

**Body Weight and Survival of Harlan vs. Charles River Sprague Dawley Rats:
Implications for Carcinogenicity Testing**

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INTRODUCTION:

A 1988 survey of member companies of the Pharmaceutical Manufacturer's Association revealed that the average survival times of rat strains commonly used in carcinogenicity studies are decreasing. Decreased survival and increased spontaneous tumor incidences have been linked to obesity in this species. The consequences of using overweight rats are relevant to carcinogenicity testing because these factors render the model less sensitive for the detection of chemically induced tumors and have the potential to confound analysis of tumor-incidence data. Several solutions to this problem have been proposed, none of which has been found to be entirely satisfactory:

- 1. Acceptance of a shorter life-span and shorter study duration have been opposed by regulatory agencies.**
- 2. Rederivation of the Charles River Sprague Dawley strain for lower weight gain and longevity would be time consuming and might select for undesirable traits as well.**

INTRODUCTION (cont'd)

3. Caloric restriction can increase the longevity of an organism. Although this approach can increase longevity, questions remain concerning "the utility and advisability of caloric restriction" as a strategy for achieving adequate survival in rat carcinogenicity studies.

Our experience in toxicity studies with rats obtained from Harlan Sprague Dawley suggested that they might not become as obese with advancing age as Charles River rats. In an attempt to find a naturally lighter, more suitable model for carcinogenicity testing, the food consumption, survival, and body-weight gains of Harlan Sprague Dawley rats were studied in three separate Bristol-Myers Squibb laboratories (New Brunswick, NJ, Syracuse, NY, and Regensburg, Germany). Data from 2-year studies of Charles River CD rats conducted in Regensburg, and in Syracuse, are presented for comparison.

ABSTRACT

At each of three Bristol-Myers Squibb sites (New Brunswick, Syracuse, and Regensburg), 100 male and 100 female Harlan Sprague Dawley outbred albino rats were maintained for two years to evaluate their survival, food consumption, and rate of body-weight gain. The rats had ad libitum access to water and ground certified rodent diet, and body weights and food consumption were measured at regular intervals. Comparisons of the results to published information and to concurrent data from studies with Charles River Sprague Dawley (CrI:CD^R BR) rats conducted at the Syracuse and Regensburg sites clearly show that the Harlan rats have lower food consumption and gain less weight as they age. Most importantly, Harlan rats have a much lower mortality rate with advancing age than the Charles River rats. These characteristics make the Harlan Sprague Dawley rat a superior model for carcinogenicity testing, because non-obese, longer-lived test animals permit the completion of such studies, with good survival.

MATERIALS AND METHODS:

	<u>New Brunswick, NJ</u>	<u>Syracuse, NY</u>		<u>Regensburg, Germany</u>	
<i>Rat Strain:</i>	Harlan Hsd: Sprague Dawley	Harlan Hsd: Sprague Dawley	Charles River Crl:CD(SD)BR	Harlan Hsd/Ola: Sprague Dawley	Charles River Crl:CD(SD)BR
<i>Source:</i>	Frederick, Maryland	Madison, Wisconsin	Wilmington, Massachusetts	United Kingdom	Sulzfeld, Germany
<i>Number on Test:</i>	100 male & 100 female	100 male & 100 female	50 male & 50 female	100 male & 100 female	70 male & 70 female
<i>Housing:</i>	Individually, Stainless-Steel Wire-Bottom Cage	Individually, Stainless-Steel Wire-Bottom Cage	Individually, Stainless-Steel Wire-Bottom Cage	Groups of 4 Makrolon Cage SAWI Bedding	Groups of 4, Makrolon Cage SAWI Bedding
<i>Food:</i>	Purina Certified Rodent Laboratory Chow #5002	Purina Certified Rodent Laboratory Chow #5002	Purina Certified Rodent Laboratory Chow #5002	SDS Rat and Mouse Maintenance Diet RM1	Altromin CRC #1321

The rats were maintained on study for 2 years. During this time, the animals had ad libitum access to water and food, and body weights and food consumption were measured at regular intervals.

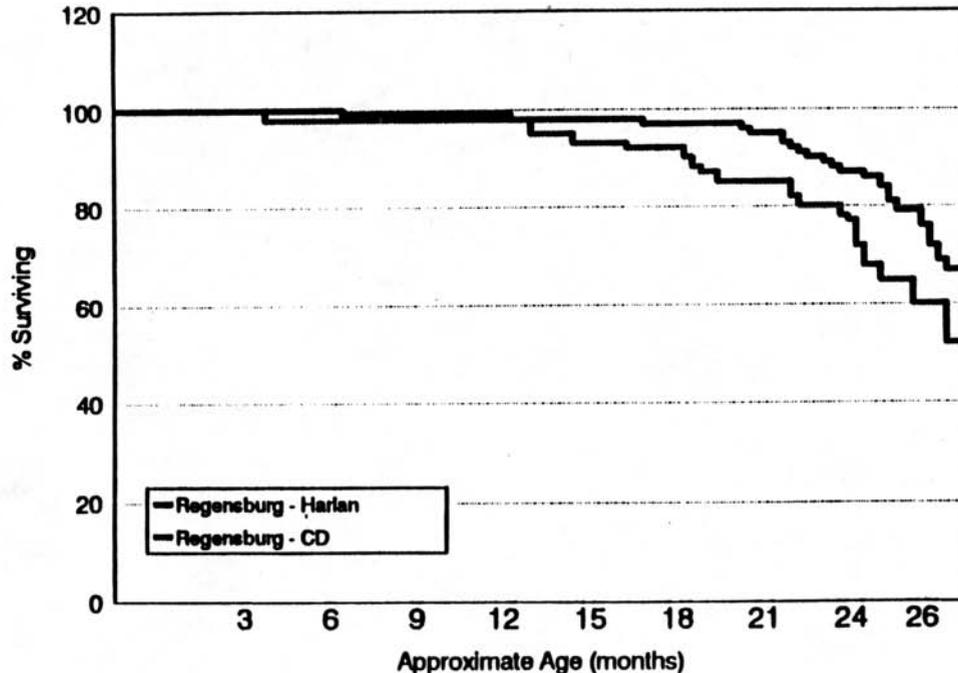
CONCLUSIONS:

Comparisons of the results from three separate lifetime studies using Harlan Sprague Dawley rats with concurrent data from studies using Charles River Sprague Dawley (Cr:CD^R BR) rats clearly show that:

- 1) Harlan rats have lower food consumption than Charles River rats.
- 2) Harlan rats weigh less than similarly aged Charles River rats.
- 3) Harlan rats live longer than Charles River rats.

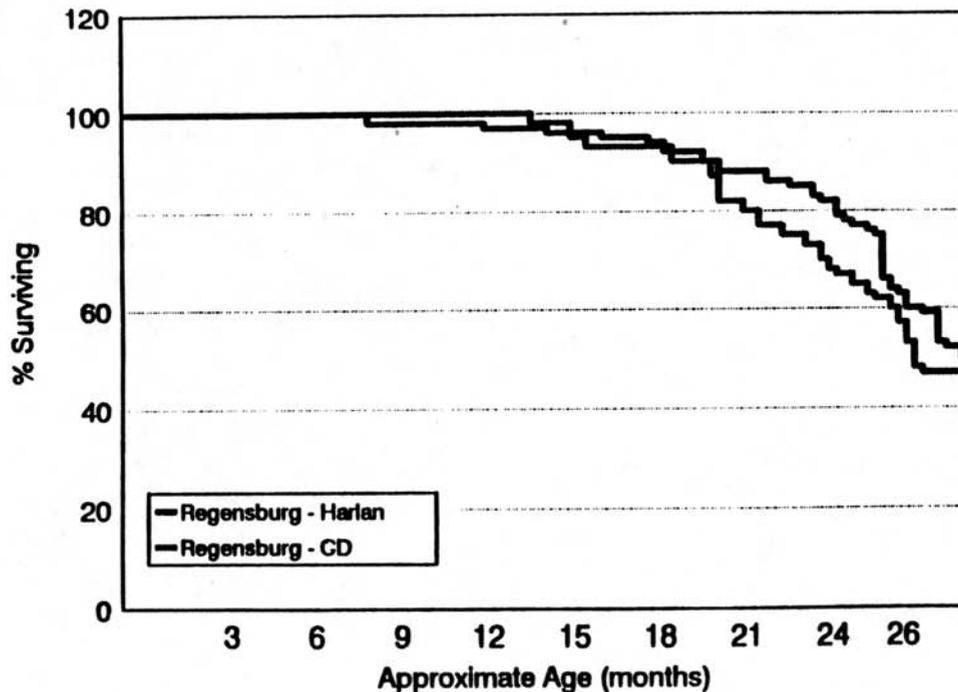
These characteristics make the Harlan Sprague Dawley rat a superior model for carcinogenicity testing.

Survival - Males



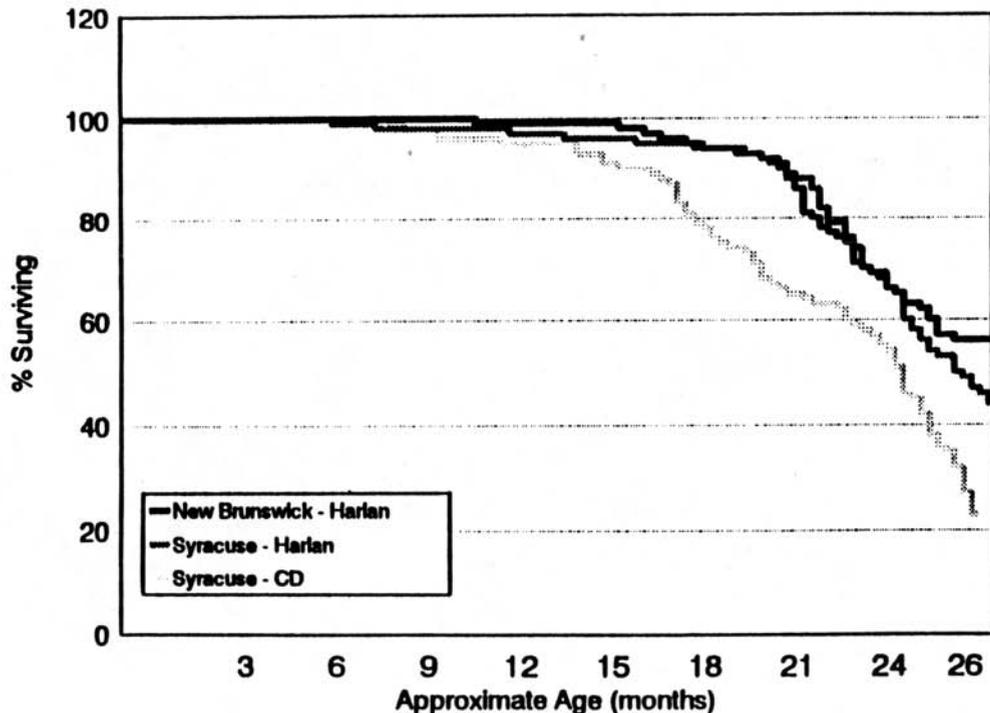
In Regensburg (group housing), earlier onset of death and a greater final mortality rate in Charles River males compared to Harlan males.

Survival - Females



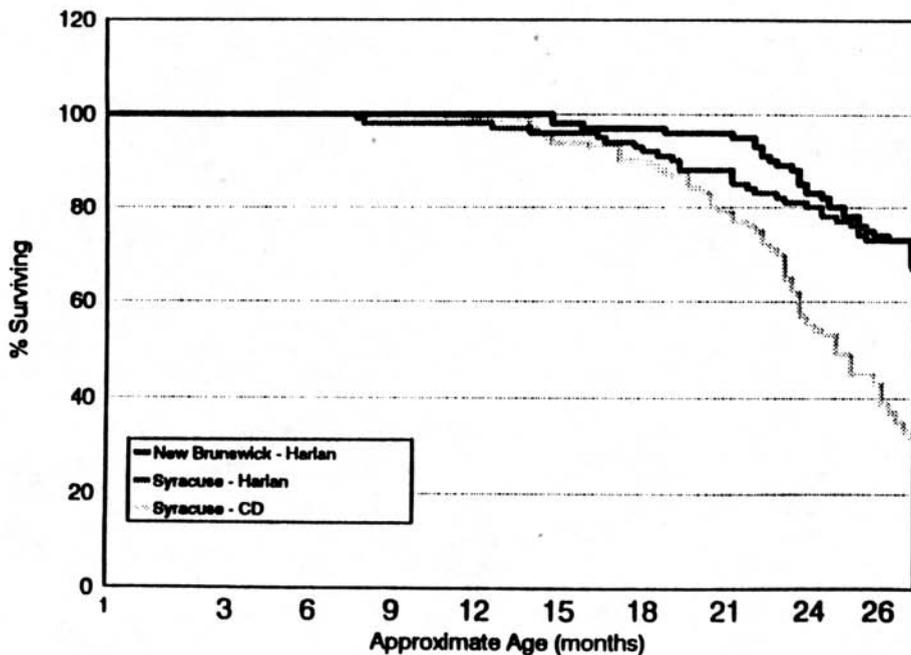
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Survival - Males



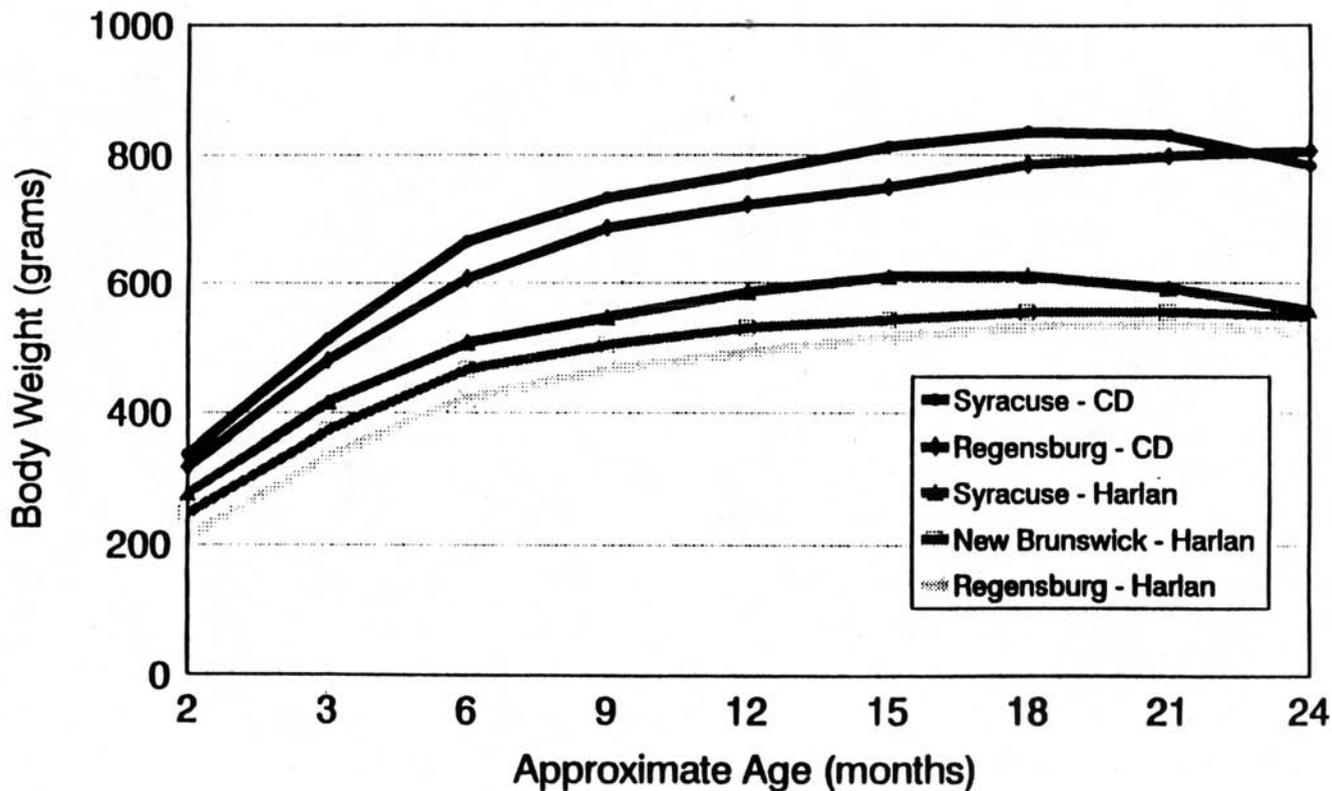
At the U.S. sites (individual housing), earlier onset of death and a greater final mortality rate in Charles River males compared to Harlan males.

Survival - Females



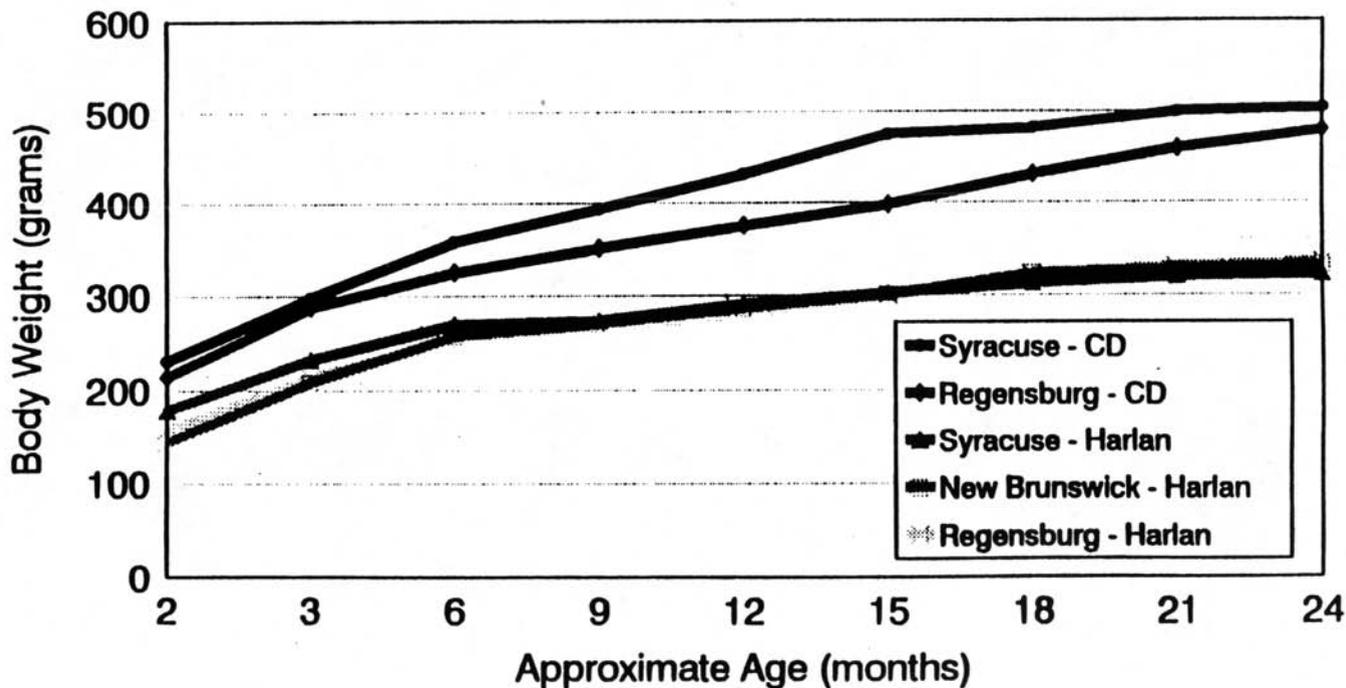
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Body Weight - Males



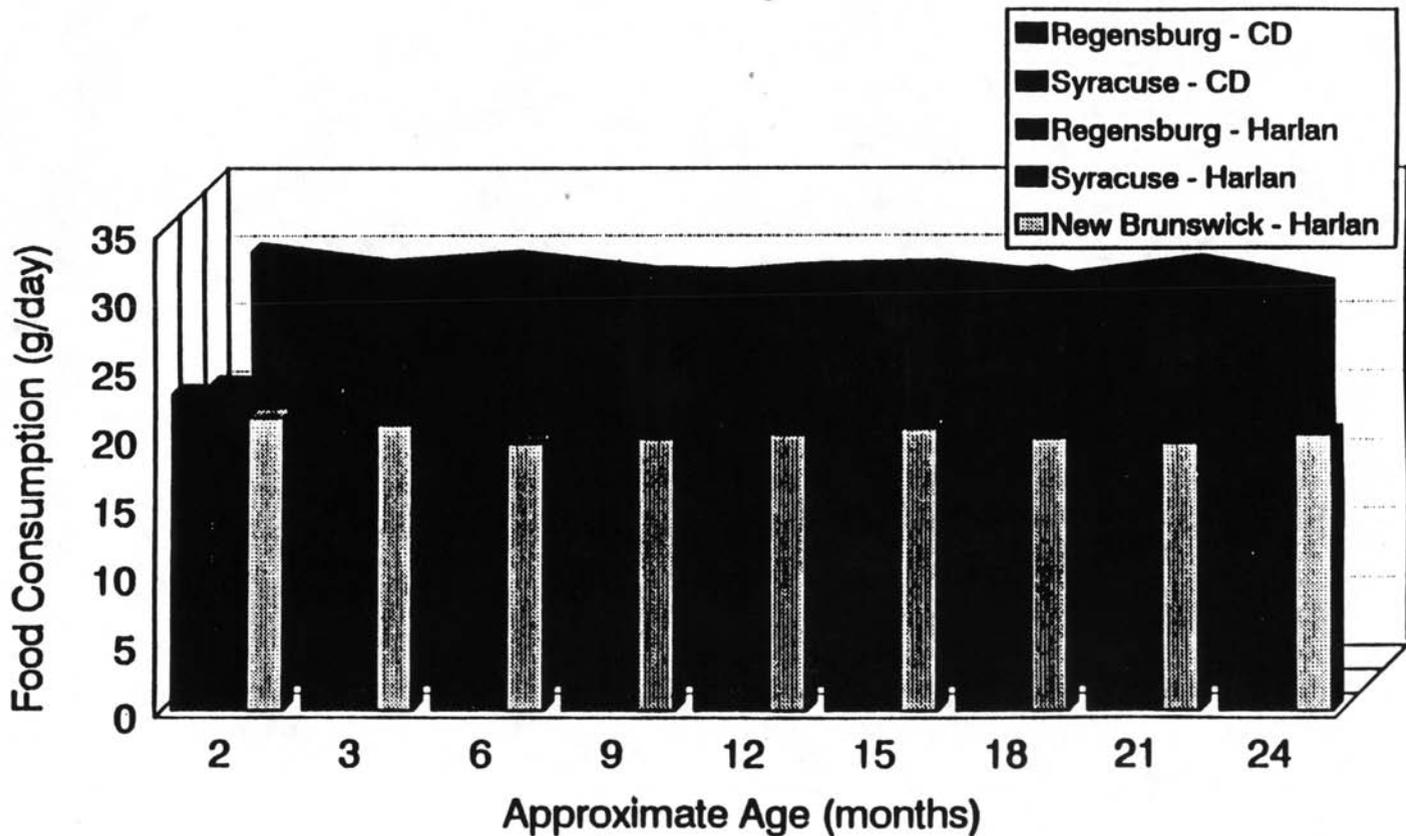
Charles River males (Regensburg-CD and Syracuse-CD) clearly exhibit greater body-weight gain than Harlan males at all sites. Between 2 and 12 months of age, Harlan rats weighed on average about 27% less, and at 24 months, 32% less than similarly aged Charles River rats.

Body Weight - Females



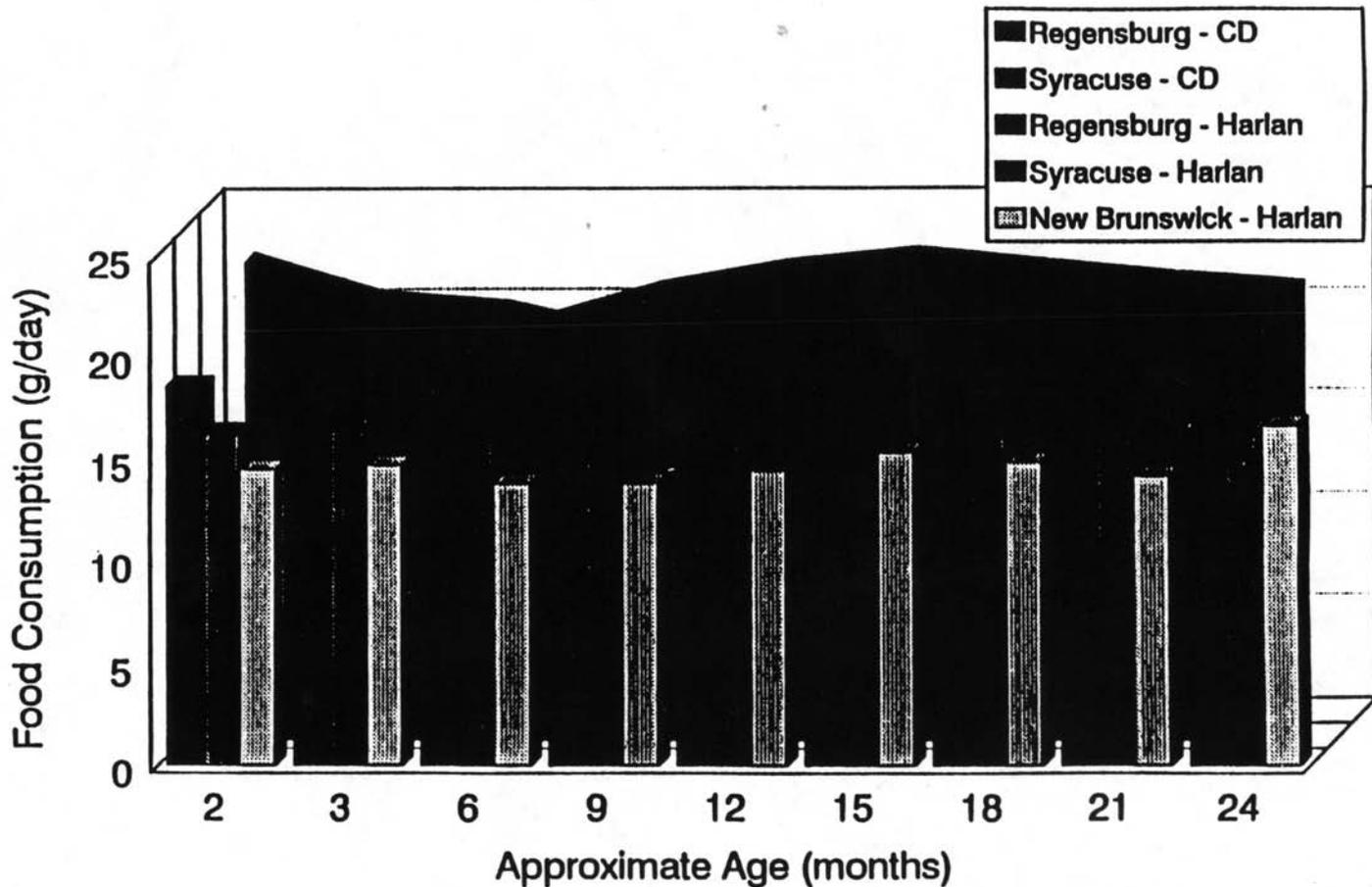
Charles River females (Regensburg-CD and Syracuse-CD) clearly exhibit greater body-weight gain than Harlan females at all sites. Between 2 and 12 months of age, Harlan rats weighed on average about 27% less and at 24 months, 33% less than similarly aged Charles River rats.

Food Consumption - Males



Food consumption in Charles River males exceeded that in Harlan males by 14% to 34% across all sites.

Food Consumption - Females



Food consumption in Charles River females exceeded that in Harlan females by 8% to 38% across all sites.