et al., 2000
Indomethacin	rat gastric and intestinal tissue	QPCR	nDNA damage not detected	Yañez et al., 2003
Lipopolysaccharide	rat liver	PCR	no direct comparison; mtDNA depletion and deletions measured	Suliman et al., 2003, 2004, 2005
Menadione	HeLa and RCSN-3 cells	Alkaline Southern Blot (mtDNA); Quantitative Alkaline Gel Electrophoresis (nDNA)	mtDNA damage detectable at doses lower than for nDNA damage	Koczor et al 2009
Methylazoxymethanol (MAM), activated (no DNA damage detected without activation)	Exposure of L1 stage <i>C. elegans</i> to 400 uM activated MAM (Eizirik and Kisby 1995) for 24 h in K medium without food led to 0.4-0.6 lesions/10 kb 24 and 48 h later, in both genomes.	QPCR	~1	unpublished data: Bess AS, Kisby GE, Meyer JN
Methylene blue, photoactivated	human fibroblasts	Southern Blot	much more mtDNA damage (nDNA damage not detected)	Anson et al., 1998
Methylmethane-sulfonate (MMS)	rat liver	gel electrophoresis, isopycnic centrifugation	~1	Wilkinson et al. 1975
	<i>C. elegans</i> dosed in liquid	QPCR	~0.5	Hunter et al., 2012
	mouse embryonic fibroblasts	QPCR	~0.67	Furda et al., 2012
	human fibroblasts	QPCR	~0.67	Santos et al. 2006
4-(Methylnitrosamino)-1-(3pyridyl)-1-butanone (NNK)	rat lung and liver	LC-ESI-MS/MS-SRM	~2-4.5	Stepanov and Hecht 2009

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	mouse brain	QPCR	~2 (Mandavilli study); no direct comparison (Yamaguchi study)	Mandavilli et al 2000, Yamaguchi et al., 2006
Methylnitrosourea (MNU)	CHO cells	Southern Blot	higher in mtDNA	LeDoux et al. 1992
N-nitroso-N-butylurea	rat liver	HPLC/RIA	2.3	Myers et al. 1988
N-methyl-N-nitrourea (DMN)	rat liver	LSC	2.9-16.9 (liver) 4.4-7.5 (kidney/heart)	Wunderlich et al. 1970
Nitrogen Mustard	CHO cells	Southern Blot	~0.67	LeDoux et al. 1992
3-Nitropropionic acid (3-NPA)	PC12 cells	QPCR	~2	Mandavilli et al., 2005
Nucleoside reverse transcriptase inhibitors (NRTIs): Zidovudine, Lamivudine or combination	pregnant mice and pups	QPCR	mtDNA damage detected; nDNA damage not measured (note that this and many other NRTI studies also showed mtDNA depletion)	Chan et al., 2007
Peroxynitrite	HASMC, HUVEC cells	QPCR	variable, up to several fold (nDNA damage often undetectable)	Ballinger et al., 2000
	mouse liver; dosing with acetaminophen	slot blot for DNA quantity, gel analysis for nDNA fragmentation	not a direct quantitative comparison; mtDNA depletion and nDNA fragmentation observed	Cover et al., 2005
Polycyclic aromatic hydrocarbons	isolated DNA	Liquid Scintillation Counting (LSC)	47 – 589	Allen and Coombs 1980
Rotenone	ARPE cells	QPCR	up to 2	Wang et al., 2009
Tert-butyl hydroperoxide	human blood lymphocytes	PCR	not a direct quantitative comparison; mtDNA depletion and damage observed	Hollins et al., 2006
Tirapazamine (with hypoxia)	LXFL529 cells	QPCR	~2	Ayala-Torres et al., 2000
Troglitazone	primary human hepatocytes	Alkaline Southern Blot	toxicity was rescued by a mitochondrial-targeted DNA repair enzyme	Rachek et al 2009

Ultraviolet C radiation	multiple models: cell culture, <i>C. elegans</i> , purified DNA	Southern Blot, QPCR	~1	LeDoux et al. 1992; Kalinowski et al., 1992; Ayala-Torres et al., 2000; Meyer et al., 2007; Boyd et al., 2010; Bess et al., 2012; Bess et al., 2013
Vincristine	Exposure of young adult (12 h post-L4) <i>C. elegans</i> to 1 mM in NGM plates for 12 h resulted in ~0.7 nDNA lesions/10 kb, vs ~0.3 mtDNA lesions.	QPCR	<1 (no mtDNA damage detected)	unpublished data: Meyer JN, Sendoel A, Hengartner MO, Van Houten B

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