

# High-Fat Diets for Diet-Induced Obesity (DIO) Models

2017- Brief Scientific Literature Review  
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Genetic and environmental factors play a role in the development of obesity, and diet is one of the main environmental factors that contribute to obesity and its related metabolic diseases. Human studies have shown that increased fat intake is associated with body weight gain which can lead to obesity and other related metabolic diseases. As such, animal rodent models are useful tools to determine the mechanistic aspects of obesity and to develop therapeutic approaches as they will readily gain weight when fed high-fat diets (1, 2). Here, we discuss important factors to consider when designing a diet-induced obesity study using animal models.

## Matched Formulas

When planning a diet-induced obesity study, the composition of the high-fat diet deserves special attention. All too often in the literature, one will find that diets used in the experiments are not well matched, thereby introducing a number of confounding factors. For example, in many cases a grain-based (GB) diet is used as a low-fat “control” diet for a purified high-fat diet.

GB diets contain plant-derived ingredients which are subject to fluctuations in the growing season and will vary in composition at the time of harvest. Thus, the nutritional composition of GB diet formulas may differ based on the types of ingredients used during manufacturing. Purified ingredients, on the other hand, are highly refined and contain one primary nutrient (i.e. corn starch for carbohydrate, soybean oil for fat). These ingredients have little variability and therefore provide consistency between batches. There are numerous differences between GB and purified diets, introducing countless variables during the data analysis, thus making it difficult to interpret the results when these diets are used together in a study (3). In addition, GB diets contain plant-based compounds such as phytoestrogens which have been shown to reduce the degree of weight gain (4) compared to purified diets. For these reasons, a properly matched control diet should be low in fat (and higher in carbohydrate) while matched in every other way to the high-fat diet. In practical terms, since most high fat diets being used today are made with purified ingredients, this means using a properly matched, low-fat purified ingredient diet as the control and not a GB diet.

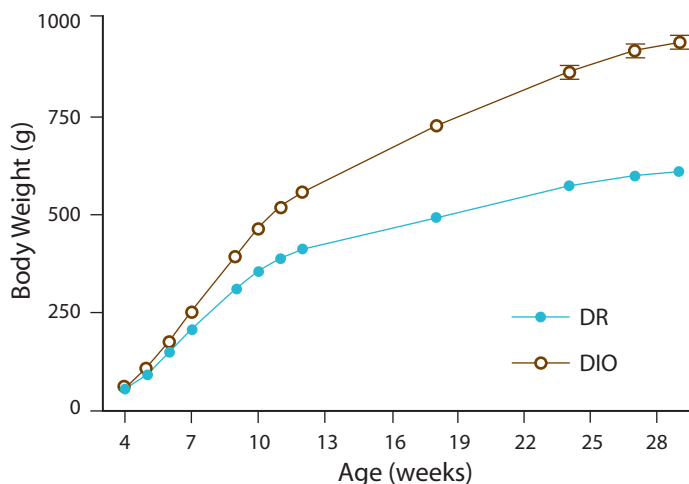


FIGURE 1. Growth rate of DIO (n = 12) and DR (n = 12) rats fed D12451 HFD (45 kcal% fat) diet used in meal analysis. Values are means ± SEM. Body weights are significantly different at all time points (p < 0.05). Graphic representation - for details see reference (34).



## Calories from Fat

High-fat diets used in laboratory research typically contain approximately 32% to 60% of calories from fat. From a nutritional perspective, a human diet of 60 kcal% fat would be considered extreme and physiologically irrelevant. That said, diets with 60 kcal% fat are commonly used to induce obesity in rodents when it is desired to promote weight gain in a short time since animals tend to gain more weight faster (5, 6), thereby allowing researchers to establish obesity-related disease models quickly and to screen their test compounds in a shorter period of time. Thus, arguments may be made for choosing to use either a very high-fat diet for rapid weight gain or a more moderate fat diet for slower weight gain to mimic human dietary fat consumption. It should also be noted that when studying the effects of a drug, bioactive food compound, nutraceutical, or genetic modification on obesity, it may be more difficult to prevent or reverse the effects of a very high-fat diet with the dietary/genetic modification, whereas it might be possible to see the effects of a therapy when using a diet containing a lower percentage of fat (i.e. 45 kcal%).

## Type of Fat

The type of fat used for the research should be considered when choosing a high-fat diet for an animal study because the fatty acid composition of the diet can affect study outcomes. Many high-fat diets used in laboratory animal research typically contain high saturated fat sources such as lard, beef tallow, coconut oil, or milk fat, or trans-fat such as hydrogenated vegetable oils, and these diets are quite capable of inducing obesity and metabolic diseases in susceptible strains (7-10). In contrast, oils rich in n-3 fatty acids and monounsaturated fatty acids (MUFAs) have been studied for their health benefits. For example, it has been shown that in animals fed similar amounts of fat, those fed diets containing fish oil did not gain as much weight (11-13) and were more insulin sensitive (14, 15) compared to those fed diets with more saturated fat. Also, a diet rich in n-3 fatty acids and MUFAs has shown to attenuate hepatic steatosis and alter hepatic phospholipid fatty acid profile in diet-induced obese rats (16). Since fatty acids can affect phenotype through a variety of mechanisms such as expression of genes involved in energy regulation and insulin function, eicosanoid production, cytokine production, membrane permeability, and alternation of gut microbiota (17-22), it is important to include information about the type and level of fat used in a study in order to allow other researchers to compare the resulting data.

## Animal Models

While most rodents tend to become obese on high-fat diets, there can be variable responses in weight gain, glucose tolerance, insulin resistance, blood lipid profiles and other parameters depending on the strain. Some inbred mouse strains such as the C57BL/6J or AKR/J mice are more susceptible to obesity when fed high-fat diets (23). However, strains that exhibit similar levels of weight gain may show different responses for other parameters. For example, when fed a 58 kcal% fat diet, C57BL/6J mice and AKR/J mice will have similar degrees of weight gain, but C57BL/6J mice are more glucose intolerant compared to AKR/J mice (23). Other strains are simply more resistant to obesity, such as the SWR/J, A/J and BALB/c mice (24-29). Even within the same strain, different phenotypical responses to high-fat diets have been observed between animals bred in different facilities (30).

Rat models including outbred Sprague-Dawley and Wistar rats are popular strains to study obesity as they readily gain weight on high-fat diets. Interestingly, these strains are known to have a variable weight gain response to high-fat diets (31, 32), with some animals rapidly gaining weight while others gain only as much weight as those fed a low-fat diet (33, 34). This variation in weight gain is thought to mimic the diverse spectrum of human obesity and is an attractive model for some researchers. In fact, Sprague-Dawley rats have been selectively bred over time to study the genetic traits of animals where the obese or lean phenotype on a high-fat diet is known from birth (33). Additionally, and in contrast to a C57BL/6J mouse model, body weight gains in these rat strains are often not very different between 45 and 60 kcal% fat diets, something researchers should consider when selecting diets for these strains (35, 36). Another strain, the F344xBrown Norway rat, has been used as an obesity model for human aging since the animals gain weight until about 30 months of age, then level off, which is similar to the weight gain pattern in the average person (37).



There has been a growing body of literature using rodents as models of human obesity, even though there are many confounding factors including species, strain, age of the animals, type of diet, level of fat, and type of control diet. Fortunately, there is a growing discussion about these issues which will help scientists design studies with tighter controlled conditions and therefore improve our understanding of obesity and related diseases.

Rodent models of diet-induced obesity continue to be widely used, valuable tools to study the mechanisms of human obesity. When designing a research study using animal models to analyze the mechanisms of human obesity, two key considerations should govern the discussion. The first factor to consider is the animal model itself- the benefits and limitations that a specific animal model will provide the study. Researchers need to also pay careful attention to the diets they choose in order to meaningfully interpret their data. Of key importance when considering the diet component in any high-fat diet (or other nutritional intervention) study is the use of a properly matched control diet which allows the researcher to assign reasons for phenotypic differences to specific dietary variables.

### The “Original” High-Fat Diets

Research Diets, Inc. formulated the “original” high-fat diet for diet induced obesity (DIO) studies in 1996. Today, our high-fat diets are the research standard for DIO mice worldwide.

(DIO) Formulas				
Product #	D12451		D12492	
	gm%	kcal%	gm%	kcal%
Protein	24	20	26	20
Carbohydrate	41	35	26	20
Fat	24	45	35	60
<b>Total</b>		100		100
<b>kcal/gm</b>	4.73		5.24	
<b>Ingredient</b>				
	gm	kcal	gm	kcal
Casein, 80 Mesh	200	800	200	800
L-Cystine	3	12	3	12
Corn Starch	72.8	291	0	0
Maltodextrin 10	100	400	125	500
Sucrose	172.8	691	68.8	275
Cellulose, BW200	50	0	50	0
Soybean Oil	25	225	25	225
Lard	177.5	1598	245	2205
Mineral Mix S10026	10	0	10	0
DiCalcium Phosphate	13	0	13	0
Calcium Carbonate	5.5	0	5.5	0
Potassium Citrate, 1 H <sub>2</sub> O	16.5	0	16.5	0
Vitamin Mix V10001	10	40	10	40
Choline Bitartrate	2	0	2	0
FD&C Red Dye #40	0.05	0		
FD&C Blue Dye #1			0.05	0
<b>Total</b>	<b>858.15</b>	<b>4057</b>	<b>773.85</b>	<b>4057</b>

Formulated by E. A. Ulman, Ph.D., Research Diets, Inc., 1/18/96 and 8/26/98. Contact us for matched control diets.

### Incorporate Test Compounds

Research Diets, Inc. will incorporate your test compound into pelleted diets for simple, safe dosing. Feeding test compounds eliminates dosing related stress to the animal, eliminates vehicle effects, and saves time and labor. Consult with one of our scientists on the formula, determine the dosage required and the diet will be produced and shipped in 5 to 7 business days



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