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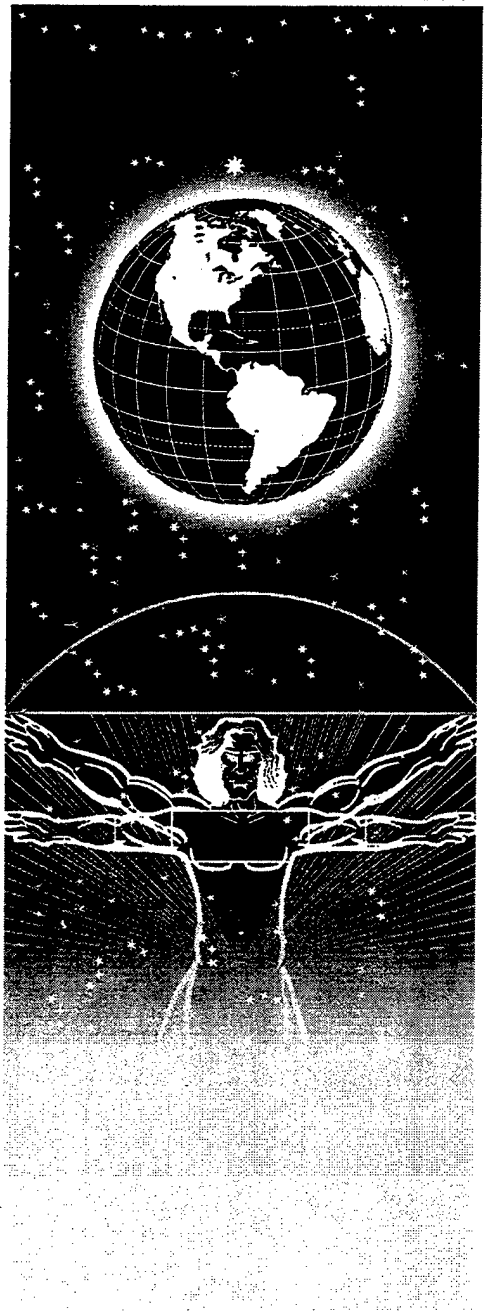

UNITED STATES AIR FORCE
ARMSTRONG LABORATORY

PERCHLORATE LITERATURE REVIEW AND SUMMARY: DEVELOPMENTAL EFFECTS, METABOLISM, RECEPTOR KINETICS AND PHARMACOLOGICAL USES

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The animal use described in this study was conducted in accordance with the principles stated in the "Guide for the Care and Use of Laboratory Animals", National Research Council, 1996, and the Animal Welfare Act of 1966, as amended.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE DIRECTOR

STEPHEN R. CHANNEL, Maj, USAF, BSC
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Perchlorate is a monovalent anion found as a soil and groundwater contaminant on govenment contractor sites and, more recently, on an Air Force site. Perchlorate is dissociated from the salt, ammonium perchlorate, which is an efficient oxidizer used in solid rocket propellant systems. This review was undertaken to evaluate the available information on developmental and reproductive effects, thyroid iodide receptor kinetics, pharmacological uses of perchlorate outside the treatment of Graves' disease, and absorption, distribution, metabolism and excretion of perchlorate. Summarization of the available information and conclusions make the data more accessible to toxicologists and review panels for consideration in study prioritization and future reference dose development.

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PREFACE

This effort was performed by Operational Technologies Corporation (OpTech) and Air Force Research Laboratory, Human Effectiveness Directorate, Operational Toxicology Branch, Wright-Patterson Air Force Base, Ohio. OpTech activities were conducted under the Project Management of Mr. Erik Vermulen, 1370 North Fairfield Road, Suite A, Beavercreek, Ohio 45432. The work was completed under U.S. Air Force Contract F41624-94-D-9003/008 between June 1997 and July 1998. Maj Stephen Channel, Director of the Operational Toxicology Branch, served as contract monitor.

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LIST OF ACRONYMS/ABBREVIATIONS

µCi	micro-Curie
µg	microgram
µL	microliter
A	minimally effective concentration for Adult hydra
ADME	Absorption, Distribution, Metabolism and Elimination
AIIT	Amiodarone Iodine Induced Thyrotoxicosis
Cl^-	chloride
ClO_4^-	perchlorate
D	minimally effective concentration for Developing hydra
dy	day
ECAO	Environmental Criteria and Assessment Office
EPA	Environmental Protection Agency
g	gram
hr	hour
I^-	iodide
IgM^-	Immunoglobulin M^-
IL-6	Interleukin-6
ip	intraperitoneal administration
ITER	International Toxicity Estimates for Risk
IU	International Unit
iv	intravenous administration
kBq	kilo-becquerel
$KClO_4$	potassium perchlorate
kg	kilogram
KI	potassium iodide
L	liter
MBq	mega-becquerel
mCi	milli-Curie
meq	milli-equivalent
mg	milligram
min	minute
mM	milli-Molar (mmol/L)
MMI	1-methyl-2-mercaptoimidazole
mmol	millimole
mo	month
mol	mole
n	number in study
NaCl	sodium chloride
$NaClO_4$	sodium perchlorate
NaI	sodium iodide
NCEA	National Center for Environmental Assessment
PBPK	Physiologically Based Pharmacokinetic
PDT	Perchlorate Discharge Test
po	*per os* (oral administration)
PPT	postpartum thyroiditis
PSG	Perchlorate Study Group
RfD	Reference Dose

SD	standard deviation
SE	standard error
SO_4^{-2}	sulfate
T_3	triiodothyronine
T_4	thyroxine
TERA	Toxicological Excellence for Risk Assessment
TSH	Thyroid Stimulating Hormone
USAF	United States Air Force
w/v	weight to volume ratio
wk	week

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PERCHLORATE LITERATURE REVIEW AND SUMMARY: DEVELOPMENTAL EFFECTS, METABOLISM, RECEPTOR KINETICS AND PHARMACOLOGICAL USES

INTRODUCTION

Perchlorate (ClO_4^-) is a monovalent anion found as a soil and groundwater contaminant on government contractor sites and, more recently, on an Air Force site. Perchlorate is dissociated from the salt, ammonium perchlorate, which is an efficient oxidizer used in solid rocket propellant systems such as those found on the Minuteman and Space Shuttle. Another user of ammonium perchlorate is the pyrotechnic industry. Perchlorate may also be found as a by-product from perchloric acid use at industrial and laboratory sites. Both sodium perchlorate and potassium perchlorate have uses in the medical community (TERA, 1996). Given that perchlorate salts dissociate freely in water, the practical toxicity of each salt may be the same or similar under environmental conditions.

Background

In 1992, the U.S. Environmental Protection Agency (EPA) Environmental Criteria and Assessments Office (ECAO, now NCEA: National Center for Environmental Assessment) was asked to develop a provisional reference dose (RfD) for perchlorate. This request came from U.S. EPA Region 9 personnel and the resulting provisional RfD was intended for use as internal guidance to approaching risk assessment at Region 9 Superfund sites where perchlorate was a contaminant of concern. ECAO set a provisional RfD of 1E-4 mg/kg/day based on an acute study in Graves' disease patients by Stanbury and Wyngaarden published in 1952 (Dollarhide, 1992). This provisional number has not been used or suggested by U.S. EPA as a regulatory level.

The provisional RfD sparked the creation of the Perchlorate Study Group (PSG). The PSG is composed of manufacturers, defense contractors and other users of perchlorate. The U.S. Air Force (USAF) is a non-voting member. The PSG met with ECAO in 1994 and then sponsored further literature searches using data not available in 1992 (ERM, 1995). The result, in 1995, was an RfD ranging from 1 to 5E-4 mg/kg/day with a total uncertainty factor of 300 based on Stanbury and Wyngaarden (1952), as well as rat studies by Shigan (1963) and Mannisto *et al.* (1979) (EPA, 1995).

Soon thereafter, TERA (Toxicological Excellence for Risk Assessment) was hired by the PSG. In February 1997, they proposed an RfD of 1E-2 mg/kg/day. Their proposal was supported by a recent short-term animal study by Caldwell *et al.* (1996). TERA then sponsored an ITER (International Toxicity Estimates for Risk) panel to review perchlorate and other chemicals in March 1997. The ITER is a program unique to TERA which provides expert peer reviews and database access to groups developing toxicity values. Although the peer panel found the database insufficient to develop an RfD, the panel provided uncertainty factors which they thought to be reasonable. Based on the 1996 Caldwell *et al.* data and the panel's total uncertainty factor of 1000, a value of 9E-4 mg/kg/day was calculated; the panel stated that the

confidence level was too low for this value to be considered an RfD. The panel made several recommendations including a 90-day rat study, a developmental neurotoxicology study and literature reviews to determine the need for additional studies (TERA, 1997a). In May, TERA assembled another peer review meeting to prioritize the list of perchlorate studies needed and to help develop protocols (TERA, 1997b).

The protocol peer review meeting in May reached consensus on effective protocol designs for a 90-day study and a developmental neurotoxicological study. It also identified the traditional Segment II Developmental Study as possibly beneficial for reducing database deficiencies. It was not known if sufficient data of this type already existed in the literature to satisfy the database requirement without funding a full Segment II teratological investigation on near term pups exposed during organogenesis. It is also possible for tests to be performed on culled pups in the developmental neurotoxicology study, if this alternative has the potential of filling a data gap identified in the literature (TERA, 1997b).

ADME (Absorption, Distribution, Metabolism and Elimination) knowledge was also identified as a focus which could assist in decreasing the sensitive population and animal to human uncertainty factors, as well as database deficiencies. Iodide receptor kinetics was another area in which increased knowledge could feasibly decrease animal to human uncertainty. The peer review panel was unaware of the extent of kinetic information available (TERA, 1997b).

Much of the knowledge on human response to perchlorate stemmed from studies on Graves' disease patients. Additional pharmacological uses of perchlorate and the outcomes of the uses were identified as data gaps by the ITER panel (TERA, 1997a).

Objective

The objective of this report was to research the current perchlorate literature on the above topics. Summarization of the available information and formulation of preliminary conclusions were intended to make the data more accessible to toxicologists and review panels for consideration in study prioritization and future RfD development. To achieve this objective, extensive literature searches were performed in the National Library of Medicine's Medline and Toxline databases. Other public databases were also queried, including the EPA's Online Library System (telnet: epaibm.rtpnc.epa.gov) and the Defense Technical Information Center unclassified unlimited technical report database (internet: www.dtic.mil/stinet/str/). Additional literature summaries will be published as separate reports.

PERCHLORATE REPRODUCTIVE AND DEVELOPMENTAL STUDIES

In the process of determining reference doses for chemical contaminants, developmental data may contribute to decreasing uncertainty associated with sensitive populations and to increasing confidence in the existing database. In the case of the perchlorate ion, it is conceivable that the developing embryo may be especially sensitive to disruption of iodide uptake or other effects. This review was undertaken to evaluate the available information on developmental and reproductive effects of perchlorate, to determine the need for additional developmental studies and to help prioritize perchlorate study needs.

In Vitro Assay

The hydra developmental toxicity assay was performed with ammonium perchlorate by Confer *et al.* (1996). In this screening test, adult and "artificial embryo" *Hydra attenuata* were exposed to ammonium perchlorate in concentrations ranging from 0.001 to 1000 mg/L. "Artificial embryos" consist of disassociated hydra cells formed into pellets. Hydra are the highest form of life with the capability of whole body regeneration; for "embryos" to develop, they must experience most of the developmental events required for embryogenesis. The hydra assay was performed in three iterations: a range finding study, an effective range study and a confirmation of the second study. The hydra were observed at 4, 18, 26, 42, 66 and 90 hours. The minimally effective concentration for adult hydra (A) was found to be 600 mg ammonium perchlorate/L, while the minimally effective concentration for the developing hydra (D) was 350 mg/L. The A/D ratio was therefore 1.71. A ratio less than 3 predicts that a chemical would be toxic to developing organisms only at levels causing toxicity in adults, while a ratio greater than 3 indicates that a chemical may be a teratogenic hazard because it results in developmental toxicity at a level which causes few or no effects in adults. Ammonium perchlorate is therefore not considered a primary developmental toxin by the criteria of this screening method.

Perchlorate Developmental Effects in Amphibians

Sodium perchlorate has been shown to inhibit metamorphosis in the South African clawed frog, *Xenopus laevis.* Although perchlorate does not affect larval immune responses, prevention of metamorphosis also precludes the development of adult-specific lymphocytes. Thymocyte and splenocyte phenotypes are also affected. To determine if these immune effects were caused by the lack of metamorphosis or a specific action of perchlorate, male and female frogs were reared in 1% (w/v) sodium perchlorate starting immediately at the conclusion of metamorphosis. The frogs were exposed for five months; the perchlorate water was changed three times per week. All treated frogs and no control frogs had large goiters; growth in treated frogs was retarded to less than half the control weight. Treated frogs also had significantly reduced numbers of circulating red blood cells. Relative thymocyte numbers were not different from controls. However, relative splenocyte numbers were significantly decreased among treated animals. Relative splenic B cells, determined by positive IgM-specific monoclonal antibody staining, numbered only 15% of control B cell levels. Some adult-specific T-cells, estimated as the immunoglobulin M^- (IgM^-) class II^+ stained lymphocytes, were produced in the treated animals, although at reduced numbers as compared with controls. The leukocyte responses to mitogens were the same in treated and control frogs. Apparently metamorphosis is necessary to develop a working adult-specific immune system; however, perchlorate significantly affects the maturation of the system which may therefore depend on thyroid hormone regulation (Rollins-Smith *et al.*, 1993).

Deposition of Perchlorate in Hen Reproductive Structures and Eggs

Since perchlorate had previously been found effective in reducing the deposition of radioactive iodide in eggs, the distribution of perchlorate in the hen and the egg was studied. Laying hens were intramuscularly administered 10 μCi $K^{36}ClO_4$ (specific activity of 1.16 mCi/g) and sacrificed at 3, 24 or 48 hours. A single hen was dosed with 10 μCi at 0, 24 and 48 hours and sacrificed

at 51 hours. Blood, organ and excrement samples were collected. Surprisingly, the perchlorate organ:blood ratio found in the right oviduct was higher than 1. In poultry, the left oviduct is functional and the right may be in different stages of non-functional development. A high ratio in the right oviduct therefore may indicate that perchlorate can be concentrated by organs in development. Of the total dose administered, 88 and 99% were recovered in the excrement after 3 and 24 hours, respectively; at 24 hours the majority of the remaining activity was found in the largest ova (Pena *et al.*, 1976).

The ten largest ova (largest designated #1, etc.) from each hen were harvested. The radioactive perchlorate concentrated in a ring adjacent to the exterior of the ova; $^{131}I^-$ was found to concentrate similarly in an earlier study. The width of the radioactive "ring" image was found to increase with time after dosing. Although the ova size in relation to development stage was not affected by perchlorate administration, the inside of the radioactive ring was found to be related to the size of the ovum at the time of administration, causing the ring to grow wider as the ovum continued apparently normal development. This deposition pattern was demonstrated in the ova of the multiple dose hen; within the wide radioactive ring were three darker concentric lines correlating to the three dosings of perchlorate. Peak deposition of perchlorate was found in ovum #5, as was the highest perchlorate ovum:blood ratio (4.5). As individual ovum:blood ratios for ova #2 through #8 were all higher than 1, an active transport mechanism for perchlorate and iodide is likely. When eggs were fractioned, the albumin or egg white was found to have the highest total activity due to its relatively large mass; however, when activity per gram of tissue was measured, the shell membrane had a higher deposition and ovum:blood ratio than the albumin, which may indicate that the membrane actively transports these ions (Pena *et al.*, 1976).

Perchlorate Effects in Developing Rats

The effect of perchlorate on implantation and pregnancy outcome was assessed in 1966 by Brown-Grant. Previous studies had shown a high uterus:plasma iodide ratio in rats and mice during early pregnancy just prior to implantation of the blastocysts (Brown-Grant, 1966). Specifically, the epithelial cells of the endometrium can accumulate high intracellular iodide concentrations during days 3 to 5 of gestation (Brown-Grant and Sherwood, 1971). This phenomenon also occurs in false-pregnant rats. Potassium perchlorate (0.25% in drinking water) had been administered in a prior study, without adverse effects on pregnancy. Subsequently, Wistar rats were administered 1.0% (w/v) potassium perchlorate or potassium chloride in drinking water from days 2 through 8 of gestation. The daily calculated intake rates were 237 and 371 mg/rat for potassium perchlorate and chloride, respectively. Rats were administered methylthiouracil 45 minutes before injection of 5 μCi sodium radioiodide ($^{131}I^-$); sacrifice was 2 hours later. Rats clearly not pregnant were sacrificed on day 20 while pregnant rats were allowed to deliver prior to termination. Pregnancy was successful in 7/11 controls and 8/11 perchlorate treated rats. Among non-pregnant animals, implantation sites were not found. Litter size, number of pups and pregnancy duration were not affected. Perchlorate administered at 1% in drinking water was not found to have any significant effect on the outcome of pregnancy (Brown-Grant, 1966).

In the same experiment, perchlorate effects on deciduoma formation in false-pregnant rats were addressed. False-pregnancy was induced by mating females with vasectomized males. Females were exposed as before on days 2 through 8 of gestation to 0.25 or 1.0% potassium

chloride or perchlorate; the 0.25 and 1.0% daily dose levels were calculated to be 63 and 246 mg potassium perchlorate/rat and 82 and 308 mg potassium chloride/rat, respectively. Deciduoma formation was induced through traumatizing one uterine horn while under anesthesia. Rats exposed to 0.25% solutions were traumatized on day 3 and sacrificed on day 7 of gestation; trauma and sacrifice occurred on day 4 and 8, respectively, in the 1.0% groups. Methylthiouracil and sodium radioiodide ($^{131}I^-$) were administered prior to sacrifice as before. Deciduoma formation was not different in perchlorate treated rats as compared to chloride treated rats for either dose level. The low dose deciduoma response rate was highly variable in both treated and control rats while, at the high dose, the decidual reaction was both massive and uniform in chloride and perchlorate treated groups. Thyroid weights were significantly increased in the 1% dosing group. Although iodide concentration of the uterus in early pregnancy was effectively diminished by either dose of potassium perchlorate, deciduoma formation was not affected (Brown-Grant, 1966).

A related study was performed by Brown-Grant and Sherwood in 1971. Wistar rats were mated shortly postpartum and the present litter culled to nine. The dams were then administered 0.1% potassium iodide or 1.0% potassium chloride, perchlorate or iodide in the drinking water until sacrifice. The average daily intake of potassium perchlorate and potassium chloride was 615 and 655 mg/rat, respectively; calculated daily doses were approximately 2440 and 2660 mg/kg bodyweight. The litters were sacrificed on day 9 or 10 of the new gestation period. The dams were then sacrificed on day 12 or 13, allowing time for the new blastocysts to implant. Potassium perchlorate again did not affect blastocyst ability to survive prior to implantation or implantation rate after lactation ceased. Relative thyroid weights of the dams and litters were significantly increased as compared to potassium chloride exposed controls. The high dose of potassium iodide (average daily intake of 234 mg/rat or approximately 1150 mg/kg) was maternally toxic, causing one-third of the dams to die. Other effects included severe body weight and fluid intake reduction, adrenal gland enlargement and increased deaths in the litters. None of the dams had implantation sites, probably due to the poor state of maternal health. The low dose (average daily intake of 50 mg/rat or approximately 215 mg/kg), however, caused no maternal or litter toxicity and the dams had a high rate of implantation. The authors did not determine the role of high iodide content in the uterus prior to implantation; lowering levels of iodide with perchlorate and moderately increasing iodide by supplementation had no effect on blastocyst implantation.

The capacity of perchlorate and potassium iodide to prevent the uptake of radioiodide in fetal and neonatal populations was tested by Sztanyik and Turai in 1988. On day 17 or 18 of gestation, pregnant albino CFY rats were administered 370 kBq (10 μCi) $^{131}I^-$ intraperitoneally, followed 20 minutes or 1 to 2 hours later by 3 or 6 mg potassium perchlorate, also given intraperitoneally. In 24 hours, fetuses whose dams had been given 6 mg (approximately 24 to 30 mg/kg bodyweight) perchlorate 20 minutes after radioiodide had taken up less than 7% of the $^{131}I^-$ as compared to the levels taken up by control fetuses, whose dams had not been administered a thyroid blocking agent. Administration of this higher dose at 2 hours allowed fetuses to take up over 58% of the control value; likewise, 3 mg (approximately 12 to 15 mg/kg) at 20 minutes only reduced the iodide concentration in the fetuses to approximately 18% of the control value. Combining perchlorate with potassium iodide was more effective than either anion alone. Only 0.1 mg of potassium iodide and 3 mg perchlorate given at 20 minutes reduced the 24 hour uptake to less than 7%. Given at 2 hours, the combined dosage lowered radioiodide uptake to 29%, approximately half of the uptake seen with 6 mg perchlorate alone. In general, fetuses whose dams were dosed on days 19, 20 or 21 of gestation took up more

radioiodide than fetuses dosed with the same anions on days 17 or 18. This increase in active concentration of iodide toward the end of gestation was seen also in control fetuses and correlated with increased function of the fetal thyroid gland. Maternal thyroid uptake of the radioiodide in the treated groups ranged from only 3 to 30% of the control maternal thyroid uptakes.

In the same study, dams were injected intraperitoneally with 370 kBq (10 μCi) $^{131}I^-$ 4 hours after delivery of their litter. After 2 more hours, they were administered 0.1 mg potassium iodide and 3.0 mg potassium perchlorate, again intraperitoneally. In 24 hours, treated sucklings took up only half the radioiodide through maternal milk as compared to control sucklings. Iodide elimination rates were not different in control and treated animals. Potassium iodide and perchlorate were found to be most effective when administered together in lower doses than when administered alone. Lowering doses reduces the potential risk of embryo- and fetotoxic effects of either anion (Sztanyik and Turai, 1988).

In a more recent study, suckling Wistar rats were made iodine deficient by giving the dams 1.23 g sodium perchlorate/L drinking water from postnatal day 0 (day of birth) through day 10. Perchlorate prevents lactational transfer of iodide; perchlorate is not believed to be transferred through the milk. Sucklings were administered labeled sodium iodide ($^{131}I^-$) and [$^{125}I^-$]thyroxine on day 10. Pups were sacrificed at 0.25, 1, 2, 4, 8, 16, 24, 36 and 48 hours after dosing. The kinetics of iodide and thyroxine (T_4) in the plasma, thyroid and skin were measured and pharmacokinetically modeled. Iodine deficiency through perchlorate administration resulted in a significantly increased body weight. Plasma iodide concentrations were significantly decreased in perchlorate treated rats as compared to controls; plasma T_4 levels were not affected. Simultaneously, thyroidal uptake of iodide and iodide derived from T_4 was significantly increased in both rate and amount. Conversely, skin uptake of both iodide forms was decreased in perchlorate treated rats. Within 15 minutes after the tracers were injected, the control rats had taken up 45% of the injected iodide into their skin; perchlorate treated rats had taken up just 27% into the skin. In a 10-day-old rat, the skin represents approximately 25% of the total body weight and can store twice as much iodide as the thyroid (Zeghal *et al.*, 1992).

Perchlorate was used to induce hypothyroidism in an investigation of selenium deficiency in the developing thyroid. Wistar rats were maintained on regular or selenium free diets and given tap water or 1% sodium perchlorate in tap water from the day of mating until the pups were 3 or 4 weeks old. Some subgroups of selenium deficient rats were supplemented with 0.5 mg/kg selenium. Selenium deficiency and perchlorate treatment both decreased pup growth; perchlorate did not further the deficit in weight gain among the selenium deficient pups. Both perchlorate administration and selenium deficiency resulted in increased relative brain weights. Thyroid weights were decreased in all perchlorate treated subgroups; histological examination revealed marked hyperplasia and near absence of luminal colloids. Perchlorate decreased T_4 levels in all subgroups. However, perchlorate treated selenium deficient pups had higher plasma T_4 levels than perchlorate treated controls on the normal diet; selenium supplementation until 4 weeks of age partially corrected this difference. Similarly, perchlorate decreased plasma triiodothyronine (T_3) levels in all groups but the decrease was not as large in selenium deficient pups. Thyroid stimulating hormone (TSH) levels were high among treated rats; again, deficient rats were not as greatly affected. Thyroid hormone production depends on hydrogen peroxide as a substrate. GSH-Px, one of the thyroid's major protection enzymes against hydrogen peroxide damage, is selenium-dependent. Lack of selenium apparently

allows for higher concentrations of peroxide and increased hormone synthesis, as illustrated under perchlorate induced hypothyroidism (Golstein *et al.*, 1988).

Perchlorate Effects in Fetal Guinea Pigs or Rabbits

In 1957, Postel reported the effects of 1% potassium perchlorate in maternal drinking water during the last 21 to 48 days of gestation in guinea pig fetuses. Subgroups of dams were subcutaneously supplemented with 0, 8, 16 or 32 μg T_3 per day. T_3 supplemented animals consumed an average of 152 mg potassium perchlorate/100 g body weight (1520 mg/kg) on a daily basis while animals receiving saline control injections consumed only 74 mg/100 g (740 mg/kg). Subcutaneous administration of 10 to 20 μCi sodium ^{131}iodide occurred 1 hour prior to sacrifice. Perchlorate exposed fetal thyroids were found to be massively enlarged, averaging over 15 times greater mass as compared to controls. The goiters were hyperplastic and highly vascular. Administration of T_3 at any level did not prevent and may have intensified development of goiters. Maternal thyroid weights and histology were not affected. Both perchlorate treated and control fetuses concentrated three times the amount of radioiodide in one hour as compared to their respective dams. The author concluded that perchlorate must enter the fetal circulation system and that fetal goiter is not attributable to decreased maternal thyroid hormones as no evidence of maternal disruption was found. Since fetal thyroids appear to be intrinsically hyperactive as compared with adults, the fetuses were more sensitive to iodide inhibition and developed goiters on a more rapid scale.

In the same study, Postel (1957) used non-pregnant females to determine if goiters could be generated in adult guinea pigs under the same conditions. These sows received 1% potassium perchlorate in drinking water for 30, 60 or 90 days. Although iodine was depleted at 30 days, no evidence of goiter could be found until 60 days, when enlargement and hyperplasia were evident. The author concluded that since, in the original experiment, dams were exposed for an average of 37 days, goiters had not had time to develop but would have likely developed if dosing had continued.

Similar results in rabbits were described by Lampe *et al.* in 1967. Dams were dosed with 100 mg potassium perchlorate/kg body weight daily mixed with feed. Dosing occurred from conception through day 21 or 28 of gestation. Maternal thyroid weights in treated animals were three times higher than control thyroids; fetal thyroids were nearly four times the control weights. The number of epithelial cells were increased and the amount of colloid decreased in treated animals. The relative volume of the stroma, the supporting matrix, was increased due to the reduced follicle sizes. Likewise, maternal thyroids showed decreased luminal size and increased epithelial cells. The authors felt these results demonstrated that the placenta is permeable to perchlorate. Because fetal thyroids were more enlarged relative to maternal glands, the fetal thyroid system is independent of the maternal system and more sensitive to changes in iodine availability.

Conclusions

The perchlorate ion is not a primary developmental toxin to *Hydra* according to the *in vitro* hydra developmental toxicity assay (Confer *et al.*, 1996). Sodium perchlorate has been shown to inhibit metamorphosis in the South African clawed frog and the suppression of thyroid

hormones by perchlorate appears to cause decreased immune capabilities in this species (Rollins-Smith *et al.*, 1993). Perchlorate invariably did not affect implantation or pregnancy outcome in several studies on rats. However, increased thyroid size has been noted in both dams and pups (Brown-Grant, 1966; Brown-Grant and Sherwood, 1971). The increase in thyroid size is coupled with decreased thyroid uptake of iodine in both. Pups appear to be affected more significantly due to the hyperactivity of the fetal thyroid toward the end of gestation (Sztanyik and Turai, 1988). Likewise, guinea pig fetuses develop goiters more quickly than adults (Postel, 1957). Similar effects are also shown in rabbits (Lampe *et al.*, 1967). The consequences of fetal goiter were not studied.

Considerable gaps still exist in knowledge of perchlorate developmental effects. A comprehensive evaluation of perchlorate's reproductive and developmental effects, including non-thyroid endpoints, has not been performed. The potential for neurobehavioral effects in the offspring has also not been determined. Two Office of Prevention, Pesticides and Toxic Substances guideline studies were initiated to determine if perchlorate has non-thyroid endpoints (90-Day Study) or if it produces behavioral deficits (Developmental/Neurobehavioral Study). The effects of iodine deficiency and hypothyroidism on human offspring are fairly well-known but not well quantified. Endemic cretinism occurs in areas where dietary iodine deficiency is prevalent and severe. Children of hypothyroid mothers are more likely to have behavioral and neurological disorders, even if the child is euthyroid (Porterfield, 1994). Perchlorate's potential role in these endpoints of iodine deficiency has yet to be verified or measured.

RECEPTOR KINETICS

Interspecies differences affect uncertainty in risk assessment. The data on receptor kinetics of both rats and humans were sought to understand and minimize this uncertainty. Understanding whether or not the thyroid iodide receptor of both species reacts in the same manner and rate to the perchlorate ion could provide justification for reducing the uncertainty factor assigned for extrapolation of animal data to humans. For this reason, the protocol peer review panel suggested data on the perchlorate discharge test (PDT) be collected (TERA, 1997b). The PDT has been performed in rats, as well as humans. Because PDT results in humans were potentially available through literature and hospital records, this diagnostic tool was investigated as a source of receptor kinetic information.

Perchlorate Discharge Test

The PDT was developed in 1957 to study Hashimoto's thyroiditis. Morgans and Trotter (1957) found that Hashimoto's sufferers discharged considerable radioiodide following perchlorate administration, indicating that the disease is characterized by a partial defect in organification of iodide. Organification is the binding of inorganic iodide to form T_4 and T_3. Since then, the PDT has been instrumental in diagnosing full or partial binding defects in thyroid patients and subclinical defects in patients' family members (Baschieri *et al.*, 1963). Although rarely used in the U.S. (Vance, 1997), the PDT is considered safe even for use in infants (al-Jurayyan and el-Desouki, 1997).

The PDT is performed in patients by first orally or sometimes intravenously administering radioiodide ($^{123}I^-$, $^{131}I^-$ or $^{132}I^-$). Radioiodide doses may range from 5 to 150 μCi but are usually fairly small (10 to 20 μCi). Perchlorate is given, theoretically, after enough time has elapsed for a normally functioning thyroid to have taken up and organified the radioiodide dose. In reality, perchlorate may be administered anywhere from ten minutes to three hours after radioiodide loading. Perchlorate is usually given by mouth (potassium perchlorate) but may also be administered intravenously (sodium perchlorate). Doses range from 400 to 1000 mg in adults. Discharge is determined by scintillation measurements taken on the neck directly over the thyroid immediately prior to perchlorate administration and at timed intervals from ten minutes up to two hours after perchlorate administration. Results are generally expressed in percentage uptake and/or percentage discharge of radioiodide. Discharge of the radioiodide dose released from the thyroid considered significant (i.e., positive) can range from any discharge (>0%) to more than 50%. Often the range of 20% to 50% discharge is considered indicative of an incomplete organification defect. Background radioactivity may be measured either over the thyroid prior to iodide administration or during the test over the thigh.

Iodide perchlorate discharge tests are similar to the PDT but utilize the administration of 0.25 to 2.0 mg stable potassium iodide as a carrier simultaneously with the radioiodide. Iodide perchlorate discharge tests are considered more sensitive to subtle organification defects, such as those defects seen in currently euthyroid patients with a history of thyrotoxicosis (Creagh *et al.*, 1994).

The PDT has been performed in the rat. However, the procedure was very different than the PDT procedure in humans and does not readily allow for comparison or extrapolation. Rats were intraperitoneally injected with 100 μL (1 μCi) $^{125}I^-$. After one to six hours, potassium perchlorate (5, 10, 25 or 50 mg/kg bodyweight) was administered, again intraperitoneally. The animals were sacrificed at 2.5 or 60 minutes after perchlorate injection. Results were expressed as thyroid:blood iodide ratios (Atterwill *et al.*, 1987).

Published perchlorate discharge data for humans and rats in spreadsheet form follow in Appendices A and B, respectively. Although most subjects were patients with thyroid problems, some normal human data were found. Please note that each sequence of three pages in the human data section are meant to be laid side-by-side and read across. The rat data are confined to two pages which again are meant to be read horizontally adjacent. Each line starts with a number for easy referencing between pages.

Conclusions

The literature review for the perchlorate discharge test was conducted because this diagnostic test initially appeared to be a source of receptor kinetics data for both rats and humans. The PDT was, unfortunately, found to be not comparable between species or even between administering physicians due to differences in methodology. Published papers on the PDT provided some limited human response data. The discharge of iodide from the thyroid due to perchlorate administration does not correlate directly to perchlorate competition at the receptors but rather signifies how inefficient the thyroid is at binding iodide over the allotted time, with large doses of perchlorate discharging "all" iodide not yet bound. In the two human studies resembling the rat PDT, Friis (1987) and Takeuchi *et al.* (1970) reported iodide uptake as

percent of administered dose prior to perchlorate administration. Although a similar measurement to the thyroid:blood ratio was reported by Atterwill *et al.* (1987) in rats, the units are not comparable and the times allowed for uptake are highly dissimilar.

PERCHLORATE ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION

At the beginning of this effort the full extent of available data on perchlorate absorption, distribution, metabolism and elimination (ADME) was not known. This summary was undertaken in order for the US Air Force, the Perchlorate Study Group and other interested parties to be aware of the information available and to make the limited metabolite data accessible for future planning efforts, possible model development and ultimately for the revised risk assessment for perchlorate. Understanding ADME may permit a decrease in the uncertainty factors for average human to sensitive human and animal to human extrapolation.

Iodide Distribution Mechanisms in Turtle Thyroids

Chow *et al.* investigated the effect of perchlorate on iodide distribution in 1982. Turtle thyroids were selected due to their huge follicle size of more than 200 μm. Northern turtles (*Chrysemys picta*) were dosed intraperitoneally with 0.2 or 2.0 x 10^{-3} mol/kg sodium perchlorate 3 hours prior to the injection of 50 μCi $Na^{125}I$. In order to prevent organification of the iodide, 20 mg/kg doses of methimazole were administered 1 hour before and 5, 12 and 20 hours after the sodium iodide. The turtles were sacrificed 24 hours post-iodide administration. The high dose effectively blocked iodide active transport and depolarized the cell membranes slightly, allowing only passive iodide transport to occur. This effect is illustrated in the extracellular fluid:cell ratio (basal cell membrane passive transport ratio) of 6:1 and in the cell to lumen ratio (apical membrane ratio) of 1:3.83. The thyroid:plasma and lumen:plasma ratios at the high dose were approximately the same at 0.49:1, which were significantly decreased from the control ratios of 162:1 and 115:1, respectively. Low dose ratios were similar to the high dose results (i.e., 0.50:1).

Perchlorate effects on chloride and potassium ion distribution in thyroid follicles were subsequently investigated in 1983 by Chow *et al.* Northern turtle thyroids were isolated and perfused with turtle Ringer solution. Chloride and potassium ion concentrations were measured in the thyroid follicle lumen and thyroid epithelial cells using ion-selective and conventional microelectrodes. Thyroid water content and electrolyte levels were determined post-perfusion. Exposure to sodium perchlorate and other drugs occurred either intraperitoneally prior to sacrifice or during perfusion. At an unspecified adequate dosage, perchlorate was found to decrease both the chloride activity and chloride concentration in the thyroid lumen, as well as the transepithelial ionic potential. Perchlorate did not affect the potassium ion except for the decreased ionic potential. Since perchlorate is known to competitively inhibit iodide transport and since the data show chloride concentrations are inhibited as compared to controls, the authors concluded that the chloride ion is apparently subject to active transport across epithelial membranes such as the thyroid epithelial cell layer.

Deposition and Elimination of Perchlorate in Hens and Eggs

The body's elimination of radioactive iodine is a historic research concern as ^{131}I is a fission product generated in nuclear explosions and reactor accidents (Simonovic *et al.*, 1972). Since perchlorate had previously been found effective in reducing the deposition of radioactive iodide in eggs, the distribution of the perchlorate itself in the hen and the egg was studied. Laying hens were intramuscularly administered 10 μCi $K^{36}ClO_4$ (specific activity of 1.16 mCi/g) and sacrificed at 3, 24 or 48 hours. A single hen was dosed with 10 μCi at 0, 24 and 48 hours and sacrificed at 51 hours. The ten largest ova (largest designated #1, etc.) from each hen were harvested. The radioactive perchlorate concentrated in a ring adjacent to the exterior of the ova; $^{131}I^-$ had been found to deposit similarly in an earlier study. The width of the radioactive "ring" image was found to increase with time after dosing. Although the ova size in relation to development stage was not affected by perchlorate administration, the inside of the radioactive ring was found to be related to the size of the ovum at the time of administration, causing the ring to grow wider as the ovum continued apparently normal development. This deposition pattern was demonstrated in the ova of the multiple dose hen; within the wide radioactive ring were three darker concentric lines correlating to the three dosings of perchlorate. Peak deposition of perchlorate was found in ovum #5, as was the highest perchlorate ovum:blood ratio (4.5). As ovum:blood ratios for ova #2 through #8 were all higher than 1, an active transport mechanism for perchlorate and iodide is likely. When eggs were fractioned, the albumin or egg white was found to have the highest total activity due to its relatively large mass. However, when activity per gram of tissue was measured, the shell membrane had a higher deposition and ovum:blood ratio than the albumin, which may indicate that the membrane actively transports these ions (Pena *et al.*, 1976).

Blood, organ and excrement samples were also collected in the Pena *et al.* (1976) study. Thyroid and blood perchlorate activities decreased quickly, denoting rapid secretion of perchlorate by the thyroid gland. At 3 hours the thyroid's perchlorate activity was nearly 37 times that of the blood. Muscle and organ samples had perchlorate organ:blood ratios of 0.6 or less. Surprisingly, the ratio found in the right oviduct was higher than 1. In poultry, the left oviduct is functional and the right may be in different stages of non-functional development. A high ratio in the right oviduct therefore may indicate that perchlorate can be concentrated by organs in development. Of the total dose administered, 88 and 99% were recovered in the excrement after 3 and 24 hours, respectively; at 24 hours the majority of the remaining activity was found in the 10 largest ova. The authors concluded that the perchlorate remaining in the edible portions of the hens was negligible. If 200 mg perchlorate/day were to be administered in order to block the uptake of radioactive iodide, the authors calculated a dose of less than 2 mg perchlorate/egg (Pena *et al.*, 1976).

Uptake and Distribution of Perchlorate in Test Mammals

The distribution of perchlorate in rabbits was first investigated in 1938 by Durand. One test group was dosed intravenously with 920 mg sodium perchlorate in a 40% solution. Key organs were harvested at 20 minutes. Rabbits in a second group were dosed intramuscularly with 800 mg perchlorate and sacrificed at 110 minutes. A third group was dosed orally with 2000 mg and terminated at 130 minutes. Urine was found to be the primary route of elimination for all methods of administration. In each group, the highest organ perchlorate concentrations were found in the adrenals and ovaries. The next highest concentrations were found in the intestinal

mucosa, spleen and gall bladder. Lower concentrations of perchlorate were reported in the gastric mucosa, testes, muscle, bone, liver, kidneys, lungs, heart and brain. In the same study, additional rabbits were dosed orally or intramuscularly and monitored for four days. No signs of toxicity were found in orally dosed animals given up to 1000 mg sodium perchlorate. Mortality occurred in rabbits dosed intramuscularly with 1500 mg while partial paralysis and edema occurred in the 500 mg group.

In 1959, Anbar *et al.* attempted to confirm the perchlorate ion's accumulation and lack of metabolism in the thyroid. White rats were intraperitoneally injected with $K^{36}ClO_4$ and the specific activity per gram of tissue was measured at 30 minutes, 4 hours and 12 hours. The thyroid perchlorate activity level was the greatest of any organ and was maximal at four hours. Salivary glands had the second highest perchlorate activity; the highest activity occurred at 30 minutes. The adrenal glands also had high activity levels and, like the thyroids, contained the most perchlorate per gram of tissue at four hours. Rabbits were also injected with $K^{36}ClO_4$. Rabbit specific activities were measured at 2 and 9.5 hours; thyroid perchlorate activity levels were again the highest of any organ and peaked at 2 hours. Rabbit testes had the next highest specific activities.

In the same study by Anbar *et al.* (1959), rats were administered $^{131}I^-$ and $^{36}ClO_4^-$ in equimolar concentrations at the same time. The thyroid:blood specific activity for iodide was slightly higher than the ratio for perchlorate (1.80 and 1.69, respectively). Most other organs took up similar amounts of either ion except for the salivary and adrenal glands; both had higher iodide organ:blood ratios (0.47 and 0.32, respectively) as compared to perchlorate organ:blood ratios (0.014 and 0.17, respectively). Rats given 0.14 mmol of both iodide and perchlorate had thyroid iodide:perchlorate specific activity ratios of 2.1, 2.7 and 2.2 at 60, 120 and 360 minutes post-administration, respectively. When goiterous rats (i.e., fed 1 mg propylthiouracil (PTU)/day for 4 weeks prior to testing) were administered 0.14 mmol of either ion individually, uptake of the ion occurred more slowly, but higher concentrations of ions were taken up over time as compared to non-goiterous control rats. Goiterous rats had thyroids nearly five times the mass of non-goiterous rats (Anbar *et al.*, 1959).

Perchlorate was substituted for iodide in a distribution study by Chow and Woodbury (1970). Male Sprague-Dawley rats and Hartley guinea pigs were functionally nephrectomized 24 hours prior to sacrifice. Rats were dosed with 0.005, 0.1 or 2.0 mmol/kg stable potassium perchlorate, each dose containing 0.5 μCi $K^{36}ClO_4$, intraperitoneally 2 to 240 minutes before termination. The calculated stable perchlorate doses were approximately 0.69, 14 and 280 mg/kg bodyweight, respectively. A group of control rats received [^{14}C]inulin, $^{35}SO_4^{-2}$ or $^{36}Cl^-$ two hours prior to sacrifice in order to determine thyroid follicle volume and intra-follicular membrane potential. Maximal thyroid:interstitial fluid perchlorate ratio was found to be inversely related to perchlorate dose. Although plasma levels of perchlorate did not differ significantly between dose groups, total thyroid concentrations of perchlorate were significantly different and, again, inversely related to dose. Rat thyroids were found to concentrate the perchlorate at lower dose levels but could not actively transport perchlorate at the higher dose level. Like $^{36}Cl^-$, $^{36}KClO_4$ passively distributes through the thyroid follicle in equilibrium with membrane potential. Active iodide transport across the basal membrane of follicle cells increases the perchlorate thyroid content. Transport across the apical membrane into the follicle lumen further increases the concentration. At the low dose (0.005 mmol/kg), the perchlorate concentration in the follicle lumen was 24 times that of the concentration in the follicular cells and 147 times the concentration in the fluid surrounding the follicles. Because perchlorate

uptake is inversely related to dose, perchlorate not only competes with iodine for active uptake but also inhibits the thyroid transport system with increasing dose.

Chow and Woodbury (1970) also dosed rats with 0.1% PTU in drinking water for 2 weeks prior to administration of 0.07 mmol/kg potassium perchlorate (9.7 mg/kg); the study timepoints were 3 minutes to 24 hours after $KClO_4$ dosage. Controls were also administered 0.07 mmol $KClO_4$, as were a small group of rats which had been hypophysectomized 4 weeks prior to the study. Chronic PTU treatment caused the perchlorate thyroid:interstitial fluid ratios to increase, as compared to similarly dosed controls. Hypophysectomy conversely caused significantly decreased uptake of perchlorate into the thyroid (Chow and Woodbury, 1970).

Finally, guinea pigs were intraperitoneally dosed with 0.05 mmol/kg $KClO_4$ (6.9 mg/kg), with or without pre-administration of 0.1% PTU for 2 weeks. Again, PTU treatment elevated the thyroidal uptake of perchlorate. Both control and PTU treated guinea pigs had higher uptake of perchlorate as compared to control and PTU treated rats. Rats reached and maintained a maximal thyroid:interstitial fluid perchlorate ratio at four hours; guinea pig ratios did not plateau until eight hours after dosing. The species appear to be different in the colloid contents of thyroid follicle lumen; rats were found to have a significantly smaller histologically determined luminal volume as compared to guinea pigs (Chow and Woodbury, 1970).

Uptake was found to be similar in male Sprague-Dawley rats maintained on the Remington low iodine diet for 4.5 to 5 weeks prior to perchlorate exposure. Rats were dosed intraperitoneally with 0.1 μCi of $K^{36}ClO_4$ at 240 μCi/mmol, which resulted in approximately 40 μg stable perchlorate per animal. The first group of animals (stable perchlorate dose approximately 0.16 to 0.20 mg/kg bodyweight) were sacrificed at 2, 8 and 24 hours after dosing; a second group whose dose approximated 0.11 to 0.13 mg/kg was sacrificed at 2, 4 and 8 hours. An additional group of rats was administered 0.2 μCi perchlorate and followed for 96 hours (approximate dose 0.22 to 0.26 mg/kg). As in the previous study, the rats reached maximal thyroid levels at approximately four hours after perchlorate administration. By 96 hours, thyroid perchlorate levels had fallen to 5% of the peak value; exponential decay was evident and the half-life was found to be approximately 20 hours over the entire time course. Perchlorate clearance rates compare favorably with previously published data for ^{131}I, indicating evidence for similar pathways for both ions. Perchlorate, however, does not undergo organification as iodide does; the perchlorate ion is excreted in the urine and no evidence of covalent binding or retention in selected organs was found (Goldman and Stanbury, 1973).

In a recent review of perchlorate toxicity, perchlorate elimination curves in rats and calves were described. Perchlorate has a two-phase decay curve in these two species. For rats, 96% of administered perchlorate is eliminated with a half-life of 1 to 2 hours. In the second portion of the curve accounting for only 4% of the dose, the half-life was 72 to 80 hours. Calves have a faster overall rate of elimination but the initial elimination is slower. The first half-life was found to be approximately 2 or 2.5 hours. The second half-life ranged from 23 to 27 hours (Selivanova and Arefaeva, 1986 as cited by Von Burg, 1995).

In 1962, Eichler and Hackenthal presented similar perchlorate elimination data. Male and female Wistar rats were subcutaneously dosed with 0.2, 1.0 or 6.0 mg $Na^{36}ClO_4$/100 g bodyweight (2, 10 or 60 mg/kg). Rats were kept in metabolism cages and total urine was collected at 1.5, 3, 6, 12, 24, 36, 48 and 60 hours. The elimination curves showed nearly linear, rapid excretion of perchlorate until six hours, at which time the curve slope started to decrease.

Rate of excretion increased with dose. The elimination rates of the different doses prior to 24 hours were significantly different from each other; after 24 hours, the elimination rates were similar. Over 60 hours, 93.4 to 97.4% of the administered dose was recovered. The pattern and speed of elimination of perchlorate were similar to other non-metabolized compounds.

Rats were also dosed by Eichler and Hackenthal (1962) with combinations of 0.2 mg sodium perchlorate and 2.44 mg sodium iodide/100 mg bodyweight or 0.2 mg perchlorate and 1.32 mg sodium thiocyanate/100 mg bodyweight. The combination of perchlorate and iodide resulted in significantly faster perchlorate discharge than the dose of 0.2 mg perchlorate/100 g bodyweight (2 mg/kg) alone, although the amount of perchlorate recovery was not improved. The perchlorate and thiocyanate combination had a slightly slower rate of perchlorate elimination than the high dose (6.0 mg/100 g or 60 mg/kg) of perchlorate alone (Eichler and Hackenthal, 1962).

Chow *et al.* (1969) compared the uptake of radio-labeled perchlorate and iodide ions against stable ions in normal and thyroid-impaired rodents. Intact male Sprague-Dawley rats were intraperitoneally exposed to 0.1, 0.2 or 5.0 meq/kg stable potassium perchlorate (14, 28 or 690 mg/kg, respectively), with $^{36}Cl^-$ at a specific activity of 25.2 μCi/mmol, 2 hours prior to sacrifice. Perchlorate at the 0.1 and 0.2 meq/kg dose levels was found to concentrate in the rat thyroid, as compared to plasma concentration, with the amount of concentration inversely related to dose. The high dose level of perchlorate did not result in concentration of perchlorate in the thyroid. Rats that had been pretreated with TSH (1 IU TSH in 0.9% saline solution intraperitoneally 18 hours prior to perchlorate administration) or propylthiouracil (0.1% PTU in drinking water for 2 weeks) also concentrated perchlorate at the lower dose levels. PTU impairs the synthesis of thyroid hormones, causing TSH to have an enhanced effect on the thyroid and increased stimulus for iodide binding. Hypophysectomized rats, i.e., rats with the pituitaries surgically removed, were not able to concentrate perchlorate as compared to intact animals at the 0.1 and 0.2 meq/kg dose levels; however, thyroid perchlorate levels at the high dose were not different for intact and altered rats. Pretreatment with TSH increased the binding of perchlorate in hypophysectomized rats, but not to the levels found in perchlorate only rats. Skeletal muscle was found to take up perchlorate, but to a lesser degree than the thyroid; muscles were not found to actively concentrate perchlorate ions.

In a subsequent study, rats were exposed to 0.005, 0.01, 0.02, 0.05 or 0.10 meq/kg perchlorate (0.69, 1.4, 2.8, 6.9 or 14 mg/kg, respectively), again with $^{36}Cl^-$ at a specific activity of 25.2 μCi/mmol under the same general conditions. Again, concentration was inversely related to dose. TSH pretreatment resulted in enhanced perchlorate concentration, with significant increases over controls at the 0.02, 0.05 and 0.10 meq/kg doses. Male albino guinea pigs were also exposed to the same dosages; guinea pigs displayed the same relationship as rats, but concentrated more perchlorate in the thyroid as compared to plasma levels. When pretreated with TSH 24 hours prior to perchlorate administration, only the 0.05 meq/kg dose group had increased concentration as compared to perchlorate only animals. Similar groups of rats and guinea pigs were exposed to the same dosages of stable perchlorate only, with the addition of radioactive $^{131}I^-$. Results were similar to the rats and guinea pigs which had received the same amount of perchlorate with $^{36}Cl^-$, with the exception of TSH pretreatment in rats which did not enhance concentration as compared to non-pretreated rats. Additional rats and guinea pigs received the same dose levels of stable iodide along with $^{131}I^-$. Effects were again inversely dose related; TSH pretreatment enhanced iodide uptake in guinea pigs but not in rats, as compared to non-pretreated animals. Overall, concentration of the ion was found to be

inversely reliant on the dose of the stable ion given. Although $^{36}ClO_4^-$ did not influence the uptake of stable perchlorate or iodide differently, $^{36}ClO_4^-$ did competitively inhibit uptake of stable ions as compared to $^{131}I^-$. Guinea pigs were found to concentrate more ions as compared to rats and TSH pretreatment uniformly enhanced the concentration effect (Chow *et al.*, 1969).

Iodide Uptake Studies

Halmi *et al.* (1956) examined iodide uptake when active transport was completely blocked with the use of sodium perchlorate. Male Sprague-Dawley rats were first administered 6 mg PTU subcutaneously to prevent iodide organification. Iodide uptake was prevented by administration of 100, 200 or 400 mg sodium perchlorate with half of each dose administered along with the PTU and the other half administered 45 minutes later along with 5 to 50 μCi $^{131}I^-$. Rats were sacrificed 1 to 1.5 hours after iodide administration. All dose levels of perchlorate were found equally effective in preventing iodide uptake. Perchlorate reduced the thyroid:blood iodide ratio from 22.7 to 0.45; radioiodide was found to take up 30% of the thyroid gland volume when entering the gland by diffusion alone. Rats sacrificed 4 to 4.5 hours after iodide administration produced similar results, indicating that equilibrium is reached prior to 1 to 1.5 hours.

In the same study by Halmi *et al.* (1956), the distribution of radioiodide in different tissues was also examined. The red blood cell:plasma, plasma:serum and whole blood:serum iodide ratios, approximately 0.6, 1 and 0.8, respectively, were not affected by perchlorate ion competition. Perchlorate also did not greatly affect the organ:serum iodide ratios of the following tissues: submaxillary gland, parotid, pituitary, adrenals, testes, spleen, kidney, lung, skin or diaphragm. Intestinal absorption of radioiodide was also not affected by perchlorate ions (Halmi *et al.*, 1956). However, perchlorate administration did affect the stomach wall:serum and gastric juice:serum iodide ratios (0.36 and 0.75, respectively) as compared with sodium chloride administered controls (1.45 and 15.8, respectively). A gastric iodide pump subject to perchlorate ion blocking appears to exist. Perchlorate did not affect the liver:serum iodide ratio at 1 to 1.5 hours post-iodide administration as compared to sodium chloride dosed controls (0.36 versus 0.38, respectively). By 4 to 4.5 hours, the liver:serum ratio had decreased in perchlorate treated rats (0.34 as compared to 0.42 in controls). Stable iodide administered instead of perchlorate had similar competitive effects on this ratio (0.34 compared to 0.47 in controls) at 4 to 4.5 hours. These data indicate that iodide does not enter the liver by diffusion alone but also may enter the liver by a quickly saturated mechanism subject to competition from stable iodide and perchlorate ions. Perchlorate appeared to accelerate renal clearance of radioiodide; sodium chloride controls had excreted 31% of the radioiodide dose in 4 hours after iodide administration whereas perchlorate treated rats had excreted 62% (Halmi *et al.*, 1956).

Wyngaarden *et al.* (1952) explored the effect of several anions on iodide discharge. Male Wistar rats were maintained on the Remington low iodine diet with 0.1% PTU for over 14 days before dosing. The rats were then administered 10 mg PTU intraperitoneally to be certain iodide organification was blocked. After 1 hour, rats were injected with 5 μg sodium iodide containing 10 μCi $^{131}I^-$. Thyroidal iodide accumulation was monitored by shielded scintillation counter for 45 minutes prior to intraperitoneal administration of 0.1 mmol of anion (approximately 80 to 90 mg/kg potassium perchlorate). Thyroid iodide was monitored at 15, 30, 45 and 75 minutes after anion administration. Background uptake of radioiodide was adjusted

by measuring, at corresponding time points, the thyroid area uptake on rats blocked with 10 mg potassium cyanate 20 to 60 minutes prior to radioiodide dosing. Percent discharge was calculated against "0%" discharge or the iodide uptake before perchlorate administration and against "100%" discharge or the amount radioiodide depleted with 0.1 mmol potassium thiocyanate administration. Perchlorate discharged the full "100%" of radioiodide within the first 15 minutes.

Perchlorate and thiocyanate effects on iodide discharge were further compared by Wyngaarden *et al.* (1952). Stepwise logarithmic concentrations from $1x10^{-4}$ mol (0.1 mmol or 80 to 90 mg perchlorate/kg bodyweight) to $1x10^{-8}$ mol ($8x10^{-3}$ to $9x10^{-3}$ mg perchlorate/kg) were administered as above. The lowest dose of perchlorate, $1x10^{-8}$ mol, discharged little or no radioiodide. Nearly "50%" discharge was reached at $1x10^{-7}$ mol or 0.08 to 0.09 mg perchlorate/kg. At this dose, perchlorate ions exceeded iodide ions by three-fold. For thiocyanate, a dose ten times higher ($1x10^{-6}$ mol) is necessary to discharge "50%" of the iodide. Nitrate, also tested as a potassium salt, caused "50%" discharge at levels between $1x10^{-5}$ and $1x10^{-4}$ mol (Wyngaarden *et al.*, 1952).

Following these discharge tests, Wyngaarden *et al.* (1952) studied the effect of these anions on iodide uptake. Again, the dose of 0.1 mmol of anion or 80 to 90 mg perchlorate/kg bodyweight was administered intraperitoneally, this time 20 minutes prior to radioiodide. A subset (2 rats) was administered 5 μg of labeled iodine while the other subset was given 100 μg. The rats receiving 100 μg radioiodide were able to trap 6 times more iodide than the 5 μg subset. The authors concluded large doses of iodide "nullify" perchlorate effects.

To determine the amount of iodide in the thyroid after multiple doses of perchlorate, Wyngaarden *et al.* (1952) placed groups of 3 rats on 17 day regimens of 0.1% PTU in the diet or 1.0% potassium thiocyanate, potassium nitrate or potassium perchlorate in the drinking water. The average daily intake of perchlorate was 233.5 mg/100 g bodyweight or 2335 mg/kg. Bodyweights for perchlorate treated rats were not different from regular diet and tapwater controls. However, thyroid weights were significantly increased and displayed marked hyperplasia and increased vascularity. Both soluble and precipitated thyroidal iodine were significantly decreased to 0.018 and 0.021 μg/mg tissue, respectively, as compared to control values of 0.099 and 0.700 μg/mg.

The effect of chronic perchlorate exposure on iodide excretion was determined by Shigan in 1963. Rabbits and white rats were orally dosed with 0.25, 2 or 40 mg perchlorate/kg bodyweight daily for 9 months. Controls were dosed with distilled water. Cardiac regulation, liver functions, hemoglobin levels and nervous activity were not affected at these doses. However, animals receiving 2 or 40 mg/kg excreted significantly higher quantities of radioiodide in 24 hours as compared to controls. The elimination curves at these doses had two distinct phases; the initial phase was much more rapid than the second elimination phase. Excretion of iodide in animals exposed to 0.25 mg/kg was not different from controls. Therefore, the author recommended 0.25 mg/kg or 5 mg/L as the maximum permissible exposure concentration for drinking water.

Inhibition of radioactive iodide uptake by perchlorate or stable iodide was studied by Sinadinovic and Jovanovic (1971). Rats were injected with 10 mg perchlorate/100 g bodyweight or 12.24 mg stable sodium iodide/100 g bodyweight prior to radioiodide intraperitoneal administration

(100.0 or 122.4 mg/kg at 0.5 or 24 hours before radioiodide injection, respectively). During the first 24 hours, approximately 90% of the radioiodide dose had been excreted in the perchlorate treated group. Only 43% of the radioiodide was excreted in the stable iodide control group. Over a five day period, the total amount of radioiodide excreted was similar in both treatment groups. Fecal elimination of radioiodide was minimal. Both treatment groups had similar elimination rates after 24 hours. Perchlorate effectively reduced the half-life of radioiodide (thereby decreasing irradiation time and shortening radioactive exposure) as compared to stable iodide controls. Although stable iodide will safely eliminate radioiodide, it is less efficient than perchlorate.

Similar results were seen by Schonbaum *et al.* (1965). Male Wistar rats were fasted for 48 hours prior to being offered salt and iodide free diet supplemented by 1% sodium iodide or 1% sodium iodide and 1.25% potassium perchlorate. An hour later, rats were dosed with 2.5 μCi $^{131}I^-$ intraperitoneally. Thyroidal region radioactivity was measured with a specially designed scintillation counter. Perchlorate treated rats excreted 19.3% of the radioiodide dose while sodium chloride treated controls excreted only 9.5%. Over 24 hours, the perchlorate group excreted 60% as compared to the controls which excreted only 50% of the original dose. When this study was repeated using 0.67% KCl for the control and 1.25% $NaClO_4$ added to the diet, sodium perchlorate treated rats excreted 73% of the iodide dose as compared to 56% for the potassium chloride controls within 24 hours. The difference in elimination between the two dose groups was most pronounced during the first four hours.

In the same study, female Wistar rats were fed the salt and sodium free diet supplemented with 1% NaCl or 1% NaCl plus 1.25% $KClO_4$ for 2 weeks prior to radioiodide challenge. In the first 24 hours, the perchlorate treated rats excreted 62% of the iodide as compared to 30% in the controls. Uptake of iodide was calculated to be 53.9% in control rats while uptake in perchlorate treated rats was only 2.6%. A group of male rats was pre-fed 1.25% perchlorate or 0.02% PTU for 2 weeks. Some PTU animals were also given perchlorate for 72 hours prior to iodide challenge. Both drugs lowered the radioactivity levels in the thyroid. Plasma radioactivity was also lowered by perchlorate whereas plasma levels in PTU rats were not different from controls (Schonbaum *et al.*, 1965).

Perchlorate was found to affect iodide uptake in other tissues as well as the thyroid. In thyroidectomized male rats, perchlorate administration prevented radioiodide uptake in the gastric region and lower abdomen as seen in thyroidectomized controls. Altered animals were provided L-thyroxine to ensure normal hormone levels. Additionally, the bladders and kidneys of the perchlorate treated group had significantly higher levels of radioactivity than the controls. Liver radioactivity was not different (Schonbaum *et al.*, 1965).

Iodine uptake after multiple doses of perchlorate was studied by Hackenthal *et al.* (1966). Male guinea pigs were subcutaneously administered 100 mg sodium perchlorate/kg bodyweight daily for 3, 12, 20, 35 or 50 days. An intraperitoneal dose of 50 μCi radioiodide was given 3 hours or 1, 4 or 6 days after cessation of perchlorate treatment. In order to prevent organification of the radioiodide, 5 mg PTU was administered subcutaneously 1 hour prior to the iodide. The animals were sacrificed 70 minutes post-iodide administration. All dosing groups had significantly increased thyroid:plasma iodide concentrations over control animals 24 hours after the last perchlorate dose. The ratio was still significantly higher than controls on the fourth day since perchlorate dosing. The group that had been dosed for 12 days in succession had thyroid:plasma iodide levels similar to those of the controls on the sixth day after perchlorate

exposure. In animals exposed to radioiodide just 3 hours after the last dose of perchlorate, the thyroid:plasma ratios were significantly increased in the 12, 20 and 35 day dosing groups. The 3 and 50 day group ratios were not different from controls. Apparently TSH levels increase after approximately 4 days (i.e., 3 days of perchlorate treatment plus 24 hours before iodide loading), resulting in thyroid:plasma values many times greater than normal. Why the ratio is not increased in the 50 days plus 3 hours group is not understood.

Hackenthal *et al.* (1966), in the same study, examined iodide uptake in other organs as well. Trachea:plasma iodide ratios were not increased at any time after only three consecutive days of perchlorate dosing. After 12 days dosing, the ratio was increased only when radioiodide was administered 3 hours after the last perchlorate dose. The 20 and 50 day perchlorate groups had significantly elevated trachea:plasma ratios 1 and 4 days after the last dose. As with the thyroid:plasma ratios, the tracheas in the 50 day perchlorate group did not take up significantly more iodide than the control group when tested only 3 hours post-perchlorate exposure. Trachea iodide uptake after multiple perchlorate dosages was similar to thyroid uptake, except the trachea was not affected until after 20 days of perchlorate treatment. The submandibular gland and parotid iodide levels were not affected by perchlorate administration (Hackenthal *et al.*, 1966).

Iodide metabolism in iodide deficient suckling rats was explored by Zeghal *et al.* in 1992. Metabolism was expected to differ in a 10-day-old rat as the skin represents approximately 25% of the total body weight and can store twice as much iodide as the thyroid. Suckling Wistar rats were made iodine deficient by giving the dams 1.23 g sodium perchlorate/L drinking water from postnatal day 0 (day of birth) through day 10. Perchlorate prevents lactational transfer of iodide; perchlorate itself does not appear to be transferred through the milk. Sucklings were administered labeled sodium iodide ($^{131}I^-$) and [$^{125}I^-$]T_4 on day 10. Pups were sacrificed at 0.25, 1, 2, 4, 8, 16, 24, 36 and 48 hours. The kinetics of iodide and T_4 in the plasma, thyroid and skin were measured and pharmacokinetically modeled. Iodine deficiency through perchlorate administration resulted in a significantly increased body weight. Plasma iodide concentrations were significantly decreased in perchlorate treated rats as compared to controls; plasma T_4 levels were not affected. Simultaneously, thyroidal uptake of iodide and iodide derived from T_4 was significantly increased in both rate and amount. Conversely, skin uptake of both iodide forms was decreased on perchlorate treated rats. Within 15 minutes after the tracers were injected, the control rats had taken up 45% of the injected iodide into their skin; perchlorate treated rats took up just 27% into the skin.

Perchlorate affects the uptake of iodide in hormone responsive breast tumors. Hormone responsive breast tumors were induced in inbred GR/AFib mice by treating ovarectomized females with progesterone and estrogen. Uptake was determined by intraperitoneally injecting half the hormone responsive tumor group with 0.23 μCi $^{125}I^-$ and the others with 0.23 μCi $^{125}I^-$ plus 10 mg sodium perchlorate. In 3 hours, perchlorate decreased iodide uptake in the thyroid by approximately 1/80 but did not affect skeletal muscle and normal mammary tissue uptake of iodide. However, perchlorate decreased the hormone responsive mammary tumor:blood iodide ratio from 5.1 to 0.7. Hormone responsive tumors take up iodide at 20 times greater rates than hormone independent tumors. Over time, hormone responsive tumors generally become hormone independent (Thorpe, 1976).

Rochman *et al.* (1977) explored *in vitro* the effects of perchlorate on dog thyroid iodide transport. A 1 mM solution of sodium perchlorate inhibited the uptake of iodide in the thyroid

slices. This concentration was also found to cause the discharge of trapped radioiodide from within the follicles (as cited in Schilt, 1979).

Perchlorate Metabolism in Humans

As early as 1868, investigators found that perchlorate is not metabolized but can be recovered intact in human urine (Rabuteau, 1868 as cited by Schumacher, 1960). Eichler (1929) successfully dosed humans with 1 to 2 grams perchlorate orally without adverse side-effects. For comparison with animal studies, the calculated dose using the default weight parameter 70 kg would be 14 to 29 mg/kg. In 12 hours, 70% of the perchlorate had been recovered in the urine; 85 to 90% had been eliminated within 24 hours (as cited by Stanbury and Wyngaarden, 1952). Schumacher (1960) cited Eichler's data differently; 75% was reported recovered in 24 hours, up to 95% was found at 72 hours and the total recovery ranged from 85 to 95%.

To demonstrate a microscopic analytical method for detection of perchlorate in urine, Kamm and Drescher (1973) orally administered 1080 mg sodium perchlorate (i.e., 15.4 mg/kg) to a 25 year old man. Total urine samples were collected every 4 hours for a duration of 40 hours. These time course data were depicted in both graphical and table formats. Within 24 hours, 87.9% of the administered perchlorate dose was detected in the urine and by 40 hours, 94.0% of the dose had been recovered. These time point data compare favorably with the results from the 1929 Eichler study.

Durand (1938) monitored the excretion of ingested sodium perchlorate in humans (784 mg or approximately 11 mg/kg using default weight of 70 kg). Perchlorate diffusion was rapid; ClO_4^- appeared in the urine within 10 minutes. Peak urine perchlorate concentrations occurred at approximately three hours. At 3, 5, 24 and 48 hours, 30, 50, 85 and 100% of the original dose had been eliminated, respectively. No evidence of reduction of perchlorate to chlorate or of methemoglobin formation was found in blood samples.

Anbar *et al.* (1959) confirmed that perchlorate is not metabolized in humans. Four patients were administered 200 mg (approximately 2.9 mg/kg using 70 kg) double labeled $K^{36}Cl^{18}O_4$ during a thyroid function exam. Urine was collected three hours after dosing. Perchlorate was found to be excreted at approximately 200 µg/min in the urine. Total urine radioactivity was divided out into $^{36}Cl^-$, $^{36}Cl^{18}O_4^-$ and $^{36}Cl^{18}O_3^- + {}^{36}Cl^-$. The results for $^{36}Cl^-$ and $^{36}Cl^{18}O_3^- + {}^{36}Cl^-$ were negligible and within the limits of experimental error. The author was able to reasonably confirm that perchlorate is not metabolized in man.

Stanbury and Wyngaarden (1952) studied perchlorate effects in Graves' Disease patients who had been discontinued from all treatment for at least a month. In the first experiment, patients orally received 30 mg 1-methyl-2-mercaptoimidazole (MMI), to block iodine organification, 1 hour prior to 10 µCi ^{131}I. Accumulation of iodine in the thyroid was monitored; 3 to 500 mg potassium perchlorate (approximately 0.04 to 7.1 mg/kg using the default weight of 70 kg) was orally administered when iodide uptake leveled off. Perchlorate caused rapid decrease of thyroid iodide; a dose of 100 mg (1.4 mg/kg) resulted in complete discharge to extra-thyroid levels. Smaller doses such as 3 or 10 mg caused significant but incomplete discharge; 10 mg (0.14 mg/kg) resulted in a thyroid iodide level 4 times the extra-thyroid level. A patient receiving PTU (200 mg) instead of MMI did not discharge iodide when $KClO_4$ was administered, although no further increase in thyroid iodide occurred. Because thyroid iodide is in an exchangeable

equilibrium favored by a high concentration gradient with blood iodide, labeled iodide is normally diluted out when large doses of stable iodide are administered. The PTU treated patient did not discharge labeled iodide even with an additional challenge of 1 g potassium iodide.

In the second experiment, patients received MMI, followed an hour later by 100 mg potassium perchlorate (1.4 mg/kg using 70 kg bodyweight). The ^{131}I tracer dose was administered at the two hour mark. For comparison, the experiment was run two days later without the administration of perchlorate. Perchlorate inhibited the uptake of iodide by the thyroid for five to six hours. The thyroid iodide level in one patient with perchlorate was only 13% of the level without perchlorate; another subject had no thyroidal uptake when compared to extra-thyroid levels. For the third experiment, patients received 100 mg perchlorate and then ^{131}I an hour later, without MMI. The same patients were given only tracer iodide in a control experiment several days later. Perchlorate continued to suppress iodide accumulation at 24 and 48 hours. One patient had accumulated only 12.9% and 11.2% of the administered dose at 24 and 48 hours, respectively; the other accumulated 21.3% and 21.0% of the given dose. Patients in these experiments were dosed up to 3 times with a maximum total dose of 600 mg potassium perchlorate without evidence of toxicity. The authors found that perchlorate efficiently displaces iodide from the thyroid and prevents iodide uptake for up to six hours. Iodide accumulation was affected for at least 48 hours. Individual thyroid iodide time course data were presented graphically in this article (Stanbury and Wyngaarden, 1952).

Using a double isotope tracer method, Burgi *et al.* (1974) examined iodine secretion from perchlorate administration in humans. Five healthy volunteers were administered 80 μCi sodium ^{125}iodide orally on day 0. This was followed by an intravenous dose of 30 μCi thyroxine labeled with ^{131}I on day 11. Blood and urine samples were collected on days 13 through 17 to serve as a control period. Perchlorate was administered at 200 mg 3 times/day (600 mg/day or 86 mg/kg/day using default weight) on days 18 through 25. Carbimazole (15 mg, 3 times/day) was also given on days 22 through 25. Perchlorate administration resulted in increased serum and urine levels of all iodine isotopes; thyroidal iodine uptake was assumed to be "completely" blocked based on these results and literature values. Non-thyroxine iodine secretion was found to be 40 μg/day during the control period and 66 μg/day under perchlorate administration alone. Non-thyroxine iodine consists of secreted triiodothyronine and secreted "endogenous" iodine, i.e., iodothyrosines hydrolyzed from thyroglobulin within the thyroid. The data indicate that perchlorate discharges a portion of, but not all, endogenous iodide as well as "transported" iodide (i.e., iodide actively transported into follicular cells from the blood and interstitial fluid). Urinary iodide time course data were presented graphically in this study.

Conclusions

Many aspects of the perchlorate ADME process were identified through this literature search. In turtles, perchlorate inhibited active iodide uptake and also affected thyroidal chloride concentration. Some passive iodide transport was indicated (Chow *et al.*, 1982 and 1983). In laying hens, the perchlorate dose was 99% excreted within 24 hours. The remaining perchlorate was primarily deposited in the ten largest developing ova; active transport of iodine or perchlorate may occur in the shell membrane (Pena *et al.*, 1976). A study in rabbits determined urine to be the primary route of elimination, regardless of the route of

administration. Aside from the thyroid, the highest concentrations of perchlorate in rabbits were found in the adrenals, ovaries (Durand, 1938) and testes; the salivary and adrenal glands in rats also had high concentrations (Anbar *et al.*, 1959). In the rat thyroid, passive perchlorate transport through the follicle was confirmed when active uptake was blocked (Chow and Woodbury, 1970). Active transport of perchlorate was possible at lower dose levels; however, high doses of perchlorate precluded the active concentration of the perchlorate ion in the rat thyroid follicle. Chronic pretreatment of rats with PTU resulted in increased amount of perchlorate taken up by the thyroid and hypophysectomy resulted in lower levels of perchlorate concentrated. Perchlorate uptake patterns were thus found to be similar to the uptake of excess iodide. Rats were found to have significantly smaller thyroid follicle lumen volumes as compared to guinea pigs (Chow and Woodbury, 1970). Goldman and Stanbury (1973) confirmed in rats that perchlorate was not metabolized, bound or retained in specific organs and is excreted in urine. They determined the half-life of perchlorate to be approximately 20 hours in rats fed a low iodine diet. Decay curves in rats and calves were found to be bi-phasic. The half life of the first phase was about 2 hours while the half life of the second phase was 72 to 80 hours and 23 to 27 hours for rats and calves, respectively (Selivanova and Arefaeva, 1986 as cited by Von Burg, 1995). Eichler and Hackenthal (1962) found the first stage of elimination in rats to last about six hours and the rate of elimination to change with dose. Nearly all of the administered dose was recovered in 60 hours. Rats and guinea pigs both were found to actively concentrate perchlorate in the thyroid at a rate inversely proportional to dose level. TSH pretreatment resulted in increased thyroidal perchlorate concentration. Guinea pigs were found capable of concentrating more perchlorate than rats (Chow *et al.*, 1969).

Perchlorate studies have also provided information on the kinetics of iodide competition. Halmi *et al.* (1956) found that 100 mg sodium perchlorate was as effective as 400 mg in reducing the concentration of iodide (i.e., thyroid:blood ratio) from over 22 to less than 0.5 in rats. Perchlorate also reduced the stomach wall:serum and gastric juice:serum iodide ratios from 1.45 and 15.8 to 0.36 and 0.75, respectively, indicating the presence of a gastric iodide pump. Perchlorate accelerated the clearance of iodide, causing over 60% to be excreted within 4 hours of administration. Wyngaarden *et al.* (1952) used 80 to 90 mg/kg potassium perchlorate to discharge "100%" of thyroidal iodide within 15 minutes in organification blocked rats. Further, only 0.08 to 0.09 mg/kg was sufficient to result in nearly "50%" discharge of iodide; at this dose, perchlorate ions exceeded iodide ions in number by three-fold. Large doses of iodide were found to negate perchlorate effects. Like perchlorate, iodide elimination curves due to perchlorate administration were also found to be bi-phasic, with the initial phase being much more rapid than the second. Perchlorate was effective in decreasing the half life of iodide; nearly 90% of the administered radioiodide dose was excreted in 24 hours (Sinadinovic and Jovanovic, 1971). Similarly, Schonbaum *et al.* (1965) showed that 62 to 72% of the iodide dose could be excreted within 24 hours. Perchlorate was found to significantly decrease the amount of iodide taken up in the skin of suckling rats; perchlorate administration in the mother prevented lactational transfer of the iodide (Zeghal *et al.*, 1992). Likewise, perchlorate decreased iodide uptake of hormone-responsive mammary tumors without affecting normal mammary tissue (Thorpe, 1976). Finally, perchlorate inhibited iodide uptake and caused discharge of accumulated iodide from *in vitro* dog thyroid slices (Rochman *et al.*, 1977 as cited by Schilt, 1979).

Available perchlorate kinetic studies in humans augment the animal data. In 1868, perchlorate was isolated from urine and presumed not to be metabolized (Rabuteau, 1868 as cited by Schumacher, 1960). Perchlorate is excreted fairly rapidly and 75 to 90% may be eliminated

within 24 hours (Eichler, 1929 as cited by Stanbury and Wyngaarden, 1952 or Schumacher, 1960). Kamm and Drescher (1973) found almost 88% to be eliminated in 24 hours and Durand (1938) reported 85% in the same time period. Traces can be found in the urine within 10 minutes of sodium perchlorate ingestion. In a double labeled isotope study, Anbar *et al.* (1959) confirmed that perchlorate was not metabolized. A dose of only 100 mg or approximately 1.4 mg potassium perchlorate/kg bodyweight was sufficient to completely discharge accumulated iodide from the thyroids of organification blocked Graves' disease patients. This dose was found to block iodide uptake for 6 hours and significantly decrease accumulation for at least 48 hours (Stanbury and Wyngaarden, 1952). Burgi *et al.* (1974) found some evidence that perchlorate discharges a portion of the organified iodine, as well as the free iodide from the thyroid follicular cells.

Much of the information needed to understand perchlorate ADME was available in the literature. However, quantitative tissue dosimetry of both iodide and perchlorate in the thyroid, serum and urine are not available. Dosimetry would be necessary for building physiologically based pharmacokinetic (PBPK) models of perchlorate kinetics and iodide inhibition. Ultimately, such models would enable prediction of perchlorate effects in humans. Numerical data reviewed here are insufficient to construct complete PBPK models but could be utilized in their validation.

PHARMACOLOGICAL USES OF PERCHLORATE

Pharmacological uses of perchlorate, other than the treatment of Graves' disease, were sought to expand the knowledge of human response to the ion. The ITER review panel suggested assembling such human data to identify cases where lower doses of perchlorate were administered as compared to doses used to treat Graves' disease and to investigate the occurrence of aplastic anemia among perchlorate treated individuals (TERA, 1997a).

Treatment of Amiodarone Iodine Induced Thyrotoxicosis

Amiodarone, used to treat ischemic heart disease and tachyarrythmias, is an iodine rich pharmaceutical. Patients may develop amiodarone iodine induced thyrotoxicosis (AIIT) (Martino *et al.*, 1987) or hypothyroidism (Martino *et al.*, 1986b) either during or after cessation of treatment. Thyroid disturbances occur not only in persons with pre-existing thyroid conditions but also in persons previously euthyroid. Thyroid disorders can cause cardiac conditions to worsen. AIIT may be diagnosed through elevated total and free serum T_3 levels (Martino *et al.*, 1987). Hypothyroidism is confirmed by low free serum T_3 and T_4 levels, extremely high TSH levels and low radioactive iodide uptake (Martino *et al.*, 1986b).

Two types of AIIT have been recently identified based on the status of the thyroid prior to amiodarone administration. Type I thyroids were abnormal prior to amiodarone administration (e.g., nodular goiter, latent Graves' disease); type II thyroids were normal. As type I AIIT is due to increased hormone synthesis, diagnosis is characterized by slightly elevated interleukin-6 (IL-6) levels, increased serum thyroglobulin levels, enlarged thyroid size and normal to increased radioiodide uptake. Type II AIIT appears to result from iodide or amiodarone damage to the thyroid and displays greatly elevated IL-6 levels with normal thyroid size and low to normal radioiodide uptake. Some patients also seem to display mixed forms of AIIT (Bartalena *et al.*, 1996).

Type I AIIT is most appropriately treated with thionamides to block thyroid hormone synthesis and potassium perchlorate to deplete iodide stores (Bartalena *et al.*, 1996). Although some seemingly Type II patients respond well to this treatment (Martino *et al.*, 1987), Type II patients respond better to glucocorticoids which help to stabilize membranes and reduce inflammation (Bartalena *et al.*, 1996). Some cases of amiodarone associated hypothyroidism may respond to perchlorate administration, which lowers the thyroidal iodide content; excess iodide can inhibit thyroid hormone synthesis (Martino *et al.*, 1986b). AIIT and hypothyroidism treatments using perchlorate are listed in Table 1.

In 1969, Weber and Wolf reported a case study in which a cardiac patient developed severe thyrotoxicosis. Treatments for the heart condition were not mentioned, but her cardiac situation prevented operative measures. Her thyrotoxicosis subsided with perchlorate dosing at 300 mg/day (4.29 mg/kg daily using default weight of 70 kg) for the first 8 weeks and, after insufficient progress, 1200 mg/day (17.14 mg/kg/day) thereafter, culminating in a total of 118 g over 5 months. Because of the dangers of long-term perchlorate administration, the patient was then given 50 mCi $^{131}I^-$, but still took perchlorate to prevent relapse prior to the iodide taking full effect. At this time, the patient developed a nephrotic syndrome with proteinuria and elevated serum albumin levels. Perchlorate administration was suspended and the nephrotic syndrome ceased after six weeks treatment with steroids, protein supplementation and diuretics. The patient was observed for ten months, during which she was euthyroid and had normal kidney function.

TABLE 1: PERCHLORATE DOSING IN AMIODARONE IODINE INDUCED THYROTOXICOSIS STUDIES

Dose	Duration	Combination	Efficacy	Side Effects	Reference
800 mg/dy (11.4 mg/kg/dy)*	2 wk + 10 dy	30 mg/dy methimazole	1/1 patient's T_3 and T_4 levels were normal in 2 wk but elevations recurred 1 wk after withdrawal; patient became euthyroid after 10 additional dy of treatment	None observed	Dal Fabbro *et al.*, 1988
800 mg/dy (11.4 mg/kg/dy)*	9-20 wk	800 mg/dy propylthiouracil	4/4 euthyroid within 20 wk	Not noted	Newnham *et al.*, 1988
900 mg/dy (12.9 mg/kg/dy)*	40 dy	400 mg/dy propylthiouracil	1/1 patient had decreased T_3 and T_4 levels at 40 dy and was euthyroid in 3 mo	Not noted	Bonnyns and Bourdoux, 1988
1000 mg/dy (14.29 mg/kg/dy)*	9-34 dy	No	5/6 patients had normal T_4 in 2 wk; TSH was normal in 3/6 patients in 2 wk; hypothyroidism recurred in 3/6 after perchlorate withdrawal [1]	None observed	Martino *et al.*, 1986b
1000 mg/dy (14.29 mg/kg/dy)*	10 dy	No	1/1 patient euthyroid in 10 dy; hyperthyroidism recurred with reduced dose (400 mg/dy) or withdrawal	None observed	Foresti *et al.*, 1989
1000 + 500 mg/dy (14.29 + 7.14 mg/kg/dy)*	3 wk + 3 wk	No	1/1 patient euthyroid in 3 wk; 4 wk later symptoms re-occurred; patient euthyroid for at least 1 yr following second 3 wk period of dosing	Not noted	van Dam *et al.*, 1993
1000 mg/dy (14.29 mg/kg/dy)*	18-40 dy	30 mg/dy methimazole	8/12 Type I patients euthyroid in 4 wk; 3/12 euthyroid with glucocorticoid augmentation	None observed	Bartalena *et al.*, 1996

Dose	Duration	Combination	Efficacy	Side Effects	Reference
1000 mg/dy (14.29 mg/kg/dy)*	16-40 dy	40 mg/dy methimazole	7/8 patients clinically euthyroid in 16-36 dy [2]	1/8 patients had mild transient neutropenia; 3/8 had mild transient epigastric distress	Martino *et al.*, 1986a
1000 mg/dy (14.29 mg/kg/dy)*	15-45 dy	40 mg/dy methimazole	17/18 patients with underlying thyroid abnormalities euthyroid in 15-90 dy 9/9 patients restored to euthyroidism in 6-55 dy	1/27 patients had transient neutropenia	Martino *et al.*, 1987
1000 mg/dy (14.29 mg/kg/dy)*	40 dy	(40 mg/dy methimazole or 400 mg/dy propylthiouracil) + amiodarone	3/3 patients euthyroid in 2-5 wk; serious heart conditions required constant amiodarone regulation	None observed	Reichert and de Rooy, 1989
1000 mg/dy (14.29 mg/kg/dy)*	4-6 mo	40 mg/dy carbimazole + amiodarone	2/2 patients euthyroid in 2 mo; TSH normal in 4 mo; serious heart conditions required constant amiodarone regulation	Not noted	Trip *et al.*, 1994

* Dose calculated using default weight assumption of 70 kg.
[1] Individual TSH and free T_4 levels at start and two months depicted in graphical form.
[2] Individual urinary iodine excretion from start to six months depicted in graphical form.

Additional Pharmacological Uses

Perchlorate facilitates the excretion of monovalent anions, including bromide. Five patients admitted for bromoureide or carbromal intoxication were administered 1200 mg sodium perchlorate. This dose equates to 17 mg/kg, using a default weight of 70 kg. Elimination of bromide before and after perchlorate administration was monitored closely. Perchlorate briefly accelerated the elimination of the bromide, although the rates of elimination before and after perchlorate's short period of effectiveness were the same. The author believes perchlorate competes with bromide for renal tubular absorption. Perchlorate was used in this case experimentally and does not replace the standard treatment for bromide intoxication, the administration of chloride, due to the potential need for repeated high dosages (Seyfert, 1979).

Recently, perchlorate was tested as a prophylactic for iodine-rich coronary angiography contrast dyes. In susceptible patients, these dyes may cause hyperthyroidism or aggravate an existing thyroid condition. Patients undergoing elective coronary angiography in an area of moderate iodine deficiency (Lower Saxonia in northern Germany) were screened for inclusion in this study. Clinical euthyroidism with thyroid autonomy (i.e., normal free T_3 and T_4 levels with low TSH levels but without goiter), a condition which may indicate increased risk of iodine induced hyperthyroidism, was necessary for inclusion in the study; only 51 of 1126 patients over a 2.5 year period qualified. Patients (17 per group) received 900 mg sodium perchlorate/day (approximately 13 mg/kg/day using default weight) orally, starting 1 day prior to angiography and lasting for 14 days. Other groups received either no prophylactic or 20 mg thiamazole/day. No side effects were noted. All groups had increased average thyroid volumes; mild nodular and diffuse goiters were prevalent in each group with no statistical differences between groups. T_3 and T_4 levels were not changed in the perchlorate and thiamazole groups but were significantly elevated in the controls. Conversely, TSH levels decreased significantly among controls while they remained at initial levels in the treated groups. Clinical hyperthyroidism was diagnosed in one perchlorate, one thiamazole and two control patients; treatment for hyperthyroidism was not necessary for any of these cases. At 30 days after angiography, iodine excretion had returned to normal in the treatment groups but was elevated nearly two-fold in the controls. Although perchlorate was not capable of preventing thyrotoxicosis completely in these patients, some protective effects were noted without adverse side effects (Nolte *et al.*, 1996).

Conclusions

In a summary of pharmacological studies using perchlorate, the doses of perchlorate were similar to the high doses used to treat Graves' disease (Stanbury and Wyngaarden, 1952), but were generally administered over shorter periods of time. Even though some amiodarone iodine induced thyrotoxicosis (AIIT) patients were treated over a relatively long duration with perchlorate (Trip *et al.*, 1994; Newnham *et al.*, 1988), no incidence of aplastic anemia was reported. One AIIT patient, however, developed transient neutropenia (Martino *et al.*, 1987). Perchlorate was also used experimentally in the treatment of bromide intoxication (Seyfert, 1979) and was tested as a prophylactic for iodine-rich coronary angiography contrast dyes without adverse side effects (Nolte *et al.*, 1996). With proper precautions, including low doses and short-term administration, it appears that perchlorate can be used safely as a pharmacological agent in humans.

RECOMMENDATIONS

This report has served to strengthen the USAF and PSG knowledge about perchlorate in the areas of reproductive and developmental toxicity, kinetics, metabolism and pharmacological use. This report has also clarified that the knowledge in each of this areas is insufficient to greatly influence the development of a high confidence, health-based RfD for perchlorate. A comprehensive examination of the potential for perchlorate to cause reproductive and developmental effects would greatly reduce data gaps. The developmental neurobehavioral study protocol reviewed in May (TERA, 1997b) was subsequently conducted to quantify these developmental effects and reduce uncertainty. In addition, a two-generation reproductive study and a rabbit developmental study were initiated to fill data gaps. A literature investigation into developmental effects of other goitrogens and into the quantification of iodine deficiency leading to adverse effects could also help strengthen the database.

Although there is considerable literature on the ADME of perchlorate, perchlorate receptor kinetic and metabolism data are currently insufficient to determine the perchlorate ion relationship with the iodide receptor in humans and test species. A series of studies to determine perchlorate and iodine kinetics and perchlorate inhibition of iodine uptake into the thyroid is needed to develop a physiologically based kinetic model for perchlorate and iodine inhibition. Such a model could be used to extrapolate perchlorate effects to the human iodide and would greatly reduce uncertainty in this area. A good understanding of perchlorate effects in the human is necessary for the development of a human health-based RfD for perchlorate. Literature searches on the iodide receptor, its capacity and receptor mediated effects (i.e., iodide uptake) in general would lend strength to the understanding of perchlorate's effect on the thyroid and contribute to model development.

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APPENDIX A: HUMAN PERCHLORATE DISCHARGE DATA

TABLE A-1: PERCHLORATE DISCHARGE TEST ADMINISTRATION AND RESULTS DATA FOR HUMANS

Row #	Subjects	n	Route	Dose $^{123}I^-$ (μCi)	Dose $^{131}I^-$ (μCi)	Time from I^- to ClO_4^- (hr)	Time from I^- to ClO_4^- (min)	Dose $KClO_4$ (mg)	Dose $KClO_4$ (mg/kg)*	Dose $NaClO_4$ (mg)	Dose $NaClO_4$ (mg/kg)*
	* Dose in adults estimated by use of 70 kg bodyweight										
1	infant	13	po	50		2	120	400			
2	human	32	po		20	2	120	1000 adult; 600 child	14.3 adult		
3	human	7	po		20	2	120	1000 adult; 600 child	14.3 adult		
4	adult	17	po	10 MBq + 500 μg KI			60	400	5.71		
5	adult	12	po	10 MBq + 500 μg KI			60	400	5.71		
6	infant		po	50		2	120	400			
7	human	18	po		(30 μCi $^{132}I^-$)		60	400			
8	human	20	po		(30 μCi $^{132}I^-$)		60	400			
9	adult	20	po		20		60	400	5.7		
10	adult	22	po		20 + 2 mg KI		60	400	5.7		
11	adult		iv or po		20-40 MBq; isotope not specified, iv		30 - 60			?	?
12	adult		iv		25		10			200	2.9
13	adult	11	iv	150			(10 - 60)			300 - 600	4.3 - 8.6
14	adult	8	iv	150			60			300 - 600	4.3 - 8.6

Row #	Time from ClO_4^- to termination (hr)	Time from ClO_4^- to termination (min)	Range $^{131}I^-$ uptake (%)	Median $^{131}I^-$ uptake (%)	Mean $^{131}I^-$ uptake (%)	SD $^{131}I^-$ uptake (%)	Range Discharge (%)	Median Discharge (%)	Mean Discharge (%)	SD Discharge (%)
1	2	120					8.0 - 74.0	34	37.54	
2	1	60							None	Not Reported
3	1	60							24.6	Confidence Limits: + 3.0
4		30					(-20) < discharge < 40			
5		30					(-15) < discharge < 30			
6	2	120								
7		50					(-60) - 13	(-2) - (-3)	(-7.77)	
8		50					14 - 79	43-52	48.85	
9		60	4.0 - 17.2	9.6			(-80.0) - 20.8	(-1.2)		
10		60	3.5 - 12.6	7.5			(-62.3) - 9.0	(-10.4)		
11		30 - 60					20 - 30			
12		10								
13		30 - 40								
14		30 - 40					5.5 - 64.8	25.2 - 29.5	31.8	?

Row #	Comments	Reference
1	Infants with enlarged ectopic thyroids & congenital hypothyroidism; 1 & 2 hr thyroid uptake and 15, 30, 45, 60, 90 & 120 min discharge measured; Discharge > 50% = virtually complete organification defect; 20 - 50% = partial organification defect	al-Jurayyan and el-Desouki, 1997
2	Normal Subjects; Thyroid binding defects present if thyroidal $^{131}I^-$ discharge is > 5% (Based on statistical analysis of 281 subjects with varied thyroid conditions)	Baschieri *et al.*, 1963
3	Pendred's Syndrome Patients; Thyroid binding defects present if thyroidal $^{131}I^-$ discharge is > 5% (Based on statistical analysis of 281 subjects with varied thyroid conditions)	Baschieri *et al.*, 1963
4	Women who had tested positive for anti-thyroid peroxidase antibodies AND had postpartum thyroiditis (PPT) 15 to 47 mo prior; Positive I^--$ClO4^-$ test > 10% discharge; 7 of 17 subjects tested positive; Confirms PPT includes I^- organification defect	Creagh *et al.*, 1994
5	Women who had tested positive for anti-thyroid peroxidase antibodies BUT had NOT had postpartum thyroiditis 15 to 47 mo prior; Positive I^--$ClO4^-$ test >10% discharge; 5 of 12 subjects tested positive; PPT I^- organification defect may occur in subclinicals	Creagh *et al.*, 1994
6	1 & 2 hr thyroid uptake and 15, 30, 45, 60, 90 & 120 min discharge measured; Discharge > 50% = virtually complete organification defect; 20 - 50% = partial organification defect	el-Desouki *et al.*, 1995
7	Normal family members of patients with unconfirmed Pendred's Syndrome	Fraser *et al.*, 1960
8	Unconfirmed Pendred's Syndrome patients	Fraser *et al.*, 1960
9	7/20 controls had discharge > 10%	Friis, 1987
10	0/20 controls had discharge > 20%; Discharge test found more sensitive with addition of KI; I^--ClO_4^- test discharge significantly ($p<0.05$) different from PDT discharge	Friis, 1987
11	At least 1 member of 7 kindreds with Pendred's Syndrome tested; At 25 min post-I^-, thyroids were gamma-camera scanned: uniform distribution of I^- not expected if patient has Hashimoto's disease or congenital hypothyroidism; Abnormal discharge = >10%	Gausden *et al.*, 1996 (PDTs done by Morgans ME, Trotter WR. 1958. Lancet 1:607-9.)
12	Neck radioactivity measured with closely collimated directional counter; Minor thyroid dysfunction considered present if difference between 10 & 20 min neck uptake values is > 0.5% of administered $^{131}I^-$ dose	Gray *et al.*, 1972, 1973 & 1974
13	Normal & untreated thyrotoxic subjects; 1/11 had positive discharge of 7.5% at 30 post-I^- administration; Binding rate calculated from this patient gives 1/0.15 min as a lower limit for an inhibited gland	Hilditch et al., 1980
14	Patients with intrinsic binding defects (familial binding defect, hypothyroidism & pituitary gland failure); Binding rates range: 1/0.006 min to 1/0.091 min; Mean binding rate: 1/0.06 min	Hilditch et al., 1980

Row #	Subjects	n	Route	Dose $^{123}I^-$ (μCi)	Dose $^{131}I^-$ (μCi)	Time from I^- to ClO_4^- (hr)	Time from I^- to ClO_4^- (min)	Dose $KClO_4$ (mg)	Dose $KClO_4$ (mg/kg)*	Dose $NaClO_4$ (mg)	Dose $NaClO_4$ (mg/kg)*
15	adult	8	iv	?			20 - 60			300 - 600	4.3 - 8.6
16	adult	11	iv	?			(10 - 60)			300 - 600	4.3 - 8.6
17	adult	12	iv	?			60			300 - 600	4.3 - 8.6
18	adult	2	iv		25		50			200	2.86
19	human	9	?					?			
20	human	12	?					?			
21	human	5	?					?			
22	adult	5	po		10	1	60	500	7.14		
23	adult	6	po		10	1	60	500	7.14		
24	adult	12	po		10 (2.5 mg carbimazole 1 hr prior)	1	60	500	7.14		
25	adult	3	po		10 (2.5 mg carbimazole 1 hr prior)	1	60	500	7.14		
26	adult	6	po		10 + 2 mg KI	1	60	500	7.14		
27	adult	8	po		10 + 2 mg KI	1	60	500	7.14		
28	adult	6	po		10 + 2 mg KI	1	60	500	7.14		
29	adult	6	po		10 + 2 mg KI	1	60	500	7.14		
30	adult	2	po		10 + 500 μg KI	3	180	500	7.14		
31	adult	4	po		10 + 500 μg KI	3	180	500	7.14		
32	adult	7	po		20 - 40		60	200	2.86		
33	adult	19	po		20 - 40		60	200	2.86		
34	adult	5	po		20 - 40		60	200	2.86		

Row #	Time from ClO_4^- to termination (hr)	Time from ClO_4^- to termination (min)	Range $^{131}I^-$ uptake (%)	Median $^{131}I^-$ uptake (%)	Mean $^{131}I^-$ uptake (%)	SD $^{131}I^-$ uptake (%)	Range Discharge (%)	Median Discharge (%)	Mean Discharge (%)	SD Discharge (%)
15		30 - 40					0 - 3.5	0	0.93	?
16		30 - 40					0 - 7.5	0	0.93	?
17		30 - 40					0 - 85.4	29.5 - 35.8	35.88	?
18		30					approximately 15			
19							1.1 - 63.5	41.2	39.39	
20							0.1 - 8	2 - 5.3	3.75	
21							0.1 - 2	0.4	0.64	
22		40							9.3	1.5
23		40							11.8	2.04
24		40							6.5	0.49
25		40							10	0.49
26		40							5.5	0.53
27		40							9.4	1.4
28		60							8.3	1.29
29		60							11.2	1.07
30		60							19.6	
31		60							22.3	3.59
32		40							(-13)	2 (SE)
33		40							(-28)	5 (SE)
34		40							26	13 (SE)

Row #	Comments	Reference
15	Euthyroid subjects; Normal discharge < 3.5% of gland uptake; Lowest estimated binding rate constant in uninhibited gland: 1/0.150 min	Hilditch *et al.*, 1982
16	Untreated thyrotoxic subjects; Discharge 7.5% or less; Lowest estimated binding rate constant in uninhibited gland: 1/0.150 min	Hilditch *et al.*, 1982
17	Patients suspected of binding defect; 1/0.003 min to 1/0.057 min binding rate range	Hilditch *et al.*, 1982
18	Previously treated hyperthyroid patients with high I^- uptake but normal serum thyroxine levels; Extrathyroidal activity counted on area below the gland	Horton *et al.*, 1975
19	Patients with Pendred's Syndrome including profound hearing loss	Jamal *et al.*, 1995
20	Patients with partial Pendred's Syndrome including mild hearing loss or abnormal PDT	Jamal *et al.*, 1995
21	Normal family members of patients with Pendred's or partial Pendred's Syndrome	Jamal *et al.*, 1995
22	Nongoitrous persons from endemic goiter area; 1 hr uptake and 10, 20, 30 & 40 min discharge monitored; PDT showed no significant difference between goitrous & nongoitrous persons	Koutras *et al.*, 1978
23	Goitrous persons from endemic goiter area; 1 hr uptake and 10, 20, 30 & 40 min discharge monitored; PDT does not indicate an I^- uptake defect	Koutras *et al.*, 1978
24	Nongoitrous persons from endemic goiter area; 1 hr uptake and 10, 20, 30 & 40 min discharge monitored; PDT + carbimazole showed a significant difference (P=0.025) between goitrous & nongoitrous peoples	Koutras *et al.*, 1978
25	Goitrous persons from endemic goiter area; 1 hr uptake and 10, 20, 30 & 40 min discharge monitored	Koutras *et al.*, 1978
26	Nongoitrous persons from endemic goiter area; 1 hr uptake and 10, 20, 30 & 40 min discharge monitored; I^--$KClO_4^-$ test showed a significant difference (P<0.025) between goitrous & nongoitrous peoples	Koutras *et al.*, 1978
27	Goitrous persons from endemic goiter area; 1 hr uptake and 10, 20, 30 & 40 min discharge monitored; a positive I^--$KClO_4^-$ test & negative PDT reflect organic binding defect	Koutras *et al.*, 1978
28	Nongoitrous persons from an area without endemic goiter; 1 hr uptake and 10, 20, 30, 40, 50 & 60 min discharge monitored	Koutras *et al.*, 1978
29	Goitrous persons from an area without endemic goiter; 1 hr uptake and 10, 20, 30, 40, 50 & 60 min discharge monitored	Koutras *et al.*, 1978
30	Nongoitrous persons from an area without endemic goiter;1 hr uptake and 10, 20, 30, 40, 50 & 60 min discharge monitored	Koutras *et al.*, 1978
31	Goitrous persons from an area without endemic goiter; 1 hr uptake and 10, 20, 30, 40, 50 & 60 min discharge monitored	Koutras *et al.*, 1978
32	Normal subjects; Uptake measured at 50 & 60 min and discharge measured at 10, 20, 30 and 40 min	Morgans & Trotter, 1957
33	Simple goiter patients; Uptake measured at 50 & 60 min and discharge measured at 10, 20, 30 and 40 min; Results not significantly different from normal patients; One patient had a positive PDT	Morgans & Trotter, 1957
34	Hashimoto's thyroiditis patients; Uptake measured at 50 & 60 min and discharge measured at 10, 20, 30 and 40 min; Results significantly different (p<0.005) from normal and other patient groups	Morgans & Trotter, 1957

Row #	Subjects	n	Route	Dose $^{123}I^-$ (μCi)	Dose $^{131}I^-$ (μCi)	Time from I^- to ClO_4^- (hr)	Time from I^- to ClO_4^- (min)	Dose $KClO_4$ (mg)	Dose $KClO_4$ (mg/kg)*	Dose $NaClO_4$ (mg)	Dose $NaClO_4$ (mg/kg)*
35	adult	7	po		20 - 40		60	400	2.86		
36	adult	7	po		20 - 40		60	400	2.86		
37	adult		po		?		60	400	5.7		
38	juvenile	4	?	100 - 300 during 1982 - 1992	50 - 100 during 1971 - 1981	?	?				
39	adult	16	po		5 + 500 μg stable I^-	3	180	1000	14.3		
40	adult	16	po		5 + 500 μg stable I^-	3	180	1000	14.3		
41	adult	20	po		5 + 500 μg stable I^-	3	180	1000	14.3		
42	adult	5	po		5 + 500 μg stable I^-	3	180	1000	14.3		
43	adult	5	po		5 + 500 μg stable I^-	3	180	1000	14.3		
44	adult	5	po		5 + 500 μg stable I^-	3	180	1000	14.3		
45	adult		po		10 - 15 (iv)		63	400	5.7		
46	adult	16	po		? (iv)		63	400	5.71		
47	adult	3	po		? (iv) + 10 IU TSH (24 hr prior)		63	400	5.71		
48	adult	18	po		? + (750 - 1500) μg $^{127}I^-$ (iv)		63	400	5.71		
49	adult	2	po		? + 1000 mg $^{127}I^-$ (iv) + 10 IU TSH (24 hr prior)		63	400	5.71		

Row #	Time from ClO_4^- to termination (hr)	Time from ClO_4^- to termination (min)	Range $^{131}I^-$ uptake (%)	Median $^{131}I^-$ uptake (%)	Mean $^{131}I^-$ uptake (%)	SD $^{131}I^-$ uptake (%)	Range Discharge (%)	Median Discharge (%)	Mean Discharge (%)	SD Discharge (%)
35		40							(-14)	7 (SE)
36		40							57	9 (SE)
37		40 - 50								
38							Nov-58	24 - 49	35.5	
39	1	60					(-31.8) - 99.0	34.1 - 35.9	32.225	
40	1	60					(-39.1) - 47.4	7.3 - 8.3	5.675	
41	1	60					(-169.5) - 9.8	(-4.3) - (-4.2)	(-18.945)	
42	1	60					(-10) < discharge < 10			
43	1	60					17.6 - 56.9	33.9	25.08	
44	1	60					(-18.5) - 14.7	(-0.7)	(-2.3)	
45		61								
46		57					(-26) - (-1)	(-13)	(-13.25)	
47		57					(-15) - (-9)	(-11)	(-11.67)	
48		57					(-56) - 47	14 - 20	7.83	
49		57					13 - 38		25.5	

Row #	Comments	Reference
35	Simple goiter patients; Uptake measured at 50 & 60 min and discharge measured at 10, 20, 30 and 40 min; Results not significantly different from normal patients	Morgans & Trotter, 1957
36	Hashimoto's thyroiditis patients; Uptake measured at 50 & 60 min and discharge measured at 10, 20, 30 and 40 min; Results significantly different ($p<0.005$) from normal and other patient groups	Morgans & Trotter, 1957
37	Thyroid binding defects present if thyroidal $^{131}I^-$ discharge is > 15%; Determined background by monitoring radioactivity in thigh	Morgans & Trotter, 1957 as cited in Gray *et al.*, 1972; Stewart & Murray, 1966
38	Juvenile onset primary reversible hypothyroidism; Note use of different isotopes during different time periods	Okamura *et al.*, 1994
39	Patients with hyperthyroid Graves' disease prior to treatment with MMI for 1 yr; 3 hr uptake and 1 hr discharge measured; Abnormal discharge = >15%	Roti et al., 1994
40	Hyperthyroid Graves' patients 40 dy after MMI treatment ended; 3 hr uptake & 1 hr discharge measured; Abnormal discharge = >15%; PDT not related to TSH, T_3 or T_4 serum levels; Graves' patients unable to organify increased I^- concentrated by hyperthyroid	Roti et al., 1994
41	NORMAL, EUTHYROID individuals, no record of thyroid disease, 16 women, 4 men, mean age = 38.3 + 3.0 yr, age range = 21 - 63 yr; 3 hr uptake and 1 hr discharge measured; Abnormal discharge = >15%	Roti et al., 1994
42	Prior to Viral Hepatitis C treatment with recombinant human interferon-alpha (r-IFN-alpha) for approximately 6 mo; 3 hr thyroid uptake and 1 hr discharge measured; Normal values = <15% discharge	Roti *et al.*, 1996
43	At conclusion of Viral Hepatitis C treatment with r-IFN-alpha for approximately 6 mo; 3 hr thyroid uptake and 1 hr discharge measured; Normal values = <15% discharge; Developed I^- organification reduction without clinical symptoms during treatment	Roti *et al.*, 1996
44	6 months after treatment with r-IFN-alpha for approximately 6 mo; 3 hr thyroid uptake and 1 hr discharge measured; Normal values = <15% discharge; I^- organification decrease resolved over time without specific treatment	Roti *et al.*, 1996
45	Measured neck radioactivity @ 57.5, 87.5 & 117.5 min from start; Sampled urine @ 64, 94 & 124 min from start; Urine used to determine extra-thyroid activity; Test negative if thyroid $^{131}I^-$ after $KClO_4$ was = or > thyroid $^{131}I^-$ before $KClO_4$	Stewart & Murray, 1966
46	Normal subjects; Test considered positive if any discharge; I^- uptake by thyroid appears to be 1st order; Data show positive correlation between I^- load & discharge; Lower I^- amounts block organification in thyroid impaired (patient data available)	Stewart and Murray, 1967
47	Normal subjects + TSH; Test considered positive if any discharge; I^- uptake by thyroid appears to be 1st order; Data show positive correlation between I^- load & discharge; Lower I^- amounts block organification in thyroid impaired (patient data available)	Stewart and Murray, 1967
48	Normal subjects; Test considered positive if any discharge; I^- uptake by thyroid appears to be 1st order; Data show positive correlation between I^- load & discharge; Lower I^- amounts block organification in thyroid impaired (patient data available)	Stewart and Murray, 1967
49	Normal subjects + TSH; Test considered positive if any discharge; I^- uptake by thyroid appears to be 1st order; Data show positive correlation between I^- load & discharge; Lower I^- amounts block organification in thyroid impaired (patient data available)	Stewart and Murray, 1967

Row #	Subjects	n	Route	Dose $^{123}I^-$ (μCi)	Dose $^{131}I^-$ (μCi)	Time from I^- to ClO_4^- (hr)	Time from I^- to ClO_4^- (min)	Dose $KClO_4$ (mg)	Dose $KClO_4$ (mg/kg)*	Dose $NaClO_4$ (mg)	Dose $NaClO_4$ (mg/kg)*
50	adult	3	po		? + 2000 μg $^{127}I^-$ (iv)		63	400	5.71		
51	adult	3	po		? + 250 mg $^{127}I^-$ (iv) + 10 IU TSH (24 hr prior)		63	400	5.71		
52	adult	3	po		? + 350 mg $^{127}I^-$ (iv) + 10 IU TSH (24 hr prior)		63	400	5.71		
53	adult	3	po		? + 500 μg $^{127}I^-$ (iv)		63	400	5.71		
54	adult	7	po		?	3	180	1000	14.3		
55	adult	7	po		? + 250 μg $^{127}I^-$	3	180	1000	14.3		
56	adult		po		? + 500 μg $^{127}I^-$	3	180	1000	14.3		
57	adult	6	po		20 - 30	3	180	1000	14.3		
58	adult	6	po		20 - 30 (+ 2000 μg $Na^{127}I$)	3	180	1000	14.3		
59	adult	12	po		20 - 30 (+ 500 μg $Na^{127}I$)	3	180	1000	14.3		

Row #	Time from ClO_4^- to termination (hr)	Time from ClO_4^- to termination (min)	Range $^{131}I^-$ uptake (%)	Median $^{131}I^-$ uptake (%)	Mean $^{131}I^-$ uptake (%)	SD $^{131}I^-$ uptake (%)	Range Discharge (%)	Median Discharge (%)	Mean Discharge (%)	SD Discharge (%)
50		57					75 - 93	83	83.67	
51		57					(-27) - (-6)	(-16)	(-16.33)	
52		57					(-22) - 10	(-17)	(-9.67)	
53		57					(-42) - (-6)	(-22)	(-23.3)	
54	1	60					(1.4) - 17.3	6.1	7.64	
55	1	60					(-1.6) - 68.5	48.3	41.86	
56	1	60								
57	1	60			5.1	1.2			(-3.4)	8.3
58	1	60			3.9	0.4			(-7.6)	4.3
59	1	60			4.9	1.6			(-4.8)	16.5

Row #	Comments	Reference
50	Normal subjects; Test considered positive if any discharge; I^- uptake by thyroid appears to be 1st order; Data show positive correlation between I^- load & discharge; Lower I^- amounts block organification in thyroid impaired (patient data available)	Stewart and Murray, 1967
51	Normal subjects + TSH; Test considered positive if any discharge; I^- uptake by thyroid appears to be 1st order; Data show positive correlation between I^- load & discharge; Lower I^- amounts block organification in thyroid impaired (patient data available)	Stewart and Murray, 1967
52	Normal subjects + TSH; Test considered positive if any discharge; I^- uptake by thyroid appears to be 1st order; Data show positive correlation between I^- load & discharge; Lower I^- amounts block organification in thyroid impaired (patient data available)	Stewart and Murray, 1967
53	Normal subjects; Test considered positive if any discharge; I^- uptake by thyroid appears to be 1st order; Data show positive correlation between I^- load & discharge; Lower I^- amounts block organification in thyroid impaired (patient data available)	Stewart and Murray, 1967
54	Euthyroid Graves' patients previously treated with ^{131}I-T_3; PDT showed no significant discharge or difference between controls, untreated or treated Graves' patients	Suzuki and Mashimo, 1972
55	Euthyroid Graves' patients previously treated with ^{131}I-T_3; 250 µg ^{127}I-ClO_4^- tests showed significant ($p<0.01$) discharge as compared to controls and untreated Graves' patients	Suzuki and Mashimo, 1972
56	500 µg ^{127}I-ClO_4^- tests showed significant ($p<0.01$) discharge in untreated and treated Graves' patients as compared to controls	Suzuki and Mashimo, 1972
57	No significant discharge of thyroidal $^{131}I^-$; Discharge > (+)20% was considered positive; Concurrent carrier iodide ($Na^{127}I$) challenge is felt to give a higher degree of diagnostic accuracy for detection of underlying binding defects	Takeuchi *et al.*, 1970
58	No significant discharge of thyroidal $^{131}I^-$; Discharge > (+)20% was considered positive; Concurrent carrier iodide ($Na^{127}I$) challenge is felt to give a higher degree of diagnostic accuracy for detection of underlying binding defects	Takeuchi *et al.*, 1970
59	No significant discharge of thyroidal $^{131}I^-$; Discharge > (+)20% was considered positive; Concurrent carrier iodide ($Na^{127}I$) challenge is felt to give a higher degree of diagnostic accuracy for detection of underlying binding defects	Takeuchi *et al.*, 1970

APPENDIX B: RAT PERCHLORATE DISCHARGE DATA

TABLE B-1: PERCHLORATE DISCHARGE TEST ADMINISTRATION AND RESULTS DATA FOR RATS

Row #		n	Route	Dose $^{125}I^-$ (µCi)	Dose $^{125}I^-$ (equivalent µL)	Time from I^- to ClO_4^- (hr)	Time from I^- to ClO_4^- (min)	Dose $KClO_4$ (mg/kg)	Time from ClO_4^- to termination (hr)	Time from ClO_4^- to termination (min)	Mean thyroid:blood $^{125}I^-$ ratio	SEM thyroid:blood $^{125}I^-$ ratio
1	rat		ip	1	100	6	3600	10		2.5		
2	rat	6	ip	1	100	1	60				4.19	0.3
3	rat	6	ip	1	100	3	180				12.01	1
4	rat	6	ip	1	100	6	360				31.7	2
5	rat	6	ip	1	100	9	540				48.34	5.3
6	rat	5 to 6	ip	1	100	3	180	0	1	60	16.82	0.8
7	rat	5 to 6	ip	1	100	3	180	5	1	60	9.36	1.2
8	rat	5 to 6	ip	1	100	3	180	10	1	60	7.82	1
9	rat	5 to 6	ip	1	100	3	180	25	1	60	7.18	0.8
10	rat	5 to 6	ip	1	100	3	180	50	1	60	5.95	0.7
11	rat	5 to 6	ip	1	100	6	360	0	1	60	26.47	3.1
12	rat	5 to 6	ip	1	100	6	360	5	1	60	22.38	1.9
13	rat	5 to 6	ip	1	100	6	360	10	1	60	18.79	1.4
14	rat	5 to 6	ip	1	100	6	360	25	1	60	18.32	1.2
15	rat	5 to 6	ip	1	100	6	360	50	1	60	16.07	0.78

Row #	Comments	Reference
1	Optimal test parameters; No discharge of radioactivity from thyroid cells (i.e., complete organification) after 6 hrs	Atterwill *et al.*, 1987
2		Atterwill *et al.*, 1987
3		Atterwill *et al.*, 1987
4	Time chosen for future work	Atterwill *et al.*, 1987
5	Increased thyroidal radioiodide uptake with increased time; No maximal accumulation displayed over 9 hrs	Atterwill *et al.*, 1987
6		Atterwill *et al.*, 1987
7		Atterwill *et al.*, 1987
8	Appeared to be dose producing maximum effect	Atterwill *et al.*, 1987
9		Atterwill *et al.*, 1987
10		Atterwill *et al.*, 1987
11		Atterwill *et al.*, 1987
12		Atterwill *et al.*, 1987
13	Appeared to be dose producing maximum effect	Atterwill *et al.*, 1987
14		Atterwill *et al.*, 1987
15		Atterwill *et al.*, 1987