N-ACETYLCYSTEINE (NAC): ITS USES AND ABUSES

Nuran Ercal

Department of Chemistry

University of Missouri-Rolla

Rolla, MO 65401

Tel: 573/341-6950

nercal@umr.edu

Hande Gurer-Orhan

Department of Toxicology

University of Hacettepe

Faculty of Pharmacy

Ankara, 06100 Turkey

handegurer@yahoo.com

NAC Structure

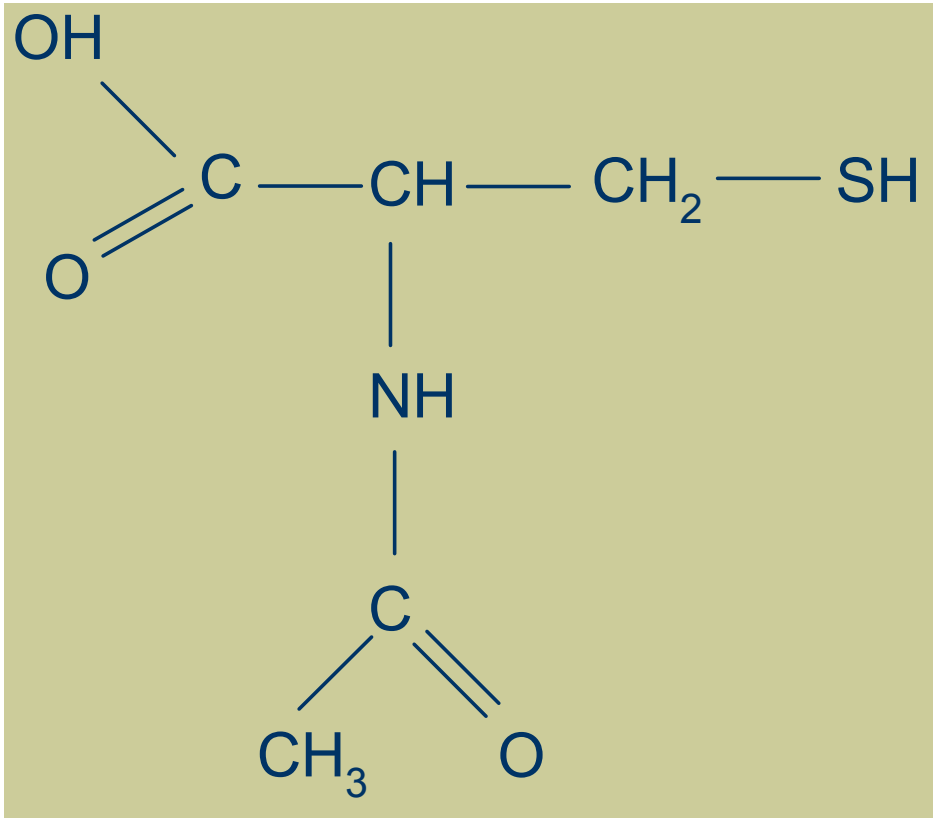
chemical formula :

$C_5H_9NO_3S$

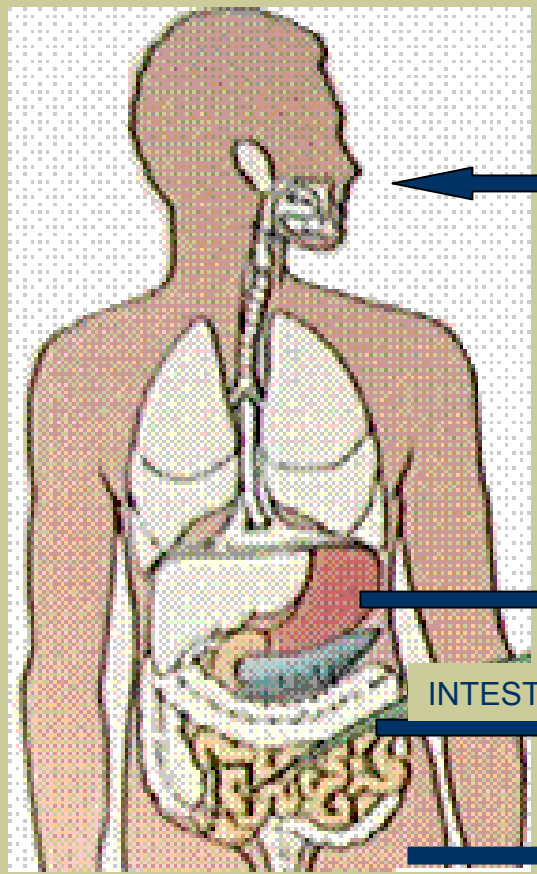
molecular weight :

163.2 g/mol

Only L-NAC is active; L-NAC is metabolized to cysteine and then GSH, but D-NAC is not.



Metabolism of NAC



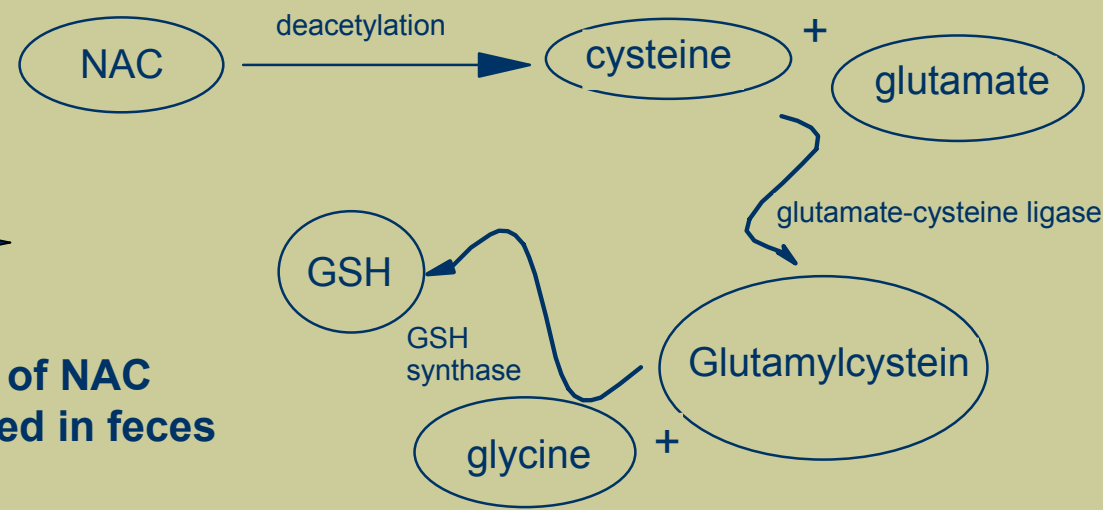
Oral NAC administration
Rapid absorption

Extensive first-pass metabolism in liver and intestine

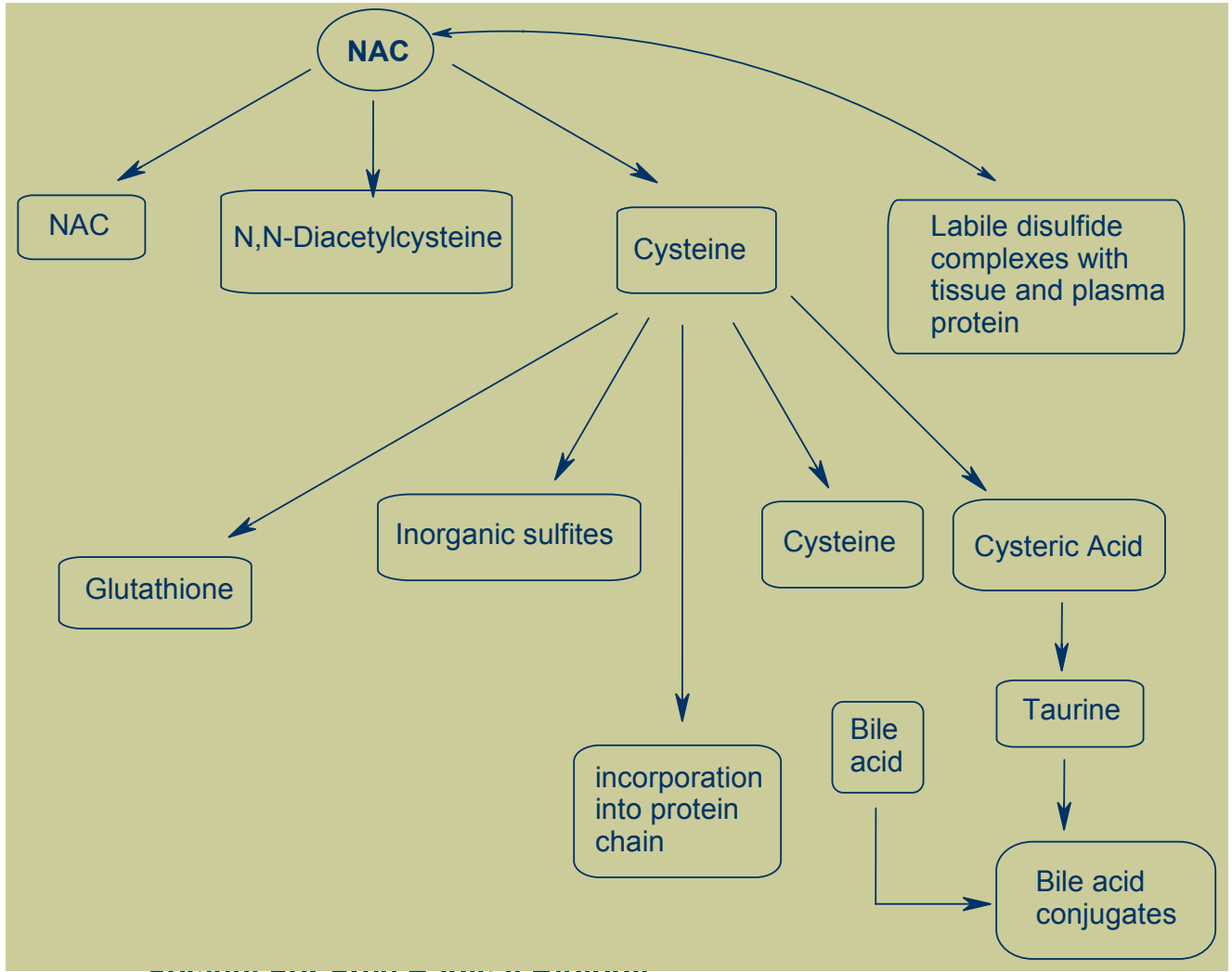
LIVER

INTESTINE

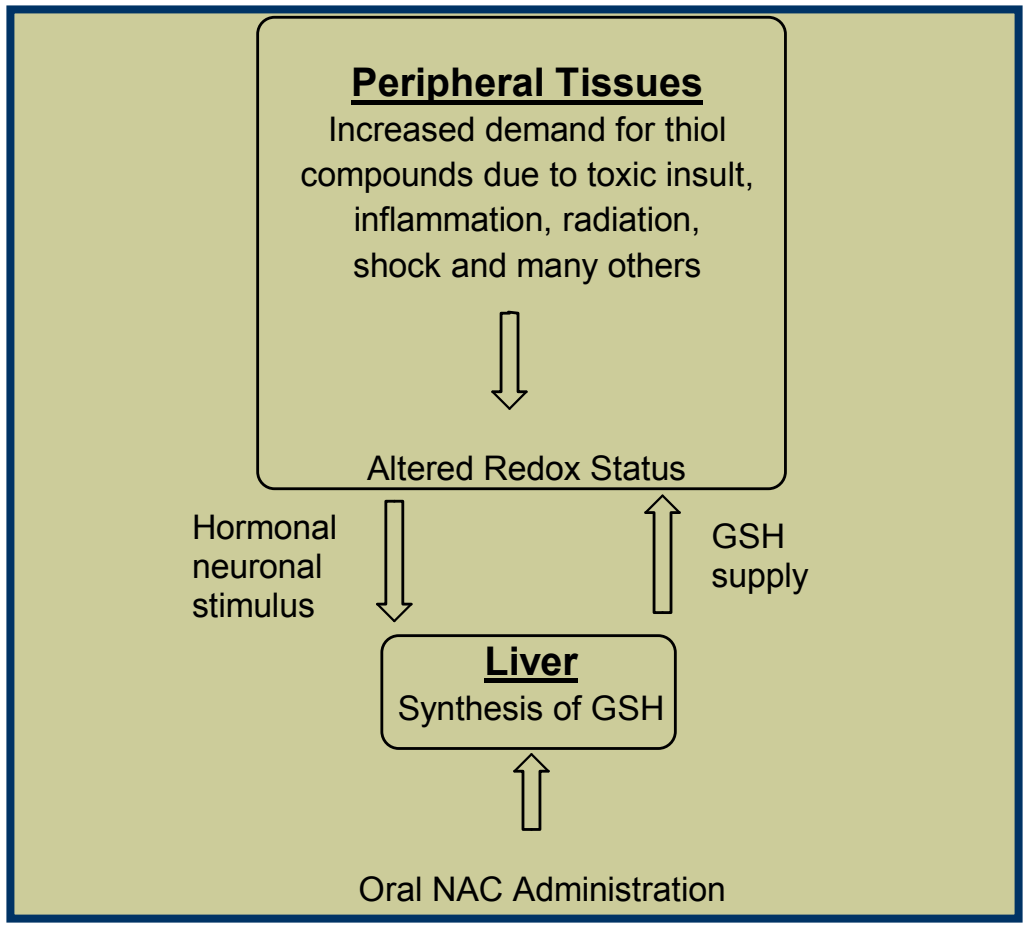
3% of NAC excreted in feces



Metabolism of NAC



Interaction between NAC and GSH Homeostasis

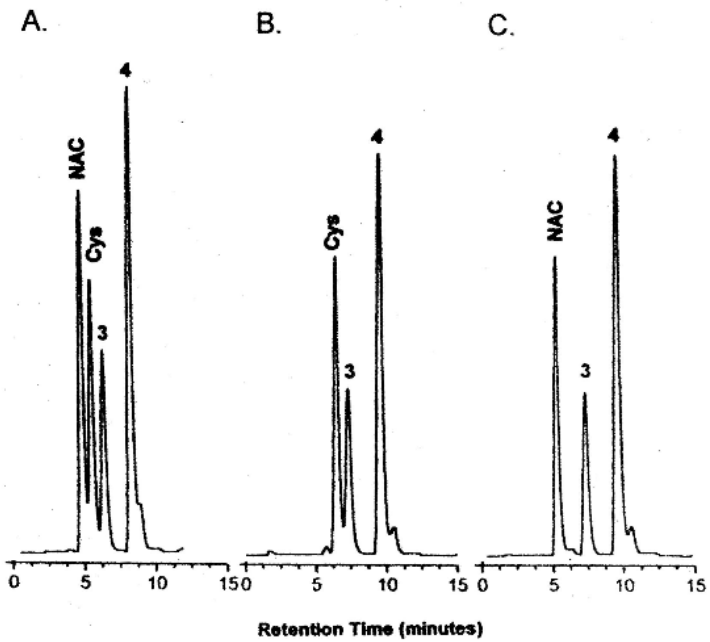


Detection of NAC in Biological Systems

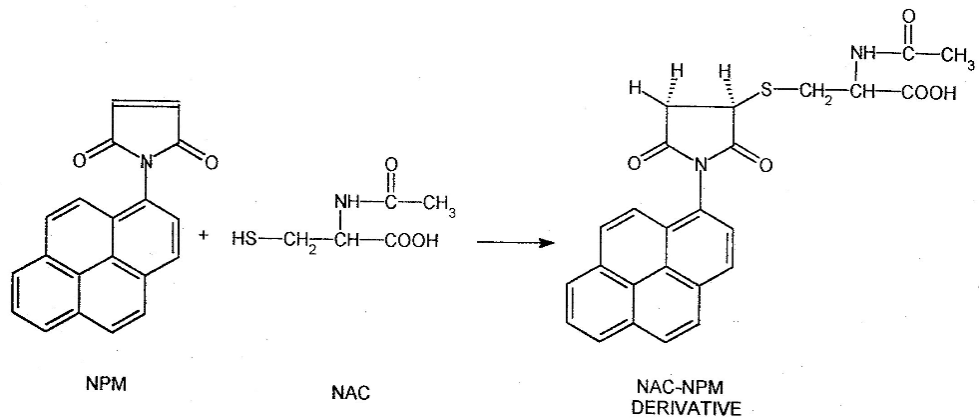
Reagents used to derivatize NAC	Reference
N-(1-Pyrenyl)maleimide	Kagedahl B & Kallberg M. *J. Chromatogr*. 229: 409,1982; Ercal N. *et al. J. Chromatogr. B.* 685: 329-334,1996.
N-(7-Dimethylamino-4-methylcoumarinyl)maleimide	Kagedahl B & Kallberg M. *J. Chromatogr.* 229: 409,1982.
4-(Aminosulfonyl)-7-fluoro-2,1,3-benzoxadiazole	Toyooka T & Imai K. *J. Chromatogr.* 282: 495,1983.
Ammonium 7-fluoro-2,1,3- benzoxadiazole	Toyooka T & Imai K. *Anal. Chem.* 56: 2461, 1984.
2,4-Dinitro-1-fluorobenzene	Lewis PA *et al*. *J. Chromatogr.* 327: 261, 1985.
Monobromobimane	Cotgreave IA & Moldeus P. *Biopharm. Drug Dispos*. 8: 365, 1987.
o-Phthalaldehyde	Gabard B & Masher H. *Biopharm. Drug Dispos*. 12: 343, 1991.
ThioGlo TM[3]	Ercal N *et al. J Chromatogr B Biomed Sci Appl* 753:287-92, 2001.

Modified from: Moldeus P & Cotgreave IA. *Meth. Enzymol.* 234: 482-492, 1994.

Detection of NAC-NPM peak in tissues by HPLC



(A) Standard chromatogram containing peaks from both the NAC-NPM (500 nM) and cys-NPM adducts.
(B) Chromatogram obtained from kidney tissue (no NAC peak).
(C) Chromatogram showing 425 nM NAC peak from liver tissue.
Peaks 3and 4 labelled in each chromatogram represent NPM-derivatized hydrolysis products.



Formation of fluorescent NAC-NPM adduct

Ercal N. *et al. J. Chromatogr. B.* 685: 329-334, 1996.

NAC as an Antioxidant

- Acting outside the cell to reduce cystine to cysteine which can be transported into the cell 10 times faster than cystine and further used in the biosynthesis of GSH.
- By facilitating GSH biosynthesis, NAC serves an indirect antioxidant role where it can enhance glutathione-S-transferase activity, supply GSH for glutathione peroxidase-catalyzed detoxification of peroxides.
- NAC can act directly on reactive radicals. It is a powerful scavenger of HOCl and is capable of reducing $HO^{\bullet}$ and H_2O_2.

Moldeus P & Cotgreave IA. *Meth. Enzymol.* 234: 482-492, 1994.

NAC in Acetaminophen Poisoning and as a Mucolytic Agent

- Probably one of the most common clinical uses of NAC is the treatment of acetaminophen poisoning (Tylenol). Acetaminophen is metabolized in the liver upon digestion and the resulting metabolite, N-acetyl benzoquinoneimine, reacts to deplete the hepatic glutathione pool. NAC acts to replenish these GSH levels.
- NAC is useful as a mucolytic agent for treatment of chronic bronchitis and other pulmonary diseases. Administration of NAC decreases cough severity and diaphragm fatigue. NAC's sulfhydryl group reacts and splits disulfide bonds in the mucous bronchial secretions. Because the mucus is broken down into smaller, less viscous units, NAC is referred to as "slime loosener"

NAC in HIV Infection

- Individuals with HIV usually have decreased GSH and cysteine levels. The net loss of sulfur in asymptomatic HIV^+ patients is equivalent to a mean loss of about 10 g of cysteine per day. NAC can completely inhibit inflammatory stimulations of HIV replication by supplementation of GSH.

  Breitkreutz R. *et al. AIDS Res Hum Retroviruses* 16: 203-9, 2000.

  Roederer M. *et al. AIDS Res Hum Retroviruses* 8: 209-217, 1992.

- NAC can inhibit NF-κB activation leading to inhibition of stimulated viral transcription and replication.

  Roederer M. *et al. Proc Natl Acad Sci USA 87: 4884-4888, 1990.*

NAC in Cancer

- According to research findings, certain types of cancer including lung, skin, head and neck, mammary, and liver can be potentially treated with NAC.
- Many *in vitro* studies conducted on human melanoma, prostate, and astrocytoma cell lines have helped to prove NAC's efficacy as a chemopreventive agent. NAC has been found to be effective in inhibiting cell growth and proliferation in all mentioned cell lines.
- Results from both cell culture and animal studies indicate that NAC administration can selectively protect normal cells, but not malignant ones, from chemotherapy and radiation toxicity.

De Flora S *et al. Toxicol. Lett*. 53: W4/L2, 1992.
De Flora S *et al. Respiration* 50: S43-S49, 1986.
De Flora S *et al. Int J Cancer* 67: 842-848, 1996.
Redondo *et al. Cytokine* 12: 374-378, 2000.
Chiao JW *et al. Int J Oncol*. 16:1215-1219, 2000.

NAC as a Metal Chelator

- NAC has been shown to be more effective than calcium EDTA or dimercaptosuccinic acid for the excretion of chromium and boron.

  Banner W Jr. *et al. Toxicol. Appl. Pharmacol*. 83: 142-147, 1986.

- It also has the ability to promote the urinary excretion of cadmium but not of lead. However, an antioxidant role was suggested for NAC in lead toxicity which can be attributed to it's free –SH group.

  Ottenwalder H & Simon P. *Arch. Toxicol.* 60: 401-402, 1987.
  Ercal N. *et al. Free Radic. Biol. Med.* 21:157-161, 1996.

NAC in Heart Diseases

- NAC acts by breaking up disulfide bonds and lowering homocysteine and lipoprotein levels.
- By replenishing depleted GSH, NAC helps to protect against ischemic and reperfusion damage.
- NAC helps to increase nitroglycerin activity. NAC especially potentiates the coronary dilating and anti-platelet effects of nitroglycerin and limits the development of hemodynamic tolerance to nitroglycerin.
- Clinical signs of myocardial ischemia, such as ST-depression, do not occur if patients are prophylactically treated with NAC.

Gavish D & Breslow JL. *Lancet* 14:202-210, 1991.
Hultberg B *et al. Clin Chim Acta* 262: 39-51, 1997.
Wiklund O *et al. Atherosclerosis* 119: 99-106, 1996.
Winniford MD *et al. Circulation* 73:138-142, 1986.

Side Effects and Safety

- Side effects common to high oral doses include nausea, vomiting, and other gastrointestinal disturbances.
- Intravenous administration has been shown, in some cases, to cause allergic reactions usually in the form of rash or angioedema.
- NAC is not recommended to be administered in conjunction with charcoal as the charcoal may interfere with the absorption of NAC.
- Since the pharmacokinetics of NAC are significantly altered in patients with chronic liver diseases, NAC administration should be carefully adjusted.

Aruoma OI *et al. Free Radic Biol Med* 6: 593-597, 1989.

Kelly GS. *Alt Med Rev* 3: 114-127, 1998.

Bulger EM & Maier RV. *Arch Surg* 136:1201-1207, 2001.

Klein-Schwartz W & Oderda GM. *Clin Toxicol* 18:283-290, 1981.

Dosage of NAC for Various Diseases

Disease	Dosage	Reference
Acetaminophen Poisoning (human)	140 mg/kg followed by 17 subsequent doses of 70 mg/kg every 4 h	Smilkstein MJ et al. *N Engl J Med 319: 1557-1562*, 1988.
Chronic Bronchitis (human)	600-1500 mg/day in 3 divided doses	Grandjean EM *et al. Pharmacol Res* 42: 39-50, 2000.
HIV infection (human)	800-8000 mg/day	Herzenberg LA *et al. Proc Natl Acad Sci USA* 94:1967-1972, 1997. Akerlund B *et al. Eur J Clin Pharmacol* 50:457-461, 1996. Dröge W *et al. Adv Pharmacol* 38: 581-600, 1997.
Cancer treatment and prevention	High doses (2-4 g daily) Information is still preliminary	Kelly GS, *Alternative Medicine Review* 3:114-127, 1998, Monograph, *Alternative Medicine Review 5:467-471, 2000.*
Chelation in metal toxicity (animal)	250-1500 mg/day	Banner W Jr. *et al. Toxicol. Appl. Pharmacol*. 83: 142-147, 1986. Khandenwal S *et al. Biochem Int* 16: 869-878, 1988.
Heart Diseases	2-4 g daily for 8 weeks	Gavish D, Breslow JL *Lancet* 337:203-204

Caution in Dosage

Caution is needed in scheduling the dosage of NAC when used in HIV$^+$ patients. In overdoses of NAC, excessive cysteine catabolism in the liver is associated with the production of protons and may inhibit urea production in favor of glutamine production, eventually to the point that toxic ammonia accumulates. Therefore, instead of supplying a constant dose of NAC, Breitkreutz R *et al.* suggested “NAC treatment with individually adjusted doses” where they decreased NAC dose whenever the plasma glutamine level exceeds a certain limit.

Breitkreutz *et al. J Mol Med* 78: 55-62, 2000

Dröge W, Holm E. *FASEB J* 11: 1077-1089, 1997

Caution in Infection and Septic States

NAC has been found to suppress respiratory burst but to augment neutrophil phagocytosis in intensive care patients. For certain pathophysiological mechanisms (such as ischemia/reperfusion, or endothelial cell activation), the effects of NAC might be favorable. However, during infection or septic states, a reduced respiratory burst might be detrimental.

Heller AR *et al. Crit Care Med* 29: 272-276, 2001

Caution in Antiviral Monotherapies

It was observed that NAC

- enhances contact dependent growth of HIV in resting peripheral blood mononuclear cells *in vitro.*
- increases the recovery of HIV from human peripheral blood mononuclear cell in severe combined immunodeficiency mice.

These might be important points to be considered for further investigations and clinical applications of NAC.

Chen P *et al*. *AIDS* 11: 33-41, 1997

NAC as a Pro-oxidant

- NAC has the potential to act as a pro-oxidant and, therefore it is not recommended that it be given in the absence of significant oxidative stress. In healthy individuals, NAC was shown to decrease the GSH level and increase the GSSG (glutathione disulfide) level, indicating that it functions as a pro-oxidant.
- It has also been reported that NAC causes oxidative DNA damage in the presence of Cu(II) both in isolated and cellular DNA. Again, in the same study, “NAC + Cu(II)” frequently oxidized thymine and guanine residues.

Kleinveld HA, Demacker PNM, Stalenhoef APH. *Eur J Clin Pharmacol* 43:639-642, 1992.

Oikawa S et al. *Carcinogenesis* 20:1485-1490, 1999.

Conclusions

- Recent studies suggest a new and important role for an old, “designated (but not approved) orphan drug”, NAC, in many clinical situations in which GSH deficiency and/or oxidative stress are involved such as HIV, rheumatoid arthritis, Parkinson’s disease, Alzheimer’s disease, diabetes, hepatitis, organ transplantation and others.
- Even though NAC has a long history of use in humans and its safety and pharmacokinetics are well established, caution needs to be taken in applications to new pathophysiologies.