2-CYCLOHEXEN-1-ONE

CAS Number: 930-68-7

NTP Nomination History and Review

NCI Summary of Data for Chemical Selection

2-Cyclohexen-1-one
930-68-7

NTP NOMINATION HISTORY AND REVIEW

A. Nomination History

1. Source: National Cancer Institute

2. Recommendation: -Toxicity
   -Mechanistic studies

3. Rationale/Remarks:
   -Widespread human exposure
   -Present as an impurity in consumer products; air and water pollutant
   -Interest in toxicity of α,β-unsaturated ketones chemical class
   -Parent compound of cyclic α,β-unsaturated ketones chemical class;
   -Lack of chronic toxicity data
   -Suspicion of carcinogenicity

4. Priority: High

5. Date of Nomination: 2/92

B. Chemical Evaluation Committee Review

1. Date of Review:
2. Recommendations:
3. Priority:
4. NTP Chemical Selection Principles:
5. Rationale/Remarks:

C. Board of Scientific Counselors Review

1. Date of Review:
2. Recommendations:
3. Priority:
4. Rationale/Remarks:

D. Executive Committee Review

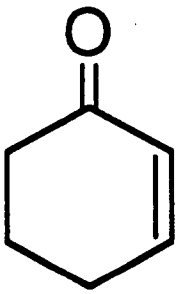
1. Date of Review:
2. Decision:

SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

CAS Registry Name:	930-68-7 (25512-62-3)
Chemical Abstracts Name:	2-Cyclohexen-1-one (8CI, 9CI)
Synonyms and Trade Names:	Cyclohexenone; 2-cyclohexenone; 1-cyclohexen-3-one; Cyclohex-2-enone; CHO; 2-CHX-1

Structure, Molecular Formula and Molecular Weight:



C_6H_8O Mol. wt.: 96.13

Chemical and Physical Properties

Description:	Colorless, slightly volatile liquid with a sweet, ketone-like odor (Levin *et al.*, 1972)
Boiling Point:	168 - 171° C @ 760 mm Hg (Levin *et al.*, 1972; Weast, 1989)
Melting Point:	-63° C (Aldrich, 1990)
Solubility:	Miscible in alcohol, acetone, benzene and water (Levin *et al.*, 1972)
Density:	0.988/gm/ml @ 20° C (Levin *et al.*, 1972)
Vapor Pressure:	1.8 mm Hg @ 25° C; 20 mm Hg @ 76° C (Levin *et al.*, 1972)

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Flash Point:	110° F (closed cup) (Levin *et al.*, 1972)
Octanol-Water Partition Coefficient (Log P):	0.61 (Sangster, 1989) ; 0.46 ± 0.01 (Higichi *et al.*, 1979)
Reactivity:	Highly reactive electrophile (Michael reaction acceptor); representative of the alicyclic conjugated enone class of ketones; undergoes asymmetrical reduction to the corresponding alcohol both chemically and microbiologically (Talalay *et al.*, 1988; Brown *et al.*, 1987; Fauve *et al.*, 1987)

Technical Products and Impurities: CHO is commercially available and considered easy to handle (Hashimoto, 1986). It is offered in practical grade (95-97% purity) by several suppliers and in pure grade (> 98%) by at least one. No information was available on impurities in commercial products; however, other products of typical liquid-phase oxidations of cyclohexene which could be present as impurities include cyclohexene oxide, cyclohexanol and cyclohexanone.

BASIS OF NOMINATION TO THE CSWG

CHO is a moderately large volume industrial chemical for which there is little health effects and toxicity information available. It is a representative α,β-unsaturated ketone, the prototype of the six member ring cyclic alkenones. In addition, it is an important structural moiety in biological chemicals, occurring as the A-ring in numerous steroids and as a structural entity in many terpenoids. Besides being used widely in industrial and academic research labs, this chemical poses an ubiquitous human exposure risk having been identified as a component of tobacco smoke and other consumed products and a contaminant of surface and drinking water.

SELECTION STATUS

ACTION BY CSWG: 9/26/91

Studies Requested: General toxicity and mechanistic studies

Priority: High

Comments: 2-Cyclohexen-1-one is a representative cyclic α,β-unsaturated ketone, with broad human exposure, potential for biological activity, and lack of chronic toxicity data. It is an environmental pollutant. The FDA representative noted that many α,β-unsaturated ketones

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were approved as food additives and indicated FDA's interest in the toxicity studies of this chemical class.

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EXPOSURE INFORMATION

Commercial Availability

Production and Producers: Cyclohexenone is produced by the liquid-phase oxidation of cyclohexene either as the intended product or recovered in substantial amount as a by-product of other related commercial syntheses such as that of 2-cyclohexen-1-ol. Other products of liquid-phase cyclohexene oxidation include cyclohexene oxide, cyclohexanol and cyclohexanone. Sharma *et al.* (1974) listed 6 additional important starting materials besides cyclohexene for the synthesis of CHO (namely, 1,3-cyclohexadiene, cyclohexanone, α-chlorocyclohexanone, α-bromocyclohexanone, cyclohexan-1,3-dione, and anisole), but in many cases the yields were poor (< 60%). They reported an improved preparative method based on the reaction of cyclohexene with chloroform and cobalt naphthenate in an atmosphere of 02 at atmospheric pressure. Their reported yield of desired product was > 80% of approximately 98% pure CHO. An Oppenauer-type oxidation of 2-cyclohexen-1-ol, catalyzed by zirconocene complexes, readily yielded 89% of CHO, according to Nakano *et al.* (1987).

Heico Chemical Co. a Division of Whittaker Corp., was the sole manufacturer of this compound reporting to the EPA's TSCA plant and production database (TSCAPP) with declared production volume of < 1,000 lbs (CIS on-line, 1991).

Directories of commercially available chemicals (Anon, 1990; Anon, 1991a) list Jarchem Industries, Inc., and George Uhe Co., Inc. as suppliers of this chemical as well as Heico. In addition, 11 catalogs of chemical suppliers list CHO as one of their products: Aldrich Chemical, Co., Alfa Products, American Tokyo Kasai, Inc., Chem Service, Inc., Fluka Chemical, Corp., Frinton Laboratories, Inc., Janssen Chimica, Lancaster Synthesis, Ltd., Pfaltz & Bauer, Inc., Riedel-de Haen, A-.G., and Wiley Organics (DIALOG, 1991).

Two companies have recently advertised the availability of CHO in chemical industry journals: Hoffman-La Roche & Co. in *Specialty Industrial Chemicals* (Anon., 1989) and Mack Chemicals/George Uhe Co., Inc., in *Chemical Marketing Reporter* (Anon, 1991b).

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Mobil Oil Corp., Philadelphia, has been granted numerous patents for the synthesis and processing of CHO. Furthermore, they reported that this reactive chemical intermediate can be produced in moderately large quantities and can be expected to show increasing production with introduction of new applications (Levin *et al.*, 1972). Other recent patent holders for synthesis and for potential or intended uses of this chemical are: Abbott Laboratories, Ajinomoto Co., Inc., American Biotechnology Co., Ltd., Asahi Chemical Industry Co., Ltd., Catalytica Associates, Hoffman-LaRoche & Co., Idemitsu Kosan Co. Ltd., Imperial Chemical Industries, Merck & Co., Inc., Mitsui Petrochemical Industries, Ltd., Ono Pharmaceutical Co., Ltd., Procter and Gamble Co., Rhone-Poulenc, Inc., Shiseido Co. Ltd., Sun Ventures, Inc., Thiokol Chemical Corp., Toray Industries, Teijin, Ltd., and VOP, Inc. Importation is expected to be a major source of this chemical in the United States.

Use Pattern: CHO is used principally as an industrial chemical intermediate with numerous applications in the chemical process industry (CPI), including use as a pharmaceutical intermediate and as an agricultural chemical intermediate. In addition, it is widely used as a reagent in academic and corporate research laboratories (Reiter and Wendel, 1982). In biochemistry and pharmacology labs it is used as a chemical intermediate and building block in the synthesis of many cyclohexenone derivatives; and in biology and physiology labs it is used as a reagent incubation, perfusion and other methods of tissue or culture treatment for its ability to deplete reduced glutathione (GSH) levels. CHO is also useful as a starting material in microbiological procedures such as microbial reduction to optically active carbonyl compounds. Thus, CHO has the potential for increasing use as a bioorganosynthetic reagent (Fauve *et al.*, 1987).

Some of the many specific present and intended uses for this chemical cited in the published literature include the following (STN International, 1991):

- commercial syntheses of 2-cyclohexen-1-ol, resorcinol, phenol and vicinyl glycols (pinacols)
- decarboxylation of α-amino acids (0.5 to 2.0 v/v % in cyclohexanol) in the commercial production of optically active amines (Hashimoto *et al.*, 1986)

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- synthesis of 11-deoxy prostaglandins by Hoffmann-LaRoche (Truesdale *et al.*, 1985)
- preparation of cyclohexenone derivatives as antihypercholesteremic agents
- preparation of a series of eicosanoid enzyme inhibitors, such as leukotriene hydroxamate analogs (Kerdesky, *et al.*, 1987)
- production of biologically active immunostimulating agents. (Immunostimulants may be useful as antitumorigenic therapeutic agents.)
- starting material for pharmaceutical intermediates to prepare anti inflammatory agents
- manufacture of fungicides and herbicides.

Specific end use applications for CHO cited in the published literature [see Search Resource List] include:

- reducing agent/neutralizer for low-odor permanent wave hair preparations (Shiseido patents, 1984 and 1985)
- carbocyclic ketone for further processing in the synthesis of liquid crystals as dielectrics in electrooptical display devices (Merck patent, 1989)
- component in semipermeable polymer membrane manufacture (Teijin Ltd. patent, 1987)
- antifungal agent/mold inhibitor for bread (effective concentration: 20 mg in a 2.6 L dessicator) (Huhtanen and Guy, 1984).

Human Exposure: No data have been reported by the National Occupational Exposure Survey (NOES) or the National Occupation Hazard Survey (NOHS) on worker exposures to CHO (RTECS on-line, 1991).

Human exposure to mutagenic α,β-unsaturated carbonyl compounds, including CHO, is said to be widespread by both exogenous and endogenous routes (Chung *et al.*, 1986). Levin *et al.* (1972) reported a case of occupational exposure involving a worker who sustained moderate skin injury following clean-up of a minor CHO spill without adequate protective gear. This citation also reported that a reaction mixture containing CHO as a major

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constituent, when tested in mammals, produced moderate acute dermal toxicity with significant eye and skin irritation.

Chung *et al.* (1988) described CHO as one of the α,β-unsaturated carbonyl compounds widespread in the human environment and having potential for ready reaction with nucleophilic biological macromolecules, including cellular DNA.

A broad population of smokers and those exposed to side-stream smoke are exposed to CHO as one of the semi-volatile components of tobacco smoke (Pettersson *et al.*, 1980).

Consumers of products containing small amounts of CHO, such as smoke flavor preparations, and workers preparing the products, may be exposed to CHO at low-levels (Baltes and Soechtig, 1979).

Low level dermal exposures may occur from the use of consumer products, including hair care products and detergents, that contain CHO as an additive.

Environmental Occurrence: CHO has been identified as one of the semi-volatile components of tobacco smoke (Mauldin, 1976; Pettersson *et al.*, 1980) and as a component of the water-soluble portion of tobacco smoke condensate (Schumacher *et al.*, 1977).

Other occurrences of CHO as an odorant or flavoring material reported in the published literature include the following:

- component of smoke flavoring material obtained by a hawthorn pit dry distillation method (Zhou *et al.*, 1988).
- an odorous substance present as a component of bitter almond and/or musk odors (Boehlens, 1976).
- volatile component of the flavor characteristic of post-fermentation-processed wild rice products (Withycombe *et al.*, 1978), of babaco fruit (Barbeni *et al.*, 1990) and of the fruit of chayote (MacLeod, 1990).

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- detected in several fractions of beech wood and in caramel color pyrolyzate.
- aroma component of the volatile fraction in a coffee roasting model system based on the reaction of serine, threonine and sucrose (Baltes and Bochmann, 1987).
- volatile component of roasting aroma based on a glucose phenylalanine model (Baltes and Mevissen, 1988).

In addition, International Flavors and Fragrances, Inc., (IFF) identified CHO as an impurity in their product, tetrahydronaphthalenone, a flavoring material and aroma/flavor enhancer for foods and pharmaceuticals intended for use in chewing gum, chewing and smoking tobacco, toothpastes, medicinal products, perfumes and colognes, hair preparations, detergents, fabric softeners, etc. CHO is also present as an impurity in commercial products of cyclohexanol at concentrations of 0.09 to 0.51% (Hashimoto *et al.*, 1985) and in technical grade cyclohexanone (Czerwinski and Stepien, 1982).

Finally, CHO has been identified as an air contaminant, water pollutant, and hazardous waste site contaminant in several citations:

- as a pollutant in river water and finished drinking water from the Smith River in North Carolina (Durell *et al.*, 1987)
- in wastewater from wood gasification
- in air samples as determined by odor sensing equipment (Abe *et al.*, 1988)
- in food and air samples based on HPLC analysis after derivatization with picric acid salts (Colgan *et al.*, 1985).

However, Dietrich *et al.* (1988) analyzed oxygenated cyclohexene derivatives, including CHO, found in methylene chloride extracts of chlorinated drinking water and attributed their occurrence to artifactual formation during sample preparation from the cyclohexene present as a preservative in commercial methylene chloride.

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Regulatory Status: CHO is listed in EPA's TSCA inventory. No standards or guidelines have been set for occupational exposures to or environmental levels of CHO. The American Conference of Governmental Industrial Hygienists (ACGIH) has not adopted a TLV/TWA for this compound. However, this group has adopted a TLV/TWA for dermal exposure to a closely related chemical, cyclohexanone, of 25 ppm (100 mg/m3) and for parent compound, cyclohexene, of 300 ppm (1010 mg/m^3)(American Conference of Governmental Industrial Hygienists, 1990).

The Mobil Oil Corporation's Medical Department independently determined that an acceptable industrial hygienic standard for workers using CHO is a TLV of 5 ppm, based on an LC_{50} in rats of 250 ppm (Levin *et al.*, 1972). No citations were found in a search of the CIS database, TSCATS, regarding testing requirements or information issued by EPA.

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports associating CHO with a cancer risk in humans were found in the published literature [see Search Resource List]. Several toxicologic studies on the effects of smoking in humans have been published and are cited in the Short-Term Tests section of this report.

Animal Data: No chronic carcinogenicity studies in animals were found in PHS-149 or other resources of the published literature [see Search Resource List]. This chemical has not been studied in a 2-year bioassay by the NTP nor reviewed as a possible carcinogen by the IARC. According to a search of the available literature and databases, it is not currently on test or scheduled to be tested in a chronic/carcinogenicity mammalian bioassay. The following acute toxicity data for CHO have been reported:

Acute Toxicity of Cyclohexenone (from Levin *et al.*, 1972)

Test	Results	Toxic Classification[a]
Oral LD_{50} (5 groups of 5 albino rats)	220 mg/kg	Toxic
Dermal LD_{50} (4 groups of 4 rabbits)	70 mg/kg	Highly toxic
Eye Irritation	Corneal and conjunctival effects in all; iridial effects	Ocular irritant
Aerosol Inhalation, LC_{100}- 1 hour or less (10 rats)	41 mg/liter	Toxic
Vapor inhalation, LC_{50}- 4 hours (10 rats)	250 ppm	

[a] As defined in Appendix to Regulations Under the Federal Hazardous Substances Labeling Act part 191, Chapter I, Title 21, Code of Federal Regulations.

Intraperitoneal mouse LD_{50}: 170 mg/kg (Sax and Lewis, 1989)

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Short-Term Tests: Lutz *et al.* (1982) tested 99.9% pure CHO in an Ames assay using *S. typhimurium* strain TA100 both with and without S9 activation. This compound was slightly mutagenic without activation (3 revertants/umole), while only 1 revertant/umole was observed with activation. The authors observed that direct acting mutagens were "more or less inactivated by S9 mix to an extent that depends on their electrophilic properties."

Chung *et al.* (1988) conducted an *in vitro* study of the reaction of CHO with deoxyguanoisine under physiological conditions. They identified and isolated with HPLC four diastereomeric adducts of the 1,N^2-cyclic type; and, further, they speculated that these adducts may be partly responsible for the mutagenicity of CHO.

Williams *et al.* (1989) tested CHO for genotoxicity in a rat hepatocyte/DNA repair test. CHO was positive for the induction of DNA repair with 1×10^{-5}M being the lowest concentration which elicited a positive response.

α,β-Unsaturated ketones, including CHO, have been identified as components of the neutrals subfraction which comprises the largest and most complex fraction (28%) of the semi-volatile (SV) constituents of cigarette-smoke condensate (CSC) (Thelestam *et al.*, 1980; Curvall *et al.*, 1984). They studied the release of tritiated uridine nucleotides from human diploid embryonic lung fibroblasts treated with CSC fractions and individual compounds. They observed that CHO did not significantly alter the permeability of human lung fibroblasts, reporting a low level of nucleotide release (3%). Curvall further noted that the neutrals subfraction of the SVs was the only fraction where significant effects occurred with doses below 1 mg/ml; activity, however, remained low at higher doses (3 and 4 mg/ml). These researchers reported that the NV is highly cytotoxic and acts as a potent inducer of sister chromatid exchanges (SCEs). As such, further health effects testing is suggested on neutral constituents of CSC.

Metabolism: Ketones are often metabolically converted to their corresponding alcohols. Thus, CHO is reduced enzymatically by aldehyde dehydrogenases with NADH as a cofactor (Haley and Berndt, 1987). According to Fauve *et al.* (1987), reduction of α,β-unsaturated carbonyls

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is carried out by many living organisms. They reported CHO to be a strong inducer of the enone reductase system of the fungus, *Beauveria sulfurescens*. It was stated that bacteria, protozoan, plant and animals cells as well as fungi all reduce the CHO carbon-carbon double bond, with identical stereochemical characteristics, while reduction of the carbonyl to the corresponding alcohol may or may not occur depending on the cell type.

Sakurai (1988) reported that the oxidative metabolism of cylcohexene by various cytochrome P-450 model systems gave rise to CHO as one of several oxidation products with varying yields depending on the components of the system. CHO arises as an intermediary metabolite in microbial biotransformations of cyclohexanol and cyclohexanone. It can be further metabolized by 2-cyclohexenone hydratase and 3-hydroxycyclohexanone dehydrogenase via 3-hydroxycyclohexanone to 1,3-cyclohexanedione which is cleared by 1,3-cyclohexanedione hydrolase to 5-oxocaproic acid (Dangel *et al.*, 1989). Leibman and Ortiz (1978) conducted a study of the microsomal metabolism of cyclohexene and drugs containing a cyclohexene ring, such as hexobarbital, in mammalian liver microsomes. They reported that, whereas allylic hydroxylation from cyclohexene to 2-cyclohexen-1-ol was observed with no detectable levels of CHO in incubation mixtures containing control liver preparations, small amounts of CHO were found in preparations from rats pretreated with phenobarbital. The urine of two pretreated rats administered 0.7 nmol of cyclohexene po contained no detectable compounds hydrolyzable to 2-cyclohexen-1-ol by β-glucuronidase, but these two animals excreted 636 and 750 nmol of CHO in 24 hours. In fact, 0.1% of the oral dose of cyclohexene was excreted as CHO in pre-treated rats, typifying a drug-metabolizing, mixed-function oxygenase-catalyzed reaction.

Structure/Activity Relationships: CHO is the first in a series of 6-member ring enones which share the common structural entity of an electrophilic olefin in conjugation with a carbonyl group (Michael acceptor). This chemical structural feature is also common to the A ring of certain endogenous and exogenous steroids. Gawronski *et al.* (1976), who studied the conformation and optical activity of CHO and its steroidal and terpenoidal polycyclic analogs, concluded that the biological activity of steroidal hormones is related to the conformation of ring A.

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Of the many ketones which, according to Marnett *et al.* (1985), may be implicated in cell damaging biotransformation reactions and may contribute to cancer in humans, several α,β-unsaturated ketone analogs of CHO have been tested for carcinogenicity or mutagenicity.

Isophorone, the 3,5,5-trimethyl substituted derivative of CHO, has been tested by the NTP in a 2 year bioassay (National Toxicology Program, 1986). Doses of 0, 250, or 500 mg isophorone/kg body weight per day were administered by gavage in corn oil to groups of 50 F344/N rats and 50 B6C3F$_1$ mice of each sex 5 days per week for 103 weeks. Isophorone was found to be carcinogenic in male rats; equivocal evidence of carcinogenicity was found in male mice but no evidence of carcinogenesis was found in female rats or mice. The NTP also tested d-carvone, which is (S)-2-methyl-5-(1-methylethenyl)-2-cyclohexen-1-one, in a 2-year gavage study in which B6C3F$_1$ mice received 375 or 750 mg/kg doses 5 days per week; no evidence of carcinogenic activity was reported. Short-term test results for d-carvone included a negative or non-mutagenic result in *S. typhimuruim* but positive for induction of sister chromatid exchanges and chromosomal aberrations in Chinese Hamster ovary cells.

d-Carvone was also found non-mutagenic by Florin *et al.* (1980) [as cited in HSDB] in *S. typhimuruim* strains, TA98, TA100, TA1535, and TA1537 both with and without S9 activation. Rockwell and Raw (1979) also reported no mutagenic activity in the urine of carvone dosed rats in *S. typhimuruim* strains TA100 and TA98 either in presence or absence of β-glucuronidase [as cited in HSDB].

In a study of compounds found in tobacco and tobacco smoke, Thelestam *et al.* (1980) reported that the terpenoid ketones examined (pseudo-ionone, β-ionone, piperitone, carvenone and carvone), but not CHO, caused some permeability-altering damage to human lung fibroblasts.

The CHO metabolite, 2-cyclohexen-1-ol, was reported by Eder *et al.* (1982) to be non-mutagenic in *S. typhimuruim* strain TA102 both with and without S9 activation.

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The saturated CHO analog, cyclohexanone, has been tested in the NCI/DCE short-term testing program with positive genotoxicity reported with activation in the mouse lymphoma assay but with negative results in the Ames *Salmonella* assay (National Cancer Institute, 1990).

Other Biological Effects: Reduced glutathione (GSH) is the most abundant low molecular weight, nonprotein sulfhydryl-containing compound in mammalian cells. It is found principally free in intracellular cytosol but a significant amount also occurs bound as GSH-protein mixed disulfides, postulated by Fischman *et al.* (1981) to play an important role in peripheral blood lymphocyte (PBL) activation. They reported that depletion of intracellular GSH by CHO caused a dose-dependent inhibition of both DNA synthesis and blast formation, the percentage of inhibition of activation by CHO correlating closely with the decrease in total GSH in both PBLs and T cells. The effective concentration of CHO added in the first 4 hours of culture (2.5×10^{-5}M) was not cytotoxic to PBLs.

Olson *et al.* (1985) reported that CHO acts as a substrate for GSH S-transferase in isolated canine parietal cells, resulting in the depletion of cellular GSH without the formation of the oxidized disulfide form of GSH (GSSG) or the stimulation of acid secretory activity. Baars *et al.* (1979) referred to documentation in the literature showing that GSH S-transferases are able to form reactive intermediates from some xenobiotics which are more toxic than the parent compounds. MacDermott *et al.* (1986) reported that the CHO-GSH reaction involves a thio-ether bond, with GSH-depletion being dose-dependent and with no increase in GSSG levels.

Schnellmann and Mandel (1986) investigated the role of GSH in normal renal function at the cellular level in rabbit proximal tubules using known GSH depletors, including CHO. They reported that the concentration of GSH was reduced and the rate of oxygen consumption was decreased in the proximal tubules as early changes of CHO-induced cytotoxicity which preceded a later event, plasma membrane damage involving lactate dehydrogenase (LDH) leakage.

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Morrissey (1986) studied whether GSH metabolism effected parathyroid secretion in collagenase dispersed bovine parathyroid cells. He found the CHO caused a rapid decrease in hormone secretions as well as GSH levels but found no CHO influence on cellular protein synthesis, indicating no specific toxic effect by the ketone.

Masukawa *et al.* (1989b) demonstrated a 50% depletion of brain GSH and a possibly-related anti-hypoxic effect in 5-6 week old male mice suggested by their observation of increased survival time under conditions of hypobaric hypoxia. After post-treatment with L-cysteine (but not D-cysteine) the anti-hypoxic effect was abolished and brain GSH level returned to about 80% of controls. In a prior publication (Masukawa *et al.*, 1989a) they reported a possibly-related finding of CHO induced hyperglycemia in mice. According to Masukawa *et al.*, (1989c), a dose of 50 - 100 mg/kg CHO administered intraperitoneally acted as a substrate for glutathione S-transferase and depletor of reduced glutathione (GSH), with significantly elevated blood glucose levels found 0.5 - 1 hour after treatment.

Sener and Malaisse (1986) studied the effects of CHO on insulin release by incubated rat pancreatic islets. They reported that CHO lowers GSH content of the pancreatic islets. GSH may be involved in the coupling of metabolic to secretory events as insulin is released in response to nutrients in the pancreatic B-cell. Therefore, CHO may impair the functional response of B-cells to either D-glucose or 2-ketoisocaproate. L-Glutamine, but not L-asparagine, was found to protect against the inhibitory action of CHO on glucose-stimulated insulin secretion.

Miwa *et al.* (1990) also studied the effect of CHO on pancreatic islets and reported that the marked inhibition of glucose-induced insulin secretion was mediated mainly through inactivation of glucokinase activity. Administration of 0 - 5 mM concentrations of CHO resulted in a dose-dependent inhibition of insulin secretion.

Talalay *et al.* (1988) studied relative potencies of quinone reductase (QR) and glutathione S-transferase (GST) induction by a group of 12 coumarin and pyran analogs, including CHO, *in vitro* in Hepa 1c1c7 hepatoma cells from female CD1 mice. The concentration of CHO

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which doubled the specific activity of QR was 28 M. The authors suggested that this relatively moderate inductive activity by CHO, which is also a substrate of GST, is related to its electrophilic nature. The authors further postulated that this compound could act as an anticarcinogenic agent by inducing cellular enzymes that inactivate reactive electrophilic forms of carcinogens.

Bannai *et al.* (1986) studied the enhancing effect on L-cystine uptake in rat hepatocytes by various electrophilic agents. They found that 0.01, 0.02 and 0.04 mM concentrations of CHO increased uptake of 0.05 mM L-cystine by 31, 86 and 181% respectively.

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