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Research Models and Services
Teklad Custom Diets

Diets to induce nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH)

DIETARY FACTORS TO STUDY NAFLD/NASH IN RODENT MODELS

Nonalcoholic fatty liver disease is the most prevalent form of liver disease in the United States [1]. The pathogenesis of simple steatosis to NASH and cirrhosis is still not fully understood, but evidence suggests progression from NAFLD to NASH requires multiple "hits" or insults [2, 3]. NAFLD is an important public health concern, however treatment options remain limited [3].

Animal models of NAFLD and NASH are helpful in proving greater understanding of disease progression, developing new treatment options and improving diagnostic techniques. Diet manipulation is a useful tool in producing rodent models of NAFLD and NASH. Key dietary factors that determine the progression of NAFLD from simple steatosis to NASH, cirrhosis, and heptacellular carcinoma are summarized in the table below.

NAFLD is a progressive disease beginning with simple steatosis that can develop to NASH characterized by hepatic inflammation, fibrosis, and/or hepatocellular carcinoma. In humans, manifestations of NASH are often associated with obesity and metabolic syndrome [2]. Dietary methods to induce NAFLD/NASH in rodents can be split into two common categories: 1) diets feed for longer periods of time to induce obesity, metabolic syndrome, and mild NASH or 2) feed a nutrient deficient diet (for example methionine) to induce hepatic features of severe NASH without inducing metabolic symptoms such as obesity and insulin resistance in a relatively short period of time.

When choosing dietary features to induce NAFLD pathologies one must consider the animal model, time frame, and desired disease outcome. More complete descriptions of dietary NAFLD/NASH models are included on the following pages with example diets.

NAFLD/NASH key dietary factors

DIETARY FEATURE	ROLE IN NAFLD/NASH DEVELOPMENT		REFERENCE(S)
	METABOLIC	HEPATIC	
Sugar	Obesity and metabolic syndrome	Promotes lipid synthesis and steatosis without fibrosis	4-6
High Fat	Obesity, dyslipidemia and metabolic syndrome	Induces steatosis	5, 7
Trans-fat	Promotes insulin resistance	Promotes steatosis, inflammation and injury	8, 9
Palmitic Acid	As part of a high fat diet weight gain with metabolic syndrome	Induce hepatocyte lipid accumulation and pro-inflammatory cytokine production *in vitro*	10, 11
Cholesterol	Hypercholesterolemia	Hepatic fat deposition and inflammation when fed in the context of a high fat diet	12, 13
Cholate	Slows growth rates preventing the development of obesity and metabolic syndrome.	Enhances cholesterol absorption, inflammation, and fibrosis	12, 14-16
Methionine	Deficiency causes weight loss. No development of metabolic syndrome.	Deficiency decreases S-adenosylmethionine (SAM) which limits glutathione, an important antioxidant, promoting inflammation and fibrosis. Limited SAM also impairs phosphyatidylcholine synthesis leading to lipid accumulation	5, 17
Choline	Limited effects on growth rates with severe restriction. Choline deficient high fat diets can lead to obesity and metabolic syndrome.	Deficiency interrupts phosphyatidylcholine synthesis and normal methionine metabolism limiting hepatic fat export leading to lipid accumulation	17-19

DIET OPTIONS FOR INDUCING OBESITY, METABOLIC SYNDROME AND MILD NAFLD/NASH

Western and fast food diets with milkfat and cholesterol

Western or fast food style diets fed to induce NASH with metabolic syndrome contain 40 - 45% kcal from milkfat (a fat source high in palmitate) with added cholesterol (0.15 – 2%) and are high in sucrose (>30%). Dietary palmitate and cholesterol have both previously been associated with the progression from simple steatosis to NASH [20-23]. These diets can induce obesity, metabolic syndrome, and simple steatosis within nine weeks of feeding [22, 24]. Increased hepatic inflammation has been observed after 12 weeks of feeding [23, 25]. NASH typically requires longer feeding with fibrosis developing within nine months and late stage fibrosis including hepatic ballooning occurring after 14 – 20 months of feeding [26-28]. In addition to feeding a high fat diet, providing a glucose/fructose mixture in the drinking water may further promote NASH development [9, 20, 28].

WESTERN AND FAST FOOD DIETS WITH MILKFAT AND CHOLESTEROL	
TD.88137	Milkfat western diet (42% Kcal fat, 0.2% total cholesterol)
TD.96121	Milkfat western diet (42% Kcal fat, 1.25% total cholesterol)

For more information about **TD.88137** download here:
inotivco.com/resources/data-sheets/88137.pdf

For more information about **TD.96121** download here:
inotivco.com/resources/data-sheets/96121.pdf

The ALIOS model: western diet with trans-fat

The American Lifestyle-Induced Obesity Syndrome (ALIOS) model involves feeding the "American fast food" diet **TD.06303** high in trans-fats and sugar. Dietary transfats from hydrogenated vegetable shortening (HVO) are associated with increased insulin resistance and hepatic inflammation in rodent NASH models [8, 9]. In addition to diet, a glucose/fructose solution is added to the drinking water and sedentary behavior promoted by removing the overhead cage feeders in this model. The ALIOS model develops obesity with insulin resistance, elevated ALT levels, and steatosis within 16 weeks [9, 29]. Increased inflammation and early development of fibrosis have been observed at 6 months [30]. After 12 months, Dowman and colleagues observed severe steatosis with fibrosis and inflammation with 50% of the mice developing hepatic neoplasms [30]. Adding cholesterol to the American Fast Food diet **TD.120330** may accelerate NASH phenotype development [31].

ALIOS DIETS	
TD.06303	ALIOS diet (22% HVO)
TD.120330	ALIOS diet with 0.2% cholesterol (22% HVO)

For more information about **TD.06303** download here:
inotivco.com/resources/data-sheets/06303.pdf

For more information about **TD.120330** download here:
inotivco.com/resources/data-sheets/120330.pdf

FPC diet: fructose, palmitate, cholesterol and trans-fat diet

The Fructose, Palmitate, Cholesterol and Trans-Fat (FPC) diet **TD.160785** is a recent NASH diet that includes Western and ALIOS model diets to achieve both metabolic and hepatic NASH features within an accelerated time frame. Like the ALIOS model, the FPC model also provides a glucose/fructose solution to the drinking water [11]. Male C57BL/6J mice developed insulin resistance and NAFLD with inflammation, hepatocyte death, and fibrosis within 16 weeks of feeding **TD.140154 (11)**. **TD.140154** is an earlier version of **TD.160785** that required palmitic acid to be sent, however we now stock it.

Key features of the FPC diet include:

- Methionine content is lower than typical rodent diets by decreasing total protein content without the supplementation of sulfur amino acids
- Choline supplementation is lower than typical rodent diets but is not considered deficient [32]
- High in sucrose (~34% by weight)
- 1.25% cholesterol
- High fat diet (52% kcal from fat). Fat sources include:
  - Milkfat provides SFA and palmitic acid
  - Hydrogenated vegetable shortening (HVO) provides trans-fats

High fat diets

Common diets to induce obesity (DIO) can be fed to induce uncomplicated NAFLD. These high fat diets typically contain 40–60% kcal from fat without supplemented cholesterol or cholate. Simple sugars such as sucrose or fructose can also be supplemented via diet or water to progress the fatty liver phenotype. Diets can be in pellet or powder/dough form depending on the formula. Some models require limited physical activity and in those cases diets can be fed inside the cage. In susceptible rodent models, high fat diets are commonly used to induce NAFLD with obesity and insulin resistance common metabolic features associated with NASH in humans. However, the degree of NASH pathology (steatosis, inflammation, and fibrosis) is limited or mild and varies depending on the animal model, length of feeding, and dietary components.

For more information see our **Diet Induced Obesity** page
inotivco.com/products-services/teklad/laboratory-animaldiets/custom-research/diet-induced-obesity

HIGH FAT DIETS TO INDUCE SIMPLE FATTY LIVER DISEASE	
TD.08811	45%kcal fat diet (21% MF, 2% SBO)
TD.06414	Adjusted calories diet (60/Fat)

For more information about **TD.08811** download here:
inotivco.com/resources/data-sheets/08811.pdf

For more information about **TD.06414** download here:
inotivco.com/resources/data-sheets/06414.pdf

DIET OPTIONS FOR INDUCING MORE SEVERE HEPATIC NAFLD/NASH WITHOUT OBESITY OR METABOLIC SYNDROME

Atherogenic diets high in fat, cholesterol, and cholate

Originally formulated to induce mild atherosclerosis in wildtype rodents, high fat diets containing added cholesterol (1 – 1.25%) and cholate (0.5% as sodium cholate or cholic acid) have also been useful in inducing NASH. This diet option includes purified "Western" style diets with increased cholesterol and cholate **TD.02028** and also hybrid diets. Hybrid diets were originally developed by Beverly Paigen and colleagues by mixing a natural ingredient mouse diet in a 3:1 ratio with a concentrated purified diet (containing 5% cholesterol and 2% sodium cholate) resulting in a diet containing ~15.8% fat, 1.25% cholesterol, and 0.5% sodium cholate **TD.88051**. Although a less refined approach, the hybrid diet is associated with increased gallstone formation and liver damage as compared to similar purified diets [33].

Atherogenic diets are able to induce varied degrees of NASH with increased hepatic inflammation with early fibrosis observed after ten weeks of feeding [34, 35]. However, the metabolic profile typical in human NASH (obesity with insulin resistance) is not recapitulated in this model with animals typically maintaining similar body weights as control fed groups [14, 35, 36] without the development of metabolic syndrome.

ATHEROGENIC HIGH FAT DIETS WITH ADDED CHOLESTEROL AND CHOLATE SOURCE	
TD.88051	Cocoa butter diet and purina mouse chow (1.25% cholesterol, 0.5% sodium cholate)
TD.02028	21% Milkfat (1.25% cholesterol, 0.5% cholic acid)
TD.09237	15% Milkfat diet (1% cholesterol, 0.5% sodium cholate)

For more information about **TD.88051** download here:
inotivco.com/resources/data-sheets/88051.pdf

For more information about **TD.02028** download here:
inotivco.com/resources/data-sheets/02028.pdf

For more information about **TD.09237** download here:
inotivco.com/resources/data-sheets/09237.pdf

Methionine/choline deficient (MCD) diets

Methionine and choline deficient (MCD) diets are amino acid defined rodent diets deficient in methionine and choline, high in sucrose (>40% by weight) with ~10% corn oil by weight. Methionine and choline deficiency decreases fat oxidation and export of fat from the liver. Dietary sucrose is necessary for hepatic lipid accumulation and oxidation [4]. The polyunsaturated fat in corn oil promotes hepatic lipid oxidation [22, 37]. Steatosis, increased serum alanine aminotransferase (ALT), inflammation, and hepatic fat oxidation has been observed within three weeks of feeding the MCD diet [4, 37] with fibrosis development after six weeks [17, 22, 38, 39]. This dietary model does not produce metabolic syndrome (an aspect of NASH in human models) and progressive weight loss (up to 40%) is associated with the MCD diet feeding [22, 40].

METHIONINE/CHOLINE DEFICIENT DIET AND CONTROL	
TD.90262	Methionine/choline deficient diet
TD. 94149	MCD control diet

For more information about **TD.90262** download here:
inotivco.com/resources/data-sheets/90262.pdf

For more information about **TD.94149** download here:
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Emerging NASH models

Dietary models of NAFLD/NASH continue to evolve with the goal of more accurately recapitulating both the metabolic and hepatic symptoms of human disease. Commonly researchers are studying the synergistic effects of various NASH dietary features to accelerate progression of the model and severity of liver disease [11, 13].

A Teklad nutritionist can work with you to formulate new diets in order to investigate novel dietary models of NAFLD/NASH.

Control diets

The choice of control diet is dependent on the specific research goal. Many researchers choose to compare their NAFLD/NASH diet-fed animals to animals fed a natural ingredient, grain-based diet (also referred to as standard diet or chow). These diets differ in the source and level of nutrients as well as in the presence of non-nutritive factors (such as phytates or phytoestrogens).

Depending on what your main comparisons are, it may be suitable to have a grain-based diet as your control/reference group. However, making such comparisons limits inferences to dietary patterns versus a specific dietary component. In some cases, such as those studies feeding amino acid defined diets like the MCD model, a matched control diet is recommended given the very different formulations and protein sources of grain-based diets.

When making inferences about specific nutrients within the diet an ingredient matched, low fat control diet may be necessary. There are many options with different levels and types of fat in addition to different types of carbohydrate ranging from sucrose (highly refined and digestible) to corn starch (refined, but more complex) to resistant starch (refined, but not fully digestible).

A very basic purified control diet would be AIN-93M **TD.94048** or AIN-93G **TD.94045**. AIN-93 diets have a moderate amount of sucrose at ~10% with fat from soybean oil providing a healthy fatty acid profile.

For more information about TD.94048 download here:
inotivco.com/resources/data-sheets/94048.pdf

For more information about TD.94045 download here:
inotivco.com/resources/data-sheets/94045.pdf

Contact a nutritionist at
askanutritionist@inotivco.com
for additional information, control diet recommendations or for a diet consultation.

KEY CONSIDERATIONS WHEN CHOOSING A RODENT DIET TO INDUCE NAFLD/ NASH

Diets to induce obesity, metabolic syndrome and mild NASH:

- Require long term feeding (4–12 months) to induce mild fibrosis
- Often add a glucose/fructose solution to the drinking water and promote sedentary behavior by removing overhead cage feeders

Diets to induce more severe hepatic NASH:

- Often do not recapitulate metabolic symptoms associated with NASH such as obesity or insulin resistance. Some models can induce weight loss.
- Commonly fed for 3–12 weeks to induce hepatic inflammation and early fibrosis

Dietary NASH models **continue to evolve** with the goal of recapitulating both metabolic and hepatic symptoms common to human disease. New diets can be formulated in order to investigate novel dietary models of NAFLD/NASH.

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