

Guidelines/Criteria	A series of contiguous papers all documenting aspects of a sin Different endpoints and the results for these endpoints are des
Reference:	Arnold DL, Stapley R, Bryce F, Mahon D. 1998a. A multigeneration study to ascertain the toxicological effects of Great Lakes salmon fed to rats: Study overview and design. Regul Toxicol Pharmacol 27:S1-S7.
In vivo Study Type Route of Administration Species & age of animals	oral diet Sprague-Dawley rats
Study Duration	2-Generation toxicity study (10 weeks before mating, 1:1 mating, appr. 70 days postweaning, one F1 male and one F1 female from 24 litters were mated within the diet groups to produce F2 litters).
Type of Mixture Binary >2 components Similar acting or dissimilar What Mode of Action was investigated?	no yes dissimilar action assumed reproduction toxicity
Parameters/End points Measured Target organs/Critical effects Pharmacological changes or adverse effects	This paper described the overall study methodology.
Individual Components Characterisation of individual compounds Name, exact chemical name, CAS no. Were dose responses established for individual components? Were no effect levels established? Were doses below the NO(A)ELs investigated?	No Rats were exposed to different concentrations of Chinook salmon caught in the Credit River, which empties into Lake Ontario (LO), or in the Owen Sound region of Lake Huron (LH). No, an environmental mixture was administered. Yes Yes
Mixtures Investigated Number of dose levels How does the mixture make-up compare to individual components? (e.g. low dose) equivalents used?) No. of technical replicates per exposure condition (<i>in vitro</i>) No. of animals per dose group (<i>in vivo</i>)	5 Dose groups, whose dietary protein consisted of casein and/or lyophilized salmon: Group 1: 20% casein (controls) Group 2: 15% casein + 5% LO salmon (LO-5%) Group 3: 20 % LO salmon (LO-20%) Group 4: 15% casein + 5% LH salmon (LH-5%) Group 5: 20% LH salmon (LH-20%) An environmental mixture was administered. not applicable
Observations/Findings	This paper described the overall study methodology - no results.
Overall opinion (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)	Valid study, sufficient animal numbers, many detailed endpoints. Represents an extreme worst case for human Great Lakes fish consumption. With different generation, two sexes and two dose levels, there is an opportunity to identify consistent effects, but few were seen, most effects being inconsistent and so not clearly treatment related. Clear liver enzyme induction (all fish fed groups), liver weight increases (LO-20% & LH-20%) and reduced vitamin A stores (LO-20%) were the only clear treatment related effects. No appreciable toxicological risk.

gle study. Overall methodology is in the first paper, and results summary in the last.
cribed below the paper in which they are reported.

<p>Feeley MM, Jordan SA. 1998. Dietary and tissue residue analysis and contaminant intake estimations in rats consuming diets composed of Great Lakes Salmon: A multigeneration study. Regul Toxicol Pharmacol 27:S8-S17.</p>	<p>Arnold DL, Bryce F, Miller D, Stapley R, Malcolm S, Hayward S. 1998b. The toxicological effects following the ingestion of Chinook salmon from the Great Lakes by Sprague-Dawley rats during a two-generation feeding-reproduction study. Regul Toxicol Pharmacol 27:S18-S27.</p>
<p>This paper describes residue and intake analyses only.</p>	<p>Reproduction toxicity: growth, feed consumption, organ weights, reproduction indices, serum chemistry, haematology, coagulation times.</p> <p>Adverse effects</p>
<p>The 5% and 20% fish diets were approximately 15x and 60x the current estimate for the Canadian public for consumption of all fish and seafood. The fresh fish did not violate any guidelines for contaminant content, but once prepared for feeding to the rats it exceeded several guidelines for individual contaminants (dioxins and mercury for LH & LO, and PCBs for LO). The LO fish were slightly more contaminated than the LH fish overall.</p>	<p>LO-20% and LH-20% both sexes: relative liver and kidney weight increases, lower blood urea nitrogen LH-20% females: Higher terminal body weight, lower number of red blood cells, haematocrit, haemoglobin and mean platelet volume, lower alanine transaminase activity All fish groups: higher creatinine levels. Overall: Tendency for the fish-fed groups to grow faster, eat more feed, and have larger litters with heavier pups. No appreciable toxicological risk to Sprague-Dawley rats growth and reproduction.</p>

Tryphonas H, McGuire P, Fernie S, Miller D, Stapley R, Bryce F, Arnold DL, Fournier M. 1998a. Effects of Great Lakes fish consumption on the immune system of Sprague-Dawley rats investigated during a two-generation reproductive study. I. Body and organ weights, food consumption, and hematological parameters. Regul Toxicol Pharmacol 27:S28-S39.	Tryphonas H, McGuire P, Fernie S, Miller D, Stapley R, Bryce F, Arnold DL, Fournier M. 1998b. Effects of Great Lakes fish consumption on the immune system of Sprague-Dawley rats investigated during a two-generation reproductive study. II. Quantitative and functional aspects. Regul Toxicol Pharmacol 27:S50-S54.
This element of the study focused on F1 and F2 animals, and also included groups of F1 animals which were switched to control diet for 3 months at 13 weeks of age.	This element of the study focused on F1 and F2 animals, and also included groups of F1 animals which were switched to control diet for 3 months at 13 weeks of age.
Body and organ weights, food consumption and haematological parameters (RBC counts, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, red cell distribution width, platelet count, platelet volume, platelet distribution width, WBC concentration and differential leukocyte counts. Potentially adverse	Immune-system related parameters: spleen T-lymphocytes, plaque-forming cell assay, lymphocyte transformation assay, natural killer cell activity, phagocytic activity of resident peritoneal cells, Listeria infectivity assay and serum cortisol. Potentially adverse
Occasional sporadic effects on food consumption not clearly treatment-related. Evidence of growth rate reduction in F1 in male LO-20% group, reversible when placed on control diet (occasional other sporadic effects not apparently treatment related). Increased liver weights in LO-20% males in F1, and LO-20% and LH-20% males in F2. Reduced thymus weight in recovery group F1 females on LO-20% diet (chance?). Other occasional sporadic organ weight effects not clearly treatment related. Sporadic effects on various haematological parameters, inconsistent between sexes and generations, but suggesting some effects of fish diet vs. control and of LO diets compared to LH diets.	Increased leukocytes and lymphocytes in spleens of F2 males fed LH salmon, especially for LH-20%. No consistent effects in plaque-forming cell assay or on phagocytic activity or Listeria infectivity, natural killer cell activity or lymphocyte transformation in response to a mitogen.

Pappas BA, Murtha SJE, Park GAS, Hewitt K, Seegal RS, Jordan SA. 1998. Neurobehavioral effects of chronic ingestion of Great Lakes chinook salmon. Regul Toxicol Pharmacol 27:S55-S67.	Seegal RF, Pappas BA, Murtha SJE, Park GAS. 1998. Neurochemical effects of consumption of Great Lakes salmon by rats. Regul Toxicol Pharmacol 27:S68-S75.
Behavioural endpoints: activity, exploration, sensorimotor function, stereotypy, spatial learning, long-term memory, response to food reward reduction.	Concentrations of biogenic amines and their metabolites and of choline acetyltransferase in 4 brain regions.
Potentially adverse	Potentially adverse
No effect on great majority of endpoints. No convincing effects at all, occasional effects being inconsistent.	There were various effect of all fish diets vs. rat chow, which in general were as common and large as the differences between fish diets. Dopamine in the substantia nigra was significantly reduced in the LO-20% group. These were all F1 results. F2 results were invalid due to inappropriate termination procedures.

<p>Iverson F, Mehta R, Hierlihy L, Gurofsky S, Lok E, Mueller R, Bourbonnais DH, Spear PA. 1998. Microsomal enzyme activity, glutathione S-transferase-placental form expression, cell proliferation, and vitamin A stores in livers of rats consuming Great Lakes salmon. Regul Toxicol Pharmacol 27:S76-S89.</p>	<p>Feeley MM, Jordan SA and AP Gilman (1998) "The Health Canada Great Lakes multigeneration study - summary and regulatory considerations." Reg Tox & Pharm v27 ppS90-S98.</p>
<p>This element of the study focussed on F0 and F1 animals only.</p>	
<p>Liver microsomal enzymes, liver immunohistochemistry (including cell proliferation measures), liver pathology and vitamin A storage.</p> <p>Potentially adverse</p>	<p>This paper summarises all findings.</p>
<p>Evidence of liver enzyme induction on all fish diets (especially LO) compared to rat chow (which can be explained by PCB content alone). No effects on cell proliferation. Reductions in vitamin A stores in LO-20% F0 adults, F1 weanlings, and F1 adult females. No adverse pathology.</p>	<p>Responses are adaptive or of limited biological significance with two exceptions i) suggestions of effect on working and reference memory of males on 20% diets and ii) reduced thymus weight in recovery group F1 females on LO-20% diet and increased leukocytes and lymphocytes in spleens of F2 males fed LH salmon, especially for LH-20%.</p>